Immunizations Should Precede Rituximab

BY DIANA MAHONEY

COPENHAGEN — Reduced responses to pneumococcal polysaccharide and neoantigen vaccination in rheumatoid arthritis patients who were treated with rituximab and methotrexate suggest that polysaccharide and primary immunizations should be administered before rituximab infusions to maximize their efficacy, Dr. Clifton O. Bingham III said at the annual European Congress of Rheumatology.

Presenting data from SIERRA (Study Investigating the Effects of Rituximab on Rheumatoid Arthritis Patients), Dr. Bingham, director of the rheumatology clinics at Johns Hopkins University in Baltimore, reported that relative to patients treated with methotrexate only, patients who were given rituximab plus methotrexate mount a comparable recall response to tetanus toxoid, a measure of retained immunity. Patients on combination therapy also showed preserved delayed-type hypersensitivity (DTH) responses to the *Candida albicans* skin test.

However, patients on combination therapy showed decreased responses to both the 23-valent pneumococcal polysaccharide vaccine (PPV23), which measures T cell–independent humoral responses, and the neoantigen keyhole limpet hemocyanin (KLH), which tests T cell–dependent primary humoral responses.

The multicenter trial included 103 patients with active RA who were stratified by age and randomized 2:1 to receive two 1,000-mg infusions of rituximab 14 days apart plus methotrexate, or methotrexate alone. Patients aged 18-65 years were included in the study if they had at least four swollen and five tender joints and had been on stable doses of methotrexate for more than 4 weeks, Dr. Bingham explained. Additionally, background corticosteroids were permitted "as long as the dose was less than 10 mg per day and stable for more than 4 weeks," he said.

Individuals older than 65 years were excluded from the study "because of the known effect of aging on immune responses," Dr. Bingham stated. Patients who received the pneumococcal vaccine within the previous 3 years, or the tetanus vaccine within the previous 5 years, and those with other uncontrolled concomitant medical illnesses or concurrent use of other disease-modifying antirheumatic drugs or biologics were also excluded, he said.

The methotrexate-only patients received the tetanus toxoid–adsorbed vaccine on day 1, the PPV23 at week 4, and KLH at weeks 8 and 9, whereas the rituximab group received the same vaccines in the same intervals beginning at week 24, Dr. Bingham said.

The *C. albicans* skin test was administered on day 1 to both groups and then again at week 12 in the methotrexate-only group and at week 24 in the rituximab group.

The study's primary end point was the proportion of patients with a fourfold increase in antitetanus IgG from prevaccination levels, measured 4 weeks after immunization, Dr. Bingham stated. Secondary end points included a twofold increase in tetanus toxoid titer; a twofold increase or an increase of more than one mcg/mL from prevaccination levels in immune response to the PPV23; postvaccination KLH titers; and postvaccination DTH reactions, based on a *C. albicans* skin test with a cutoff of 5 mm of induration, he said.

With respect to baseline demographics, the patients in both groups were similarly matched except for baseline steroid use and positive skin test at baseline, Dr. Bingham noted. Baseline steroid use was higher in the rituximab group (42%), compared with 19% in the methotrexate-only group, whereas the proportion of patients with a positive skin test was lower in the rituximab group (48%), compared with 71% in the methotrexate-only population, he said.

An evaluation of B cells in the rituximab group at the time of vaccine administration showed that "peripheral B-cell depletion was as expected," Dr. Bingham said.

"At 24 weeks, when the tetanus toxoid was administered, 92% of the patients remained B cell depleted; at 28 weeks, when the pneumococcus vaccine was given, 89% were B cell depleted; and at 36 weeks, when the KLH was given, 76% of the patients were B cell depleted."

Regarding the study end points, there was no significant difference between the methotrexate-only patients and the rituximab patients in their responses to the tetanus vaccine at either the fourfold or twofold titer increase thresholds, Dr. Bingham stated.

"What was striking, actually, is that even in patients treated with methotrexate only, the tetanus responses were somewhat low, with only 39% of the rituximab-treated group and 42% of the methotrexate-only group demonstrating a fourfold titer rise."

Significantly fewer of the rituximab patients responded to at least one pneumococcal serotype of the PPV23 (57% vs. 82% of the methotrexate-only group) and to KLH (47% vs. 93%), said Dr. Bingham. "The mean titers were also lower in the rituximab-treated patients."

Although many patients in the rituximab group were able to mount an immune response to the vaccinations, "it did appear that neoantigen responses to KLH and T cell–independent responses to pneumococcal polysaccharide vaccination were decreased," according to Dr. Bingham.

The only significant predictor of vaccine response was IgG2 level at the time of immunization for tetanus, PPV23, and KLH vaccines, he said, noting that "age, methotrexate dose, concomitant corticosteroid use, diagnosis of diabetes mellitus, skin test anergy [less than 5-mm induration], IgM, IgA, total IgG, and IgG1, IgG3, and IgG4 subsets were not predictors of immunization response, nor did rituximab affect total IgG or IgG2 levels."

