Index Measures Partial Improvement in SLE

BY KATE JOHNSON

MONTREAL — A proposed new tool that is sensitive enough to measure partial improvement in systemic lupus erythematosus could open the door to more precise monitoring of therapeutic response in both research and clinical practice, reported Dr. Zahi Touma at the annual meeting of the Canadian Rheumatology Association.

Currently, improvement in disease activity, or response to treatment, can be measured only as absent or present, using the SLEDAI-2K (Systemic Lupus Erythematosus Activity Index–2K), explained Dr. Touma, a clinical research fellow in rheumatology at the center for prognosis studies in the rheumatic diseases at the University of Toronto. However, this index is not designed to detect small but clinically meaningful improvements, he noted.

So his group developed a modified version, the SRI-50 (SLEDAI-2K Responder Index–50), which has been designed to capture at least a 50% response on the SLEDAI-2K. "We aimed to show a 50% improvement, because this was felt by clinicians to reflect a significant improvement," he said in an interview.

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Major Finding: The SRI-50 tool signaled 50% improvement in 13 of the 24 SLEDAI-2K descriptors and in six of the nine assessed organ systems, findings that were undetected by the less-sensitive SLEDAI-2K.

Data Source: Results of SRI-50 in 100 patients.

Disclosures: Dr. Touma said he had no relevant financial conflicts to disclose.

The SRI-50 covers the same nine organ systems and uses the same 24 descriptors as does the SLEDAI-2K, said Dr. Touma. Scoring for each descriptor of SLEDAI-2K is halved to generate a new weighted score for each descriptor of the SRI-50.

For example, in a case of lupus nephritis that involves proteinuria at a level of serum protein in urine of 4 g/day, the SLEDAI-2K score would be 4.

At follow-up, a decrease in proteinuria to 2 g/day would generate the same SLEDAI-2K score of 4 (which is generated by any proteinuria above 0.5 g/day), but on the SRI-50, it would represent a 50% improvement and thus a score of 2.

To test the new measure, Dr. Touma's group performed a cross-sectional study of 100 patients who had experienced lupus flares or had persistently active disease.

The SLEDAI-2K was administered at the initial visit and then again after 1-3 months of treatment with prednisone and an immunosuppressant (hydroxychloroquine, azathioprine, methotrexate, or mycophenolate mofetil). The SRI-50 was also administered at the second visit.

Scores were calculated using a data retrieval form, with a range of scores from 1 (best) to 10 (worst) for each of the 24 descriptors. "It's very important to have a data retrieval form because if you are dealing with rash or arthritis you need a very accurate, standardized method of documentation," he said.

For 72 patients, the SLEDAI-2K provided a satisfactory assessment at the second visit because their disease had either resolved completely or remained unchanged. However, for the remaining 28 patients, the SRI-50 signaled partial improvement that was undetected by the less-sensitive SLEDAI-2K. Among these patients, a 50% improvement was detected in 13 of the 24 descriptors and in six of the nine organ systems, said Dr. Touma.

Among these 28 patients, 90% were female, 53% were white, 16% were black, 10% were Chinese, and 21% were "other." Their mean age at diagnosis was 32 years, and their mean duration of disease at first study visit was 13 years. Varying levels of disease activity were recorded at the first visit.

Three subjects had a SLEDAI-2K score of 2; three had a score of 4; six had a score of 6; six had a score of 8; three had a score of 10; two had a score of 12; one had a score of 16; one had a score of 18; two had a score of 20; and one had a score of 21.

Dr. Touma said the goal of the study was primarily to develop a more sensitive tool to measure outcomes in clinical trials. However, he believes the SRI-50 will also play an important role in clinical practice, where "it is always crucial to be able to show that a patient is responding to medical treatment." ■

Delaying Ambrisentan Cuts Long-Term Lung Capacity

BY BRUCE JANCIN

SAN DIEGO — In patients with pulmonary arterial hypertension, a short delay in starting endothelin receptor antagonist therapy with ambrisentan proved to have long-lasting deleterious consequences in the ARIES-E trial.

One hundred ARIES-E participants who received ambrisentan (Letairis) after completing 12 weeks of double-blind placebo responded with a less robust improvement in exercise capacity during 2 years of follow-up than did 197 patients who were on ambrisentan from the start. The group on placebo before ambrisentan never caught up in terms of 6-minute walk distance, Dr. Aaron B. Waxman reported at the annual meeting of the American College of Chest Physicians.

