Focus on Nonsteroidal Options

SLE *from page 1*

patients in the phase II study who were not seropositive for antinuclear antibodies or anti–double-stranded DNA antibodies; it extended the response time to 52 weeks, and it utilized a new composite end point, called the SLE Responder Index, to measure an individual patient's improvement from baseline, Dr. Wallace explained.

The primary efficacy end point was changed from the SELENA (Safety of Estrogens in Lupus Erythematosus–National Assessment) modification of the SLE disease activity index (SELENA-SLEDAI) to the SLE Responder Index at week 52, which is based on a reduction from baseline of at least 4 points on the SELENA-SLEDAI disease activity scale; no new severe (grade A) lupus flares according to the BILAG (British Isles Lupus Assessment Group) scale and not more than one moderate (grade B) disease activity flare; or no worsening on the physician's global assessment (Arthritis Rheum. 2009;61:1143-51). "The new index looks at whether the patient feels better, whether the doctor thinks the patient feels better, and whether there are any new disease manifestations," said Dr. Wallace. Given the heterogeneous nature of lupus and the longstanding difficulty of assessing disease activity in clinical trials, the responder index "represents a breakthrough for finally utilizing a methodology that enables researchers to demonstrate disease improvement," he said.

And although the success of the SLE Responder Index is limited to just one data set, "the fact that it worked prospectively and not just post hoc should be encouraging to drug developers," said Dr. Furie. "Perhaps it will become the standard or at least serve as the foundation for further refinements."

On the heels of the belimumab announcement was the news that another experimental lupus drug, epratuzumab, performed well in a phase IIB clinical trial. In a 12-week, dose- and regimen-ranging, placebo-controlled study comprising 227 patients with moderately to severely active lupus, epratuzumab (a humanized anti-CD22 monoclonal antibody) demonstrated a "clinically meaningful" effect over placebo, according to a press release issued by Belgium's UCB SA, which bought rights to epratuzumab from Immunomedics Inc. Specifically, at week 12, the treatment effect of epratuzumab was nearly 25%, compared with placebo, the report noted.

If one or both of these new drugs ultimately receive Food and Drug Administration approval for the treatment of lupus, they most likely will be used initially in patients who have chronically active disease despite treatment with steroids or other immunosuppressive therapies, according to Dr. Wallace. "Belimumab in particular does not work fast. It is not a replacement for corticosteroids in the treatment of acute disease."

The new SLE Responder Index 'represents a breakthrough for finally utilizing a methodology that enables researchers to demonstrate disease improvement.'

If approved, belimumab will be a major advance for those with moderate or inadequately controlled disease activity who require prednisone, because it may enable lower corticosteroid doses, according to Dr. Michelle Petri, professor of rheumatology at Johns Hopkins University, Baltimore.

"The reality is prednisone is not going away. Approximately, 80% of our lupus patients are on it—and for good reason, as it remains the most effective immunosuppressive therapy we have for the disease, and it works fast. The problem is that nearly 80% of organ damage in lupus is directly or indirectly due to steroids," Dr. Petri said at the annual meeting of the European Congress of Rheumatology this year in Copenhagen.

The risk for prednisone-associated organ damage increases by an order of magnitude as the cumulative dose increases, said Dr. Petri, referring to a recent study in which she and Mae Thamer, Ph.D., from the Medical Technology and Practice Patterns Institute in Bethesda, Md., evaluated the effect of corticosteroid use in 525 patients with incident SLE who were enrolled in the Hopkins Lupus Cohort. Using a marginal structural model to adjust for time-dependent confounding associated with disease activity, the investigators determined that patients who received cumulative doses of prednisone in the lowest range (0-180 mg/month) had only a small increased risk of irreversible organ damage, compared with nonprednisone use (hazard ratio, 1.16), whereas the risk among those receiving cumulative doses in the highest range (more than 540 mg/month) was more than doubled (HR, 2.51). The hazard ratios for the middle-range doses (180-360 mg/month and 360-540 mg/month) were 1.50 and 1.64, respectively (J. Rheumatol. 2009;36:560-4).

The study findings answer an important question in the management of lupus, she said: "When should immunosuppressive treatment be added in order to minimize prednisone use and reduce the risk of organ damage?

"When you look at the models, it's pretty clear that when the prednisone gets above 11 mg daily, there is a huge increase in the hazard ratio for organ damage," said Dr. Petri. "That is when to start to think about adding other therapies, if you haven't already, to achieve better control of disease activity and to limit the prednisone dose." It is at this point, she noted, that the expansion of treatment options is needed.

