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 John 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.

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 or tetanus vaccine within the previous 3-5 years, and those with other uncontrolled 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 said. 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.

At baseline, the patients in both groups were similarly matched except for baseline steroid use and positive skin test, Dr. Bingham noted. Baseline steroid use was 42% in the rituximab group and 19% in the methotrexate-only group, whereas the proportion of patients with a positive skin test was 48% in the rituximab group and 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 said. "What was striking, ac-

tually, 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."

An evaluation of the secondary end points showed that 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%), Dr. Bingham said. "The mean titers were also lower in the rituximab-treated patients," he said.

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," Dr. Bingham said. 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."

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The findings provide a rationale for administering polysaccharide and primary immunizations before rituximab infusions in RA patients, Dr. Bingham concluded. During the question-and-answer session, he agreed that in some patients in whom pretreatment immunization is not feasible, reimmunization may boost the level of immune response. "Even during the period of B-cell depletion, 57% of the rituximab group did respond to at least one serotype and 42% responded to at least two serotypes, so there is some efficacy," he said.

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