

## Novel Therapies to Modify Scleroderma Are Emerging

BY PATRICE WENDLING

CHICAGO — Several pioneering treatment approaches have emerged to modify the vascular and fibrotic disease in scleroderma, Dr. Frederick Wigley said at a symposium sponsored by the American College of Rheumatology.

Dr. Wigley, director of the scleroderma center at Johns Hopkins University in Baltimore, discussed several of these novel therapies that are being studied and/or are in use, including the following:

► **Bosentan.** This endothelial inhibitor is approved in the United States and Europe to manage the symptoms of pulmonary artery hypertension (PAH). Two trials in scleroderma show that bosentan (Tracleer) reduces digital ulcers but has no benefit on Raynaud's attacks, Dr. Wigley said.

► **Tyrosine kinase inhibition with imatinib mesylate.** Industry-sponsored trials are underway evaluating imatinib (Gleevec) in systemic sclerosis and PAH, and dasatinib (Sprycel) in scleroderma pulmonary fibrosis.

► **Immunoablation with and without stem cell transplantation.** This should be looked at as "an experiment in progress," Dr. Wigley said. In a pilot study of 34 patients with poor prognosis for systemic sclerosis, major improvements in skin and overall function were reported in 17 of 27 evaluable patients who survived 1 year after high-dose immunosuppressive treatment and autologous hematopoietic cell transplantation (*Blood* 2007;110:1388-96). These results came at a cost, however, with relapse occurring in 10 survivors and 23% of the 34 patients dying as a result of the procedure.

► **Statins.** These drugs have shown some benefit in early trials, possibly because they display pleiotropic effects on en-

dothelial function that could potentially delay vascular injury. Levels of circulating endothelial precursor cells, reduced in scleroderma, were increased up to eightfold after 12 weeks of therapy with atorvastatin (Lipitor) 10 mg/day in 14 patients with systemic sclerosis in an open-label pilot study (*Arthritis Rheum.* 2006;54:1946-51). Endothelial markers improved and fewer new digital ulcers occurred with atorvastatin 40 mg/day for 16 weeks vs. placebo in 86 patients with scleroderma (*J. Rheumatol.* 2008;35:1801-8).

► **ACE inhibitors.** These agents have been shown to improve 12-month survival in patients with systemic scleroderma-induced renal disease, which is often associated with corticosteroids. ACE inhibitors can be used with angiotensin II receptor blockers (ARBs), calcium channel blockers, and prostaglandins when full doses of an ACE inhibitor do not control a crisis. The true benefits and risks of combining an ACE inhibitor with other agents in scleroderma have not been fully studied, Dr. Wigley said. ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial), which did not include scleroderma patients, showed that the use of combined ARBs and ACE inhibitors was associated with worse renal outcomes in high-risk patients.

► **Prostaglandins.** When administered intravenously, prostaglandins are an option for reducing digital ulcers, Raynaud's attacks, and PAH associated with scleroderma. Two trials are underway to evaluate oral formulations of iloprost and treprostinil in vascular scleroderma and Raynaud's, he said.

Dr. Wigley disclosed receiving research grants from MediQuest Therapeutics Inc., Novartis Pharmaceuticals Corp., and United Therapeutics Corp., and honoraria from MediQuest. ■

## Sorting Out Vasculitis Damage From Disease

BY PATRICE WENDLING

CHICAGO — Vasculitis is less likely to kill affected patients than are complications arising from the drugs used to treat it. So thinking about vasculitis in terms of disease activity and disease damage may help avoid overtreatment.

In vasculitis, damage occurs in two peaks. The first is the direct result of the vasculitis itself, such as pulmonary fibrosis and renal insufficiency that are the direct consequence of disease flare. The second peak results from the untoward effects of therapies such as cyclophosphamide and glucocorticoids that accumulate in patients over time, Dr. Philip Seo said at a symposium sponsored by the American College of Rheumatology.

This accumulation of damage actually predicts increased mortality and is important in the way clinicians think about their patients when deciding what to do next, said Dr. Seo, codirector of the Johns Hopkins Vasculitis Center in Baltimore.

"It's important to recognize in patients that there are manifestations that are clearly due to vasculitis that are not going to be amenable to immunosuppressive therapy, and really should not be treated as such," he said. "Because the more immunosuppressive therapy you use, the more likely [patients] are to accrue damage as a consequence, and that just becomes an endless cycle."

