Scleroderma Recommendations Cover All Bases

The guidelines are considered a 'good first step' in providing evidence-based management advice.

BY NANCY WALSH
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BARCELONA — The first evidence-based recommendations issued by the European League Against Rheumatism for the management of systemic sclerosis address the current and future challenges in the treatment of this clinically heterogeneous condition.

The preliminary recommendations, which are based on research evidence, expert opinion, and clinical experience, have been formulated by a EULAR task force that included experts in systemic sclerosis from Europe, the United States, and Japan, according to Dr. Marco Matucci-Cerinic, professor of rheumatology and medicine at the University of Florence (Italy).

The recommendations include treatment considerations for digital vasculopathy and disease manifestations in the lung, skin, kidney, and gastrointestinal tract. They were summarized by Dr. Matucci-Cerinic at the annual European Congress of Rheumatology as follows:

► **Vasculopathy.** Among the first-line therapies recommended for reducing the frequency and severity of attacks of scleroderma-associated Raynaud's phenomenon are calcium channel blockers. Significant clinical benefits for these drugs were demonstrated in a meta-analysis that included six small trials (Arthritis Rheum. 2001;44:1841-7).

Prostacyclins, particularly iloprost, also are recommended for vasculopathy. Two randomized clinical trials have demonstrated benefits for these agents in the treatment of Raynaud's phenomenon and for healing digital ulcers.

A third recommendation for scleroderma-associated vasculopathy involves the use of endothelin receptor antagonists such as bosentan. Two large studies found that bosentan can prevent the development of new digital ulcers and improve hand function, although it did not affect healing of ulcers.

► **Pulmonary arterial hypertension.** Bosentan and another endothelin receptor antagonist, sitaxsentan, are strongly recommended for the treatment of pulmonary arterial hypertension, Dr. Matucci-Cerinic said. Also recommended is the phosphodiesterase inhibitor sildenafil, which improved exercise capacity and functional class in a high-quality clinical trial, he said. Epoprostenol is another agent that can be considered a feasible treatment for severe pulmonary arterial hypertension in systemic sclerosis.

► **Interstitial lung disease.** Two randomized controlled trials published in recent years form the basis of a recommendation favoring the use of cyclophosphamide in patients with scleroderma-associated interstitial lung disease despite the potential toxicity of this treatment.

► **Renal crisis.** "We all know that ACE inhibitors are helpful in renal crisis, but there are no randomized controlled trials," Dr. Matucci-Cerinic said. Despite this lack of evidence, the expert recommendation is that angiotensin-converting enzyme inhibitors should be given.

With regard to corticosteroids, these drugs clearly are associated with a high risk of renal crisis in patients with systemic sclerosis. If they are used, patients should be very carefully monitored for blood pressure and kidney function, he said.

► **Skin involvement.** Two randomized clinical trials provided evidence for the use of methotrexate to alleviate the cutaneous manifestations of scleroderma, particularly in early diffuse disease.

► **Gastrointestinal manifestations.** Thus far there have been no randomized trials evaluating therapies for the various gastrointestinal disorders associated with systemic sclerosis. "Nonetheless, expert opinion tells us that we should be employing drugs such as proton-pump inhibitors, prokinetic agents, and antibiotics for bacterial overgrowth," he said.

► **Research agenda.** Because many gaps and uncertainties remain in the understanding and treatment of systemic sclerosis, a research agenda was also established, Dr. Matucci-Cerinic said. Among the concerns that were identified as warranting further investigation and analysis were the safety and efficacy of long-term cyclophosphamide and mycophenolate mofetil and the use of sildenafil for Raynaud's phenomenon. Evidence for the safety and efficacy of ACE inhibitors in renal crisis also should be pursued, and clearer guidelines on their use should be developed.

Another member of the guidelines task force, Dr. Daniel E. Furst, said in an interview that these guidelines combine what is clear from the medical literature with experience from experts and patient representatives. "While these recommendations are preliminary and undoubtedly will change as more data become available, they are a good first step toward helping rheumatologists treat systemic sclerosis," said Dr. Furst, who is Carl M. Pearson professor of medicine and director of the Rheumatology Clinical Research Center, University of California, Los Angeles. ■

Biologics Promising in Lupus, but More Research Is Needed

BY NANCY WALSH
New York Bureau

VIENNA — Early results with biologic therapy for systemic lupus erythematosus show promise, but the results of controlled trials are needed before these drugs can be widely used in lupus, according to Dr. Martin Aringer of the department of rheumatology, Medical University of Vienna.

