Immunization in Rituximab: Timing Matters

BY DIANA MAHONEY

The timing of influenza and pneumococcal vaccinations can substantially influence the degree of antibody response in rheumatoid arthritis patients taking rituximab, concluded investigators in two independent studies.

Rituximab, which acts by depleting B cells, also reduces patients' humoral and cellular immune responses, they said.

In one of the two studies reported in Arthritis & Rheumatism, Dr. Sander van Assen of the University Medical Center Groningen (the Netherlands) and colleagues investigated the efficacy of influenza vaccination in RA patients who are treated with rituximab. They also assessed the duration of the possible suppression of the humoral immune response following rituximab treatment, and observed a decreased humoral response following vaccination that was modestly restored 6-10 months after rituximab administration (Arthritis Rheum., 2010;62:75-81).

The study comprised two groups of RA patients—a rituximab group and a methotrexate group—and one group of 29 healthy controls. The rituximab group consisted of 23 patients, 22 of whom received two cycles of 1,000 mg of the biologic with 100 mg intravenous methylprednisolone, and 1 patient with mixed cryoglobulinemia who received four cycles of 375 mg/m^2 of rituximab. The rituximab group was further classified into an "early" subgroup consisting of 11 patients who received influenza vaccination 4-8 weeks after rituximab administration, and a "late" subgroup that included 12 patients who received the vaccination 6-10 months after rituximab. The methotrexate group included 20 patients who received a minimum of 10 mg methotrexate per week, eventually with additional disease-modifying antirheumatic drugs (DMARDs). Influenza vaccines were administered intramuscularly to all of the study participants between October 2007 and January 2008, the authors wrote.

Immediately before and a mean 28 days after vaccination, blood was drawn from all patients to measure CD19+ cell counts, C-reactive protein levels, erythrocyte sedimentation rates, and anti-influenza antibodies. Compared with baseline measures, geometric mean titres (GMTs) for all three influenza strains tested (A[H3N2], A[H1N1], and B) increased significantly in the healthy controls and the methotrexate group, but not in the rituximab group as a whole, the authors reported. In the late rituximab subgroup, a rise was noted in the GMTs for the A(H3N2) and A(H1N1) flu strains, "indicating some recovery of the humoral immune response 6-10 months after treatment with rituximab," they wrote.

With respect to CD19+ cell counts, the baseline measures for both the early and late rituximab subgroups were comparable. At 28 days after vaccination, however, significantly more B cells were present in the late vs. early group, according to the authors.

Seroconversion and seroprotection occurred less often in the rituximab group than in the methotrexate-treated group for both influenza A strains. Seroprotection occurred less often in the rituximab group than in the healthy controls for the A(H1N1) strains, the authors wrote. Of the three cases of seroconversion and six cases of seroprotection observed in the rituximab group, all but one of the seroprotection cases occurred in the late rituximab subgroup, they stated.

For the greatest immune response, polysaccharide and primary immunizations should be administered to patients prior to their receiving their rituximab infusions.

An examination of vaccination safety showed no differences among the three groups regarding the occurrence of side effects, the authors wrote. Also, disease activity in the methotrexate and rituximab groups, assessed with the DAS28 prior to and 7 and 28 days after vaccination, was not influenced by vaccination.

Because patients who were treated with rituximab appear to have a "severely hampered" humoral immune response to the trivalent subunit influenza vaccination, preemptive influenza vaccination should be considered prior to rituximab administration, the authors wrote, noting the importance of yearly influenza vaccination, given the increase in anti-influenza titers observed in previously vaccinated patients.

In the second study, a controlled trial by Dr. Clifton O. Bingham III of Johns Hopkins University, Baltimore, and colleagues, the investigators examined the immunization responses (humoral immunity and the cellular immune response) of rituximab-treated RA patients who received tetanus toxoid, 23-valent pneumococcal polysaccharide (PPV23), and keyhole limpet hemocyanin (KLH) vaccines, and they evaluated the effects of rituximab-induced CD20+ B-cell depletion on immune responses to these vaccinations (Arthritis Rheum. 2010;62:62-74).

