Belimumab Benefits Seen in Lupus, Analysis Shows

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

DR. GINZLER

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[suppl. 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., manufacturer of LymphoStat-B, and GlaxoSmithKline. Dr. Ginzler has previously disclosed receiving research grants from Human Genome Sciences. ■

Persistent Proteinuria in SLE Predicts Renal Relapse

BARCELONA — Factors that were predictive of relapse in lupus nephritis after induction therapy were persistence of proteinuria and abnormal C4 levels, and patients having received cyclophosphamide for less than 2 years, Dr. Eva Salgado reported at the annual European Congress of Rheumatology.

Considerable variability is seen in the clinical course and response to therapy in patients with systemic lupus erythematosus (SLE) who develop nephritis, and it would be useful to identify factors that are associated with relapse so that more aggressive treatment could be used from the outset, explained Dr. Salgado of Hospital 12 de Octubre, Madrid.

A study was therefore conducted that included all 128 patients diagnosed with SLE and nephritis in the rheumatology department of Dr. Salgado's hospital between 1977 and 2007.

A total of 114 of the patients were women, and more than 95% were white. Mean age at the appearance of nephritis was 30 years, and mean time from the diagnosis of SLE was 2 years.

Renal biopsy at the time of diagnosis of nephritis showed minimal changes in 2%, mesangial glomerulonephritis in 18%, focal proliferative glomerulonephritis in 12%, diffuse proliferative glomerulonephritis in 55%, and membranous glomerulonephritis in 13%.

At the time of initiation of induction therapy, 29 patients had some degree of creatinine increase, Dr. Salgado reported in a poster presentation.

Induction therapies included corticosteroids alone in 23% of patients, corticosteroids plus cyclophosphamide in 65%, azathioprine in 10%, and mycophenolate mofetil in 2%. Mean duration of induction therapy was 27 months.

A total of 71% of patients showed a complete response to induction therapy, while 24% had a partial response and 5% did not respond.

After the initial response, 59% received maintenance therapy with antimalarial drugs, azathioprine, or both.

During a mean of 13 years of follow-up, 34 patients experienced renal relapse, at a mean of 51 months after the end of induction therapy.

Multivariate analysis found that relapse was independently associated with persistence of abnormal C4 levels or residual proteinuria greater than 0.5 g/day after the completion of induction therapy, and duration of cyclophosphamide therapy for less than 2 years, according to Dr. Salgado.

Factors that were not predictive of relapse included histologic findings, age at SLE or nephritis diagnosis, delay in induction therapy, use of maintenance therapy, or other clinical characteristics.

Six patients developed end-stage renal failure and 14 died. Relapse was predictive of long-term renal failure but was not associated with increased mortality in this group of patients, Dr. Salgado observed. ■

B-Cell Depletion With Rituximab Appears Promising for Myopathies

BARCELONA — Clinical improvement in a small series of patients with inflammatory myopathies treated with rituximab suggests that B-cell depletion may prove useful in these disorders, according to Dr. Marlies Blom of the department of rheumatology, Radboud University Nijmegen (the Netherlands) Medical Centre.

Among seven patients with dermatomyositis, polymyositis, or antisynthetase syndrome, two infusions of 1,000 mg rituximab 2 weeks apart resulted in a mean 30% increase in muscle strength at 3 months, Dr. Blom reported in a poster session at the annual European Congress of Rheumatology.

Among seven patients, two infusions of 1,000 mg rituximab 2 weeks apart resulted in a mean 30% increase in muscle strength.

Patients' subjective reports of improvement in muscle strength were confirmed by handheld dynamometry.

The patients ranged in age from 38 to 58 years, and the duration of their disease ranged from 3 to 16 years. Four of the seven were female.

Previous treatments included oral and intravenous prednisone, methotrexate, azathioprine, cyclophosphamide, interferon, etanercept, and intravenous immunoglobulin.

A mean 13% improvement was reported on Health Assessment Questionnaire (HAQ) scores, and improvements also were seen in levels of creatine phosphokinase, a marker of disease activity.

In one patient, a muscle biopsy taken 4 months after treatment showed a total absence of CD20+ B cells. This patient's Disease Activity Score–28 (DAS28) score fell from 6.8 to 4.5 after 3 months, according to Dr. Blom.

After initial good response, three patients required retreatment for exacerbations of myositis at about 6 months.

No serious adverse events were observed and immunoglobulin levels remained within normal levels.

These results suggest that B cells play an important role in the pathogenesis of inflammatory myopathies, Dr. Blom noted.

Another recent report suggested that a possible rationale for considering B-cell depletion as a therapeutic strategy in dermatomyositis was that treatment with rituximab had previously been shown to result in improvements in muscle strength in humorally mediated autoimmune peripheral neuropathies (Arthritis Rheum. 2005;52:601-7).

The importance of humoral immunity in dermatomyositis also is suggested by the observation that perifascicular endothelial immunoglobulin and complement deposition are thought to result in the muscle ischemia and atrophy (J. Rheumatol. 2006;33:1021-6).

Furthermore, the observation that there are antibodies specific for myositis also supports the concept of B-cell–mediated humoral abnormality in dermatomyositis (Medicine [Baltimore] 1991;70:360-74). ■

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