



COURTESY DR. FRANCESCO ZULIAN

Capillaroscopy changes typical of juvenile systemic sclerosis usually appear after Raynaud's phenomenon and the appearance of serum autoantibodies.

Raynaud's Precedes Autoantibodies' Onset in Juvenile Systemic Sclerosis

BY NANCY WALSH
New York Bureau

ABANO TERME, ITALY — Childhood-onset systemic sclerosis is different from adult-onset scleroderma, typically being characterized by less internal organ involvement and lower mortality

rates, Dr. Francesco Zulian reported at a congress on skin, rheumatism, and autoimmunity.

According to data from the Padua international database that includes 1,000 juvenile patients with various types of scleroderma, 153 have systemic sclerosis, said Dr. Zulian of the pediatrics/rheumatology division at

the University of Padua (Italy).

The average age of systemic sclerosis onset was 8.1 years, and the disease duration at diagnosis was 1.9 years. The female to male ratio was 3.6:1.0, and 139 of the patients had the diffuse subtype of systemic sclerosis, he said. The limited subtype is more common among adults.

The first manifestation of systemic sclerosis in children typically is Raynaud's phenomenon. This is followed by the appearance of autoantibodies, and then capillaroscopy changes.

The pattern of autoantibodies is different from that seen in adults with scleroderma. Antinuclear antibodies

Skin involvement accounts for 60% of juvenile systemic sclerosis symptoms in children, which is much lower than that found in adults.

were seen in 81% of the pediatric patients, compared with 94% of adults, whereas anti-Scl-70 antibodies were seen in 34% vs. 43%, respectively, Dr. Zulian said.

Rheumatoid factor was found in 17% of

the children, compared with 23% of the adults, he added.

Anticentromere antibodies were found in 7.1% of children in the database, compared with 23% of adults, which reflects the lower prevalence of the limited subtype of systemic sclerosis in children, he said.

The most frequent manifestations were Raynaud's phenomenon, which was seen in 84% of the juvenile patients, and skin induration, which was found in 76%. Abnormal lung function tests were seen in 40% of the patients and pulmonary fibrosis in 25%.

Skin involvement accounts for 60% of symptoms in children, which is much lower than in adults. It is also more difficult to make the diagnosis in young patients, Dr. Zulian said.

Musculoskeletal involvement also was quite common, with arthralgias reported by 36%, arthritis by 27.5%, and muscle weakness by 24.2%. Gastroesophageal reflux was found in 30%, but small-bowel involvement was rare.

"In 127 patients we have enough data to make some conclusions about outcome," Dr. Zulian said. At present, 15 (11.8%) of the patients have died, 10 of cardiac failure, 2 of renal failure, 2 of respiratory failure, and 1 of septicemia. Of these 15, 4 died within the first year after diagnosis, and 11 within 5 years of diagnosis. "This means that there is a group of patients who have a very aggressive course of disease and who did not respond to treatment," he said.

Organ involvement is the major predictor of poor outcome, so those who present with early respiratory, cardiac, or gastrointestinal involvement must be evaluated and treated aggressively, he said. ■

levels are at least partly associated with impaired ET_B receptor-mediated clearance.¹³ Furthermore, the long-term administration of a selective ET_B receptor antagonist was found to have unfavorable effects on vascular remodeling.⁴ This is in sharp contrast to the benefits of selective ET_A antagonism.¹⁴

THE DIFFERENCE LIES IN ET_A SELECTIVITY

Vasoconstriction, cellular proliferation, and vascular remodeling are the hallmarks of PAH.¹² Studies have demonstrated that selective ET_A antagonists play a pivotal role in the regulation of ET-1 levels in PAH and have been beneficial for vascular remodeling.^{4,7,13}

ET-1 AND RECEPTOR-MEDIATED ACTIVITIES

Highly selective ET_A blockade maintains ET-1 clearance, NO and PGI₂ levels, and reduces or maintains circulating ET-1 levels, resulting in vasodilation, increased blood flow, and repair of remodeled vasculature compared to less selective agents.^{5-7,14} (See Figures 1,2)

HOW SELECTIVE TO ET_A SHOULD TREATMENT BE?