Data from the European Vasculitis (EUVAS) Study Group show that only 73% of patients with vasculitis were alive at 5 years. Impaired kidney function was a significant predictor of poor outcomes, whereas younger age was a clear benefit. Notably, vasculitis was not the No. 1 killer. The top three causes of death were infection, cardiovas-

cular events, and malignancy, "all of which can relate back to the drugs we use to treat these patients," said Dr. Seo, who reported no relevant conflicts of interest.

The WeCLOT (Wegener's Clinical Occurrence of Thrombosis) trial highlighted the increased risk of venous thromboembolism (VTE), reporting a VTE incidence rate of 7 per 100 person-years in 167 patients enrolled with active Wegener's granulomatosis and no prior VTE events (*Ann. Intern. Med.* 2005;142:620-5). To put this in context, patients with Wegener's are 23 times more likely than the general population to have a venous thromboembolic event and 7 times more likely to do so than patients with lupus, which is conventionally considered to be the prothrombotic disease, he said.

Perhaps less well known is the increased risk for solid malignancies. The 5-year follow-up data reported in 2008 from WGET (Wegener's Granulomatosis Etanercept Trial) showed a 4.4-fold increased risk of solid malignancies in patients with Wegener's who were treated with etanercept (Enbrel) and cyclophosphamide. It has been unclear whether this finding can be generalized beyond this population, but new unpublished data from 469 of 554 patients enrolled in the EUVAS Long-Term Follow-Up Study are moving in the same direction, Dr. Seo said. EUVAS investigators identified 31 solid malignancies (6.6%) including 8 prostate, 5 lung, and 4 bladder cancers, as well as 22 skin malignancies (3.8%).

Dr. Seo highlighted nasal blockade/chronic discharge/crusting (32%), hypertension (22%), hearing loss (20%), chronic sinusitis (12%), and osteoporosis (10%) as a short list of other common damage. ■

## Should Rheumatologists Be Managing CVD in Lupus?

BY SALLY KOCH KUBETIN

NEW YORK — Young women bear the greatest relative risk of atherosclerotic disease in lupus. However, advice on managing cardiovascular disease is not evidence based. Rather, rheumatologists must rely largely on data from studies of heart disease in other high-risk groups and on the collective wisdom of rheumatologists who are experienced in managing cardiovascular disease in patients with lupus.

Consider giving lupus patients a baby aspirin a day, as she does, Dr. Susan Manzi suggested at a rheumatology seminar sponsored by New York University Hospital for Joint Diseases. Although the data have not shown it to lessen the MI risk in women as it does in men, it does protect them somewhat against stroke.

Despite the scant data on effective management of cardiovascular disease (CVD)

in lupus, there are ample data on CVD prevalence among women in general and those with lupus in particular. About one-third of deaths in lupus occur in patients who are younger than 45 years of age. And one-third of those deaths are due to atherosclerosis. In some of her earlier epidemiologic research, Dr. Manzi, director of the Lupus Center of Excellence at the University of Pittsburgh, compared the rate of MI in a cohort of 498 women with lupus to that reported among 2,208 women in the Framingham heart study who did not have lupus (*Am. J. Epidemiol.* 1997;145:408-15). In 35- to 44-year-olds, lupus women had a 50-fold increased risk of MI. After age 44, as women entered menopause, those with lupus were still two to four times more likely to have an MI as were those without lupus, she said.

Subclinical atherosclerotic disease is

likewise more prevalent in patients with lupus. In one study of 197 lupus patients and an equal number of controls, findings from carotid ultrasonography showed that 37% of lupus patients vs. 15% of controls had asymptomatic carotid plaque (N.

**Although there are no data to support its reduction of their MI risk, giving women with lupus a baby aspirin per day may protect them somewhat against stroke.**

*Engl. J. Med.* 2003;349:2399-406).

Other data show that women with lupus are more likely than their lupus-free peers to have progressive atherosclerosis. Serial carotid artery ultrasound exams of 217 patients with lupus (mean age at baseline, 45 years) and 104 age- and sex-matched controls showed that plaque

was present at baseline in 31% of the lupus patients and 17% of controls. At follow-up, 40% of lupus patients had plaque, compared with 20% of controls; interval between scans was 4 years for patients and 5 years for controls. Plaque had progressed in 27% of the lupus patients and only 10% of controls (*Arthritis Rheum.* 2008;58:835-42).

The ultimate question has been whether atherosclerotic disease detected on imaging predicts future events in patients with lupus. In a study recently presented at the ACR meeting in 2008, the presence of carotid plaque and greater intima-media thickness predicted the time to incident stroke, MI, cardiovascular accident, or coronary artery bypass graft over a 10-year period in 289 patients with lupus. This suggests that these measures may be used as surrogate end points in future clinical trials. ■