Lupus Features Vary Dramatically by ANA Status

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AMSTERDAM — New pieces of the clinical, serologic, and therapeutic puzzle of systemic lupus erythematosus have emerged in a post hoc analysis of a study evaluating belimumab, an investigational agent that targets B cells.

Review of data from a large, phase II study found that patients who are antinuclear antibody (ANA) positive exhibit different clinical and serologic features than do patients who are ANA negative, according to Dr. Michelle Petri, who presented her observations in a poster session at the annual European Congress of Rheumatology.

Those who were ANA positive were more likely to have a history of renal or hematologic involvement, exhibited higher disease activity, and required more prednisone, she reported. For example, the analysis determined that at baseline, 34% and 59% of seropositive patients had renal and hematologic involvement, respectively, compared with 19% and 33% of seronegative patients.

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DR. PETRI

Seropositive patients also had significantly higher levels of IgG, IgA, and IgE, and B-lymphocyte stimulator (BLyS), which is a potent costimulator of B cells. Elevated levels of BLyS, seen in 51% of the seropositive patients and in 24% of the seronegative patients, are thought to play a role in B-cell–mediated autoimmunity, according to Dr. Petri, professor of rheumatology, Johns Hopkins University, Baltimore.

ANA-positive patients also had lower levels of CD20-positive B cells, as well as lower levels of naive, activated, and memory B cells. This suggests that SLE disease activity may relate to B-cell dysfunction and that B-cell–directed therapy "would be appropriate" in serologically active, ANA positive patients, Dr. Petri commented. This connection needs to be proved in a subsequent trial, "but it makes sense in terms of what we know about lupus," she added.

These observations were derived from a trial that compared intravenous belimumab (LymphoStat, Human Genome Sciences, Rockville, Md.), 1, 4, or 10 mg/kg with placebo plus standard of care treatment in 449 patients. The drug was given on days 0, 14, 28, and then monthly for 52 weeks at 59 sites in North America.

Investigator-determined standard of care treatment included the use of nonsteroidal anti-inflammatory drugs, antimalarials, corticosteroids, and immunosuppressants.

The primary end points of the trial were percent change in SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment Trial-Systemic Lupus Erythematosus Disease Activity Index) at week 24 and time to first flare over 52 weeks.

These end points were not met, according to Dr. Dan Wallace, who presented the data at the meeting, which was sponsored by the European League Against Rheumatism. The reason for the failure to reach statistical significance was the inclusion of ANA-negative patients in the trial, Dr. Wallace said in an interview. "A lot of those patients probably did not have lupus." For inclusion in the study, patients had to have been ANA positive at some time in the course of their disease, but at the time of screening only 72% were serologically active, with an ANA titer of 1:80 or higher and/or an antidouble-stranded DNA level of 30 IU or greater, said Dr. Wallace of the David Geffen School of Medicine, University of California, Los Angeles.

"If you analyze only those who are ANA or anti-DNA positive the end points were met and the drug was quite effective." Serologic findings seen in the study included significant reductions in various types of B cells, including a median 54% reduction in CD20-positive cells, a 62% reduction in plasmacytoid cells, and a 70% reduction in activated B cells, Dr. Wallace reported.

Serologically active patients also showed stabilization of disease on individual organ domains as measured by the British Isles Lupus Assessment Group (BILAG) scores, according to Dr. Richard Furie of North Shore–Long Island Jewish Health System, Manhasset, N.Y. ■