With respect to other steroid-sparing options, however, the "ideal" immunomodulatory therapy in lupus continues to be the antimalarial hydroxychloroquine (Plaquenil) Dr. Petri said. Hydroxychloroquine "has been shown to prevent severe flares in lupus. It also reduces the risk of lupus nephritis, organ damage, cardiovascular risk factors, and thrombosis, and it improves survival." In reality, she added, "if we could just convince our patients to stay on Plaquenil, I don't think we would need as much immunosuppressive therapy."

In fact, hydroxychloroquine is undergoing a rebirth of sorts, according to Dr. Furie. "Many people believe that all SLE patients should be on this drug. It's effective and fairly benign, and we are learning that it has pleiotropic effects," he said, including protection against thrombotic events and a beneficial effect on lipid profiles, which could potentially help reduce SLE patients' high risk of cardiovascular disease.

The recent finding by Spanish investigators that antimalarial drugs are more effective in SLE patients with polymorphisms on the tumor necrosis factor–alpha (TNF-alpha) and interleukin-10 (IL-10) genes associated with unusually high TNF-alpha levels and unusually low IL-10 levels may eventually allow the identification of lupus patients who are the most likely to benefit from antimalarial therapy (J. Rheumatol. 2008;35:1559-66).

Finally, the lupus research community is encouraged by the development of new recommendations for monitoring SLE in clinical practice, which were introduced at the annual European Congress of Rheumatology this year by Dr. Marta Mosca of the University of Pisa (Italy), the lead author of the recommendation paper, which is slated for publication in the Annals of the Rheumatic Diseases later this year. The guidelines are intended to provide a "road map" for clinicians in terms of assessing disease activity, kidney and other organ involvement, comorbidities, and the various cardiovascular, ophthalmologic, neuropsychiatric, and other risks associated with SLE and its treatment.

"The guidelines will be an important tool for helping rheumatologists make clinical management decisions," said Dr. Mosca. "As new therapies are developed, the guidelines will help ensure the quality control of patient care and will allow us to better standardize the collection and comparison of data in observational studies." ■

Provisional Criteria Define Very Early Systemic Sclerosis

BY DIANA MAHONEY

New provisional criteria for the diagnosis of very early systemic sclerosis aim to close the "unacceptably wide" gap between the onset of early signs of the autoimmune connective-tissue disease and the time of disease diagnosis, according to Dr. Marco Matucci-Cerinic.

The current diagnostic standard is based on the signs and symptoms of overt disease "and does not adequately address the earliest disease predictors," said Dr. Matucci-Cerinic, professor of rheumatology and medicine at the University of Florence (Italy). In addition to helping rheumatologists in practice, the proposed criteria could also be valuable to the EULAR/ACR systemic sclerosis reclassification project, they stated (Ann. Rheum. Dis. 2009;68:1377-80).

"Systemic sclerosis has the highest case-specific mortality of any of the connective tissue diseases, which is likely due to the fact that the disease is often well established by the time it is diagnosed," Dr. Matucci-Cerinic said at the annual European Congress of Rheumatology in Copenhagen in June.

In an effort to bridge the gap, Dr. Matucci-Cerinic and colleagues in the VEDOSS (Very Early Diagnosis of Systemic Sclerosis) project of the EULAR Scleroderma Trials and Research (EUSTAR) group have developed evidence-based criteria for the diagnosis of very early disease.

The proposed definition requires three major criteria (including Raynaud's phenomenon, disease-specific antibodies, and pathognomonic microvascular alterations detected by nailfold videocapillaroscopy), or two major criteria and one additional criterion (including calcinosis, puffy fingers, digital ulcers, dysfunction of the esophageal sphincter, telangiectasia, and ground glass appearance on high-resolution chest CT), Dr. Matucci-Cerinic said.

Based on the criteria, patients with Raynaud's phenomena and hand edema ("puffy fingers"), which commonly present together in early disease, should be referred for capillaroscopy as well as serology to detect antinuclear, anticentromere, antitopoisomerase I, and extractable nuclear antigen antibodies.

An important component of the VEDOSS project is the European Union–wide call for primary care clinicians to refer all patients who exhibit two or more of the early symptoms to a rheumatologist or scleroderma center, he said.

To date, several drugs—including ACE inhibitors, calcium channel blockers, cyclophosphamide, methotrexate, and endothelin receptor antagonists—have improved the outcomes of patients with established disease, according to EULAR/EUSTAR systemic sclerosis treatment recommendations issued earlier this year (Ann. Rheum. Dis. 2009;68:620-8). The possibility that earlier, more aggressive treatment with these or other agents that are being evaluated in clinical trials might alter the progression of disease and potentially prevent irreversible organ damage warrants investigation, said Dr. Alan Tyndall of the University of Basel (Switzerland). ■