Dr. Bingham has served as a consultant to Genentech Inc. and to Roche. ■

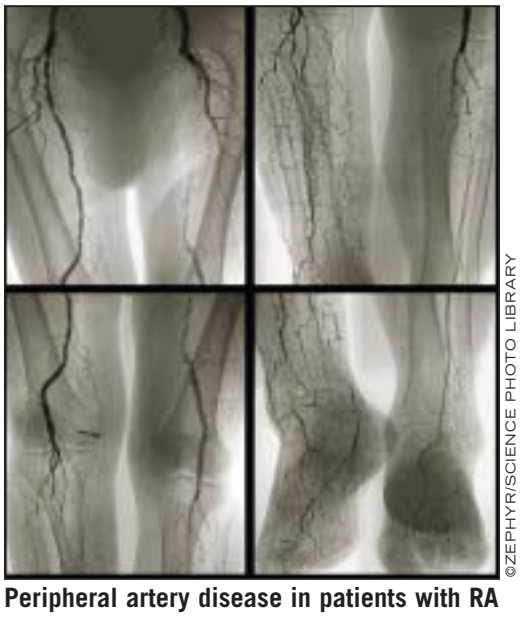
PAD Prevalent in Arthritis Patients

BY MITCHEL L. ZOLER

COPENHAGEN — Patients with rheumatoid arthritis have a substantially higher prevalence of peripheral artery disease than do similar people without RA, based on a case-control study with 101 subjects.

PAD "should not be overlooked in rheumatoid arthritis patients," Dr. Suzan Abou-Raya said at the annual meeting of the European Congress of Rheumatology. RA patients "should be regularly screened [for PAD] to help reduce their incidence of cardiovascular morbidity and mortality," said Dr. Abou-Raya, a researcher in the geriatric unit at the University of Alexandria (Egypt).

The study enrolled 64 consecutive RA patients (38 women and 26 men), with an average age of 55 years and an average RA duration of 12 years. The patients had no history of cardiovascular disease. Dr. Abou-Raya and her associates also enrolled 37 healthy controls without RA or cardiovascular disease who were matched with the cases by age, sex, body mass index, and their conventional cardiovascular-disease risk factors. All the cases and controls were nonsmokers. The average total cholesterol level was about 190 mg/dL. The researchers assessed PAD by the ankle brachial index (ABI). They measured arterial pressure with a Doppler ultrasound velocity detector at two ankle sites: posterior tibial and dorsalis pedis. An ABI ratio of 0.9 or less in an artery meant it was obstructed; a ratio of 1.0 to less than 1.3 was normal, and a ratio of 1.3 or greater meant an incompressible artery (a marker of significant calcification). Abnormal ABIs, either obstructed or incompressible, existed in 19 RA patients (30%) and in two controls (5%), a statistically significant difference. In a total of 256 arteries examined in the 64 RA patients, 10 (4%) were obstructed and 20 (8%) were incompressible. That's significantly higher than in 148 arteries examined in the 37 controls, with two obstructed (1%) and one incompressible (1%).



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Peripheral artery disease in patients with RA can be present even in people with no history of cardiovascular disease.

In a multivariate analysis, clinical characteristics of the RA patients that significantly correlated with an abnormal ABI were RA disease duration, serum level of C-reactive protein, and a worse score on the Health Assessment Questionnaire (HAQ).

Dr. Abou-Raya said that she and her associates had no financial disclosures. ■

Disease Markers Not Tied to Fatigue in RA

Conventional measures of disease activity, such as swollen joints, do not appear to be associated with fatigue in rheumatoid arthritis, according to a study that examined fatigue assessments from more than 16,000 rheumatoid arthritis patients in the U.S.

Reports of fatigue were closely associated with patient-measures of pain. But fatigue was weakly associated with clinical measures of inflammation such as sedimentation rate, joint swelling, joint tenderness, and physician-reported global assessment, Dr. Martin J. Bergman said at the annual European Congress of Rheumatology.

The results are not meant to downplay the impact of fatigue in RA patients, he said. Fatigue is a common and devastating complaint for many patients with RA, said Dr. Bergman, a Philadelphia-area rheumatologist.

In addition to examining levels of fatigue among RA patients, the researchers collected data on reported fatigue from about 3,500 patients with fibromyalgia and 4,600 patients with osteoarthritis. As with the patients with RA, these other patients were asked to rate their problems with "unusual fatigue" over the past week on a scale of 0-10.

The findings show that fatigue was common not only in fibromyalgia and rheumatoid arthritis but also in patients with osteoarthritis.

—Mary Ellen Schneider