Promising Treatments, Markers Target Lupus

BY DIANA MAHONEY

A number of groundbreaking developments in systemic lupus erythematosus have injected a much-needed boost into the lupus community, which has been repeatedly disappointed by setbacks and failures in clinical trials of "promising" new agents.

Clinicians are optimistic about two positive late-stage clinical trials, the validation of an evidence-based responder index to measure disease activity, the discovery of genetic markers that may help predict the clinical outcome of patients who are treated with existing therapies, and the introduction of new guidelines to facilitate and better control clinical trials, according to Dr. Richard Furie, chief of rheumatology and allergy–clinical immunology at North Shore–Long Island Jewish Health System in New York.

In fact, the announcement in July that the monoclonal antibody belimumab showed effectiveness against lupus in the first of two phase III clinical trials—the first drug to ever do so, according to a statement from Human Genome Sciences, which codeveloped the biologic with Glaxo SmithKline—was in some ways a surprise. The drug, which inhibits the biological activity of B-lymphocyte stimulator (BLyS), had nearly been counted out after it failed to meet its primary efficacy end point in a phase II clinical trial, except in a subgroup of patients who experienced a statistically significant improvement in lupus signs and symptoms, according to Dr. Daniel J. Wallace of the University of California, Los Angeles.

Based on extensive post hoc analysis of the phase II data, investigators identified factors that could have contributed to the negative trial and redesigned the study accordingly. The revised trial excluded the 28% of 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 SLE Responder Index 'represents a breakthrough' in detecting disease improvement.

DR. WALLACE

"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," Dr. Wallace said. 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," Dr. Furie said. "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 of 227 patients with moderately to severely active lupus, epratuzumab (a humanized anti-CD22 monoclonal antibody) showed a "clinically meaningful" effect over placebo, according to a statement by Belgium's UCB SA, which bought rights to epratuzumab from Immunomedics. 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,

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according to Dr. Wallace. "Belimumab in particular does not work fast. It is not a replacement for corticosteroids in the treatment of acute disease."

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, said 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; 36:560-64).

"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," Dr. Petri said. "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," Dr. Mosca said. "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." ■