The study enrolled 103 patients aged 18-65 years who had active RA and were receiving a stable dosage of 10-25 mg/wk of methotrexate from 26 U.S. centers between January 2006 and December 2007. Patients were stratified by site and age (18-50 years and 51-65 years) and then were randomized in a 2:1 manner to receive either two cycles of 1,000 mg rituximab (open label) 2 weeks apart plus a stable dose of methotrexate (68 patients), or methotrexate alone (32 patients). In the rituximab-plus-methotrexate group, 100 mg of methylprednisolone was administered intravenously before each rituximab infusion, the authors wrote.

Patients in both groups received the tetanus toxoid adsorbed vaccine, PPV23, KLH, and a *Candida albicans* skin test according to the protocol schedule. Antitetanus, antipneumonococcal, and anti-KLH serum IgG levels were measured prior to and 4 weeks following each respective vaccine administration, and the delayed-type hypersensitivity (DTH) skin test response was measured 2-3 days following placement, the authors wrote.

An analysis of the results showed that patients in both groups responded similarly to tetanus toxoid vaccine, with 25 patients in the rituximab group (39%) and 11 patients in the methotrexate-only group (42%) showing a more than fourfold risk in antitetanus IgG titer, and 35 rituximab patients and 16 methotrexate patients demonstrating a more than twofold rise, the authors reported. Similarly, they wrote, "the ability to maintain a positive DTH response to the *C. albicans* skin test was comparable in both groups," confirming that rituximab had no incremental effect on the patients' ability to mount a DTH response.

Significant differences were observed in the responses to PPV23 between the two groups, with only 57% of patients in the rituximab group demonstrating a twofold rise in titer in response to one or more serotypes, compared with 82% of the methotrexate-only patients, the authors reported. Similarly, only 47% of the rituximab patients had detectable anti-KLH IgG, compared with 93% of the methotrexate-only group, they noted.

"Because neoantigen and polysaccharide responses are B-cell dependent, decreased responses to KLH and [PPV23] are consistent with rituximab's mechanism of action," the authors observed. "Despite peripheral B-cell depletion, however, responses to the KLH and [PPV23] vaccine were not completely abrogated in the present study," they wrote, referring to the 47% of rituximab patients who had a quantifiable anti-KLH response and the 57% and 43% of rituximab patients who mounted responses to at least one and two pneumococcal serotypes, respectively. The authors concluded that for maximized vaccination response, "polysaccharide and primary immunizations should be administered prior to rituximab infusions."

Although both of these studies provide some insight into the effects of rituximab therapy on immune function, "they fall short in offering clues about the causal mechanisms," Dr. E. William St. Claire of Duke University Medical Center in Durham, N.C., wrote in an editorial (Arthritis Rheum. 2010;62:1-5). ■

Disclosures: *The study reported by Dr. van Assen and colleagues was supported by Roche Nederland and Solvay Pharmaceuticals. The authors reported no additional conflicts of interest. The study reported by Dr. Bingham and colleagues was supported by Genentech Inc. The authors reported having financial relationships with Genentech, Roche, and Merck & Co. One of the authors served on Merck's data and safety monitoring board, and three of the authors own stock or stock options in Genentech. Dr. St. Clair disclosed having financial relationships with Biogen Idec Inc.*

OMERACT to Consider 'Absence of Disease' as Outcome

NEW YORK — Building on the work in developing a clinical definition of remission in rheumatoid arthritis, a group of clinicians and researchers is interested in creating a complementary patient term called "absence of disease."

Rheumatologists from around the world will begin discussing how to develop this patient-centered definition in Malaysian Borneo in May at the next meeting of OMERACT (Outcome Measures in Rheumatology), an international network aimed at improving outcomes assessment in rheumatology.

It's important to ask patients for their view of what "absence of disease" means, because they see "remission" so differently from the way physicians do, Dr. Maarten Boers, a member of the OMERACT executive committee, said at a rheumatology course sponsored by New York University. The current remission term is a classic physician-centric definition that is largely based on inflammation, he said.

"If you talk to patients, they talk about totally different things than we talk about in terms of disease," Dr. Boers, a professor at VU University Medical Center in Amsterdam, said in an interview.

Although patients were involved in developing the remission definition by OMERACT, that dimension wasn't fully studied. This time around, the organization plans to spend about 2 years performing qualitative work. They won't have to start from scratch, though, Dr. Boers said, because there has already been qualitative work done on a related issue: the impact of disease, which could be interpreted as the opposite of the "absence of disease" concept.

—Mary Ellen Schneider

Disclosures: *Dr. Boers said he had no relevant financial disclosures to make.*