The complexity of lupus provides multiple potential targets for biologic response modifiers, including the B cell, which is quantitatively and functionally abnormal in lupus; the interface between B cells and T cells; and various cytokines involved in the inflammatory response, Dr. Aringer said at the 16th Congress of the European Academy of Dermatology and Venereology.

B cell–depleting therapies being evaluated in lupus include monoclonal antibodies against the surface antigens CD20 (rituximab) and CD22 (epratuzumab).

The first study of rituximab in lupus was an open-label trial that included 17 patients with longstanding, clinically active disease. Mean age was 37 years, prednisone dosage was 13 mg/day, and Systemic Lupus Activity Measure (SLAM) score was 8.8.

Patients received either a single infusion of 100 mg/m^2 of rituximab, a single infusion of 375 mg/m^2, or four weekly infusions of 375 mg/m^2.

A total of 11 patients achieved B-cell depletion, and in these patients SLAM scores improved significantly, with improvements persisting for 12 months (Arthritis Rheum. 2004;50:2580-9).

Only three patients showed a decline in autoantibody levels, which suggests that the role of B cells in lupus is autoantibody independent, Dr. Aringer said.

In another study that included six patients with refractory disease, rituximab was given as two infusions of 500 mg along with two infusions of 750 mg of cyclophosphamide and high-dose corticosteroids. One patient was lost to follow-up, but the remaining five all improved clinically and serologically, with decreases in anti–double-stranded DNA antibodies, erythrocyte sedimentation rate, and urinary protein-to-creatinine ratio (Arthritis Rheum. 2002;46:2673-7).

"B-cell depletion does seem to be one way to check autoimmunity," Dr. Aringer said. "Either way is probably fine, with rituximab alone or in combination with cyclophosphamide. It's not clear which is better," he said. This may be an option for patients who do not respond to other therapies, but controlled data are lacking at this point, he said.

B-cell immunotherapy using epratuzumab was evaluated in an open-label study that included 14 patients with moderately active lupus. After receiving four doses of 360 mg/m^2 all patients improved clinically by at least 50% (Arthritis Res. Ther. 2006;8:R74).

"We can also target the contact between T cells and antigen-presenting B cells with the costimulatory blocker abatacept," he said. "We don't yet have published human experience with this, but we have spectacular mouse data on the combination of abatacept and cyclophosphamide—better than anything that was used before in this mouse model," he said. Two human trials are ongoing, one with the combination and the other with abatacept alone. "We will know very soon if this works."

'We have spectacular mouse data on the combination of abatacept and cyclophosphamide—better than anything that was used before' in a mouse model.

"Finally, our focus in the last couple of years has been on targeting the downstream inflammatory response using tumor necrosis factor blockade," he said.

Despite the fact that tumor necrosis factor (TNF) is very high in the serum of patients with lupus and correlates with several measures of disease activity, the widely available tumor necrosis factor–α blockers have not been given much consideration in lupus.

One reason for this is that approximately 15% of patients with rheumatoid arthritis and Crohn's disease being treated with these drugs develop anti–double-stranded DNA and anticardiolipin antibodies, and some develop drug-induced lupus, according to Dr. Aringer. Also, some mouse models have suggested worsening of nephritis, although others have demonstrated delay in disease.

Despite this controversy, but with the reassuring observation that the antibodies clear on withdrawal of the drug, Dr. Aringer and his colleagues performed the first open-label trial of infliximab in lupus.

Six patients each received four infusions of 300 mg of infliximab on day 0 and at weeks 2, 6, and 10 in addition to immunosuppression with methotrexate or azathioprine.

Global disease activity decreased in all patients during the treatment period, and there were no flares in a follow-up period of 52 weeks, he said.

In the three patients who had arthritis, there was rapid improvement with no swollen joints being seen during treatment, although symptoms returned about 8 weeks after the final infusion (Arthritis Rheum. 2004;50:3161-9).

There was an increase in anti–double-stranded DNA antibodies in four patients, and one patient developed antiphospholipid and anticardiolipin antibodies and a deep venous thrombosis. "This was the only immunologic adverse event we saw," he said.

Marked improvements were seen in longstanding proteinuria among all four patients with nephritis, with a decrease of 60% or more within a few weeks. "More than 3 years later these patients continue to have very low level proteinuria. We can't explain this, but we think it's important," he said.

A larger, controlled trial of infliximab is now underway, he said. ■