At the 12-week mark in the double-blind ARIES-1 (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study) and ARIES-2 trials, patients on ambrisentan from the outset had a mean 42-m gain in 6-minute walk distance over their baseline of 345 m. Patients who received placebo before ambrisentan averaged a 1-m decline from baseline.

After 2 years of follow-up in ARIES-E (the extension study), patients who had been on ambrisentan from the start had a mean 30-m improvement in 6-minute walk distance compared with baseline. Patients on placebo for 12 weeks before receiving ambrisentan had a mean 10-m improvement, according to Dr. Waxman of Massachusetts General Hospital, Boston.

The rate of clinical worsening at 1 year was 16% in the group on ambrisentan from the outset, compared with 24% in those who got placebo first. By 2 years, however, the clinical worsening rate was similar in both groups, at about 30%. The 2-year survival rate was 88% in the all-ambrisentan group and 86% in patients who got placebo followed by ambrisentan.

Ambrisentan was well tolerated in ARIES-E, with mild to moderate peripheral edema the most common adverse event. Liver enzymes were elevated during 2 years of follow-up in seven patients on ambrisentan from the start and six patients on placebo followed by the endothelin receptor antagonist. ■

Disclosures: *The ARIES trials were funded by Gilead Sciences Inc., which manufactures Letairis. Dr. Waxman disclosed serving on advisory boards for Gilead and United Therapeutics Corp.*

Oral Imatinib Shows Promise for Pulmonary Arterial Hypertension

BY BRUCE JANCIN

SAN DIEGO — Imatinib may have a future as a treatment for pulmonary arterial hypertension.

The oral tyrosine kinase inhibitor significantly improved exercise capacity in a phase II study, as reflected in increased 6-minute walk distance in a patient subgroup with a baseline pulmonary vascular resistance (PVR) of at least 1,000 dyne*sec/cm^5.

Additional benefits seen with imatinib (Gleevec)—again restricted to patients having PVR elevated above the 1,000-dyne threshold—included significantly increased cardiac output, reduced mean pulmonary arterial pressure, and decreased PVR, Dr. Robyn Barst reported at the annual meeting of the American College of Chest Physicians.

Those findings in a post hoc analysis of the phase II data provided the impetus for the ongoing phase III IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized Efficacy Study).

IMPRES is a 24-week, double-blind clinical trial evaluating the safety and efficacy of the tyrosine kinase inhibitor as add-on therapy in 200 patients with pulmonary arterial hypertension (PAH) who are in functional class II-IV and remain symptomatic on two or more PAH therapies. Participants, all of whom had a baseline PVR of at least 1,000 dyne*sec/cm^5, are randomized to oral imatinib at 400 mg once daily or placebo, explained Dr. Barst, professor of pediatrics at Columbia University in New York.

The phase II study involved 59 patients with PAH. Overall, the primary end point of that study (the mean change in 6-minute walk distance during 24 weeks) was not significantly different between the imatinib and placebo groups.

However, roughly half of the subjects in the phase II study had a baseline PVR of 1,000 dyne*sec/cm^5 or more. In that subgroup, imatinib was associated with a mean 64-m increase in 6-minute walk distance from a baseline of 352 m, whereas the placebo group experienced a mean 32-m decrease over the 24 weeks, a highly significant between-group difference.

In addition, mean pulmonary arterial pressure improved by a mean 8.4 mm Hg in the imatinib group, which was significantly better than the mean 2.8–mm Hg reduction with placebo. Cardiac output increased by a mean 1.3 L/min from a baseline value of 3.0 L/min with imatinib, compared with a 0.2-L/min gain with placebo. PVR dropped by a mean 576 dyne*sec/cm^5 from a baseline value of 1,431 dyne*sec/cm^5 with imatinib, compared with a mean 122-dyne*sec/cm^5 reduction in the control group.

Imatinib is approved for the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors, and several other malignancies. The rationale for developing the drug as a possible treatment for PAH lies in imatinib's ability to inhibit platelet-derived growth factor receptor alpha and beta kinases. Platelet-derived growth factor and its receptor have been implicated in the pathogenesis of PAH, a progressive disorder with a poor prognosis for which no cure exists, she noted. ■

Disclosures: *Both the phase II study and IMPRES were funded by Novartis. Dr. Barst disclosed serving as a consultant to Novartis and several other pharmaceutical companies.*