TNF Inhibitors Reduce Cardiovascular Risk

BY AMY ROTHMAN SCHONFELD

FROM A RHEUMATOLOGY MEETING SPONSORED BY NEW YORK UNIVERSITY

NEW YORK – Tumor necrosis factor inhibitors reduced the risk of myocardial infarction, stroke, and cardiovascular-related disease in patients with rheumatoid arthritis, according to Dr. Jeffrey D. Greenberg, who presented the findings at the meeting. Methotrexate was not associated with a reduced risk of cardiovascular events, and prednisone use was associated with a dose-dependent increased risk.

The findings come from CORRONA (Consortium of Rheumatology Researchers of North America), a registry of patients with RA or psoriatic arthritis. The study population involved 10,156 patients followed for a median of 23 months. A subset analysis was performed and 88 patients were identified who had experienced nonfatal myocardial infarction (n = 26), transient ischemic attack or stroke (n = 45), or CV-related death (n = 17) (Ann. Rheum. Dis. 2011;70:576-82).

In an editorial accompanying Dr. Greenberg's report (Ann. Rheum. Dis. 2011 70:561-2), Dr. Johan Askling of Karolinska University Hospital, Stockholm, and Dr. Will Dixon of the University of Manchester (England) praised the study's methodology and transparency. But they noted that other studies, like those published by the British Society for Rheumatology Biologics Register (BSRBR), do not support a CV protective effect for TNF inhibitors.

Nonbiologic disease-modifying antirheumatic drugs (DMARDs) other than methotrexate served as the reference cohort for all comparisons. Relative to nonbiologic DMARDs, methotrexate use was associated with a nonsignificant reduction in risk (hazard ratio 0.83, 95% confidence interval 0.44-1.57). In contrast, patients using a TNF inhibitor had a 61% lower risk of the primary composite CV end point (HR 0.39, 95% CI 0.18-0.74).

Dr. Greenberg also showed significant reductions in risk for those taking TNF inhibitors compared with those taking nonbiological DMARDs, as measured by a composite end point that included CV deaths (HR 0.39, 95% CI 0.19-0.82) and a composite end point that excluded CV deaths (HR 0.35, 95% CI 0.16-0.74), and nonfatal MI (HR 0.24, 95% CI 0.06-0.95). There was a trend toward reduced risk for nonfatal TIA/stroke (HR 0.44, 95% CI 0.18-1.09). "These data indicate that TNF antagonists may represent a therapeutic strategy to attenuate the heightened CV risk experienced by RA patients," Dr. Greenberg said.

"As expected, there was a dose-dependent increased risk of CV events with steroids," said Dr. Greenberg of New York University. Prednisone doses of 1-2.5 mg and 3-7 mg almost doubled the risk (HR 1.90 and 1.89, respectively) while doses greater than 7 mg tripled the risk (HR 3.00, 95% CI 1.44-6.25) ($P = .04$).

Dr. Greenberg advocates a three-step strategy to decrease CV risk in RA. The first is to adhere to recommended CV disease prevention, screening, and guidelines. This includes management of "traditional" CV risk factors such as blood pressure, diabetes, lipids, smoking, and obesity, he said. The second component – as supported by his study's results – is to minimize use of NSAIDs and steroids, and to utilize steroid-sparing options if possible. The third component is to aim for tighter control of RA disease activity.

For patients at increased CV risk, "I would treat RA aggressively," said Dr. Greenberg. Even so, he acknowledged that it has not been proved that the strategy would alter the natural course of developing CV disease. Measures that should be targeted might include a specific disease activity score, C-reactive protein levels, or other inflammatory biomarkers, he said. ■

VITALS

Major finding: Relative to nonbiologic DMARDs, methotrexate use was associated with a nonsignificant reduced risk (HR 0.83, 95% CI 0.44-1.57) of the primary composite CV end point of myocardial infarction, stroke, and CV-related death in patients with rheumatoid arthritis. Patients using a TNF inhibitor had a 61% reduced risk (HR 0.39, 95% CI 0.18-0.74) of the end point.

Data source: Longitudinal cohort study of the CORRONA registry.

Disclosures: Dr. Greenberg has done consulting for Centocor, CORRONA, Novartis Pharmaceuticals, Roche Laboratories, and UCB. He has received research and grant support from the Arthritis Foundation and the National Institutes of Health. He receives consulting fees from, or owns stock shares in, AstraZeneca, CORRONA, Genentech, Novartis, and Pfizer.

