Combined End Point Shows Belimumab's Strength

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BARCELONA — Significant improvements in disease activity were observed among lupus patients treated with belimumab in a new analysis of data from an earlier study using a combined response end point, Dr. Ellen Ginzler said at the annual European Congress of Rheumatology.

The analysis used an evidence-based combined response end point that has been developed to improve the assessment of responses to drug intervention in clinical trials for systemic lupus erythematosus. "The heterogeneity of lupus disease manifestations contributes to the difficulty of using a single index to adequately assess therapeutic response," Dr. Ginzler explained.

Belimumab (LymphoStat-B) is a monoclonal antibody that binds with high specificity to B lymphocyte stimulator (BLyS),

A single index cannot adequately assess treatment response in this heterogeneous disease.

DR. GINZLER

which, being a potent costimulator of B cells, is thought to play a role in B-cell–mediated autoimmunity.

In the original analysis of the study results, the primary end point—reduction in disease activity as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) as modified for the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) at 24 weeks—was not met.

The study included 449 patients with lupus who were randomized to receive placebo or belimumab in doses of 1, 4, or 10 mg/kg on days 0, 14, 28, and then monthly for 52 weeks. The study continued in open-label fashion through week 76.

A subsequent analysis, however, determined that significant benefits were seen at 52 weeks among the 72% of patients who were serologically active at baseline, with titers of antinuclear antibody of 1:80 or greater and/or titers of anti-double-stranded (ds) DNA of 30 IU or greater (Arthritis Rheum. 2006;54[9]:S258).

Responses among this cohort have now been analyzed according to the new combined response end point, which defines efficacy as an improvement in SELENA-SLEDAI of four points or more and a British Isles Lupus Assessment Group (BILAG) score that reflects the number and severity of organ system flares.

The combined end point also reflects physician's global assessment and patient health-related quality of life as evaluated on the Short Form (SF)-36.

"Using this combined outcome efficacy measure, the response to belimumab therapy among patients who were serologically active at baseline was 46%, which is highly statistically significant at 52 weeks compared to a response rate of 29% with placebo," said Dr. Ginzler, who is professor of medicine and chief of rheumatology, State University of New York, Brooklyn.

By week 76 the response rate had risen to 56%.

At baseline, the mean SELANA-SLEDAI score was 9.6. Patients in the active treatment groups had 29% and 38% reductions in SELENA-SLEDAI scores at weeks 52 and 76, respectively.

At week 52 the belimumab-treated patients had fewer shifts to worse scores in three of the eight BILAG organ systems: musculoskeletal, neurologic, and cardiovascular-respiratory.

Patients who were classified as responders on the composite end point also had greater reductions in activated B cells and anti-ds DNA antibodies, along with greater improvements in the SF-36.

Combining multiple disease activity measures into a response end point improved the assessment of variable disease activity and was predictive of biomarker and quality of life improvements, Dr. Ginzler said.

"This combined end point has now been accepted by regulatory authorities and is being used in two global phase III studies of belimumab that have recently begun enrollment," she said.

The studies are being sponsored by Human Genome Sciences, Inc., the manufacturer of LymphoStat-B, and GlaxoSmithKline.

Dr. Ginzler has previously disclosed receiving research grants from Human Genome Sciences. ■