Anti-TNFs Use in Pregnancy Still Requires Caution

BY DENISE NAPOLI

FROM ANNALS OF THE RHEUMATIC DISEASES

Pregnant women taking tumor necrosis factor inhibitors at conception experienced a higher rate of spontaneous abortion than did patients who did not.

The data were culled from the British Society for Rheumatology Biologics Register.

Despite its relatively large size, the study was unable to control for the looming possibility that disease severity itself plays a role in adverse pregnancy outcomes, the authors said.

"[W]ithout further evidence, guidelines that suggest these drugs should be avoided at the time of conception must remain" in place, recommended Dr. Suzanne M.M. Verstappen of the University of Manchester's Arthritis Research UK Epidemiology Unit, and her associates.

The investigators looked at women in the register who received adalimumab, etanercept, or infliximab either at conception or at any time prior to conception.

A subset was also exposed to methotrexate and/or leflunomide at time of conception in addition to the anti-TNFs, two drugs with a "known risk of adverse pregnancy outcomes," according to the authors.

A fourth cohort with active rheumatoid arthritis had no history of anti-TNF use but rather received nonbiologic disease-modifying antirheumatic drugs, excluding methotrexate and leflunomide (Ann. Rheum. Dis. 2011 [doi:10.1136/ard.2010.140822]).

Among cohort Ia, which included 20 women (21 pregnancies) who took anti-TNFs plus either methotrexate and/or leflunomide at conception, there were 10 live births, 4 terminations, and 7 (33%) spontaneous abortions (miscarriages occurring prior to 20 weeks or to viability outside the womb).

Among cohort Ib, which included 44 women who took anti-TNFs at conception, but not methotrexate or leflunomide, there were 50 pregnancies.

They included 32 live births among this cohort, 4 terminations, 12 spontaneous abortions (24%), and 2 intrauterine deaths (occurring post-20 weeks).

There was also one neonatal death registered.

The women who had taken anti-TNFs in the past, but not at the time of conception (cohort II), did have seemingly better outcomes: The 59 pregnancies (54 women) resulted in live births in 46 cases (including one of two twins), terminations in 2, and spontaneous abortions in 10 (17%).

There were two intrauterine deaths, including the twin death.

Finally, among the 10 pregnancies in 10 women who had no history of anti-TNF use (cohort III), there were 0 terminations and 1 spontaneous abortion (10%).

The baseline disease activity score–28 (DAS28) was significantly higher in the anti-TNF cohorts, vs. cohort III: 6.5, 6.1, and 6.0 in cohorts Ia, Ib, and II, respectively, vs. 5.1 in cohort III.

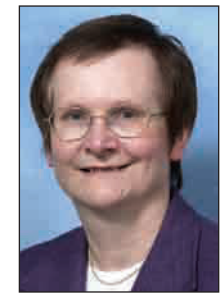
Dr. H. Michael Belmont, medical director of New York University's Hospital for Joint Diseases, as well as the director of the lupus clinic at Bellevue Hospital, New York, commented that, until more data are available, "The default choice would be to avoid these drugs during pregnancy. Starting their use in a women contemplating conception should be delayed based on the data on hand."

The study investigators disclosed that the British Society for Rheumatology receives restricted income from Abbott Laboratories, Biovitrum, Roche, Shering-Plough, and Wyeth Pharmaceuticals.

They added that they had no personal competing interests in relation to this study. ■

VIEW ON THE NEWS

What I Tell My Pregnant Patients



The only way to definitively address the question of risk associated with anti-TNFs and pregnancy would be to conduct a randomized controlled trial, according to Dr. Deborah P.M. Symmons.

There are, however, a few problems with that strategy. "Clearly, this would be very difficult to design, would need to be very large, and is never going to happen!" she joked.

"Beyond that, we have to wait for anecdotal evidence to accumulate."

In the meantime, she said, "We advise all patients with rheumatoid arthritis to discuss a planned pregnancy with their rheumatologist prior to conception in order to make prospective plans about what to do about treatment. There are a number of other antirheumatic drugs, for example methotrexate and leflunomide, which carry a substantially higher risk than has been seen with anti-TNF therapy so far. However, many patients on anti-TNFs take them with another antirheumatic drug."

According to Dr. Symmons, when treating a female patient of child-bearing age, "I would share what is currently known about the risks and benefits of continuing anti-TNF therapy with the woman with RA and let her ask further questions and make up her own mind about what to do.

"This study is reassuring for us to continue our current practice."

DR. SYMMONS *is one of the authors of the current study as well as a professor of rheumatology and musculoskeletal epidemiology at the University of Manchester, England. She had no financial interests to disclose.*