The more selective, the better. One should always be aware of the varying degrees of selectivity, as they equate to differences in blockade of the ET_A and ET_B receptors and resulting levels of ET-1.^{8,15,16} Figure 3 illustrates the difference between a less selective agent and highly selective agents. These in vitro selectivity ratios demonstrate the stark differences in ET_A selectivity. Figure 4 depicts how agents with low selectivity of the ET_A receptor (<2400) increase ET-1 levels whereas highly selective ET_A receptor (>2400) antagonists have been shown to

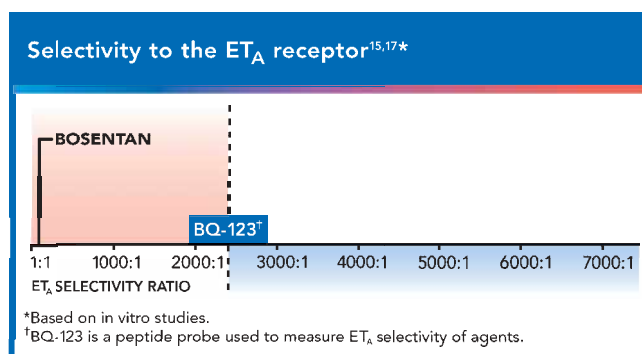


Figure 3

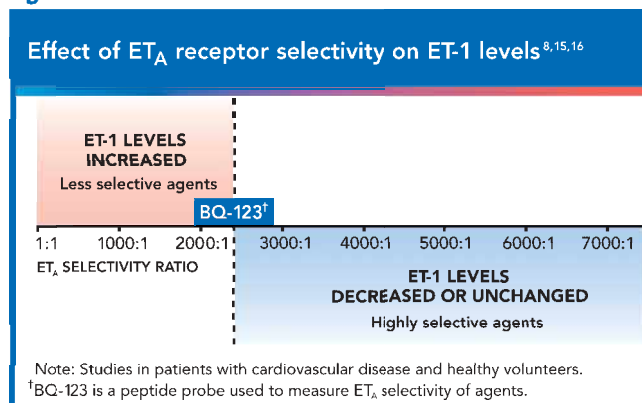


Figure 4

decrease ET-1 levels or leave them unchanged.^{6,8,15} The benefits of ET_A selectivity are being recognized.

TOWARD BETTER OUTCOMES IN PAH

Currently, there are no highly selective ET_A antagonists available for the treatment of PAH. In vivo studies have shown that highly selective ET_A antagonism may lead to better overall outcomes.^{7,8,12}

References: 1. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest*. 2001;120:1562-1569. 2. Lüscher TF, Yang Z, Tschudi M, et al. Interaction between endothelin-1 and endothelin-derived relaxing factor in human arteries and veins. *Circ Res*. 1990;66:1088-1094. 3. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988;332:411-415. 4. Murakoshi N, Miyauchi T, Kakinuma Y, et al. Vascular endothelin-B receptor system in vivo plays a favorable inhibitory role in vascular remodeling after injury revealed by endothelin-B receptor-knockout mice. *Circulation*. 2002;106:1991-1998. 5. Peacock AJ, Rubin LJ, eds. *Pulmonary Circulation: Diseases and Their Treatment*. 2nd ed. London: Arnold; 2004. 6. Fukuroda T, Fujikawa T, Ozaki S, Ishikawa K, Yano M, Nishikibe M. Clearance of circulating endothelin-1 by ET_B receptors in rats. *Biochem Biophys Res Commun*. 1994;199:1461-1465. 7. Verhaar MC, Strachan FE, Newby DE, et al. Endothelin-A receptor antagonist-mediated vasodilatation is attenuated by inhibition of nitric oxide synthesis and by endothelin-B receptor blockade. *Circulation*. 1998;97:752-756. 8. Halcox JPJ, Nour KRA, Zalos G, Quyyumi AA. Coronary vasodilation and improvement in endothelial dysfunction with endothelin ET_A receptor blockade. *Circ Res*. 2001;89:969-976. 9. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328:1732-1739. 10. Hankins SR, Horn EM. Current management of patients with pulmonary hypertension and right ventricular insufficiency. *Curr Cardiol Rep*. 2000;2:244-251. 11. Spieker LE, Noll G, Ruschitzka FT, Lüscher TF. Endothelin receptor antagonists in congestive heart failure: a new therapeutic principle for the future? *J Am Coll Cardiol*. 2001;37:1493-1505. 12. Jeffery TK, Wanstall JC. Pulmonary vascular remodeling: a target for therapeutic intervention in pulmonary hypertension. *Pharmacol Ther*. 2001;92:1-20. 13. Lüscher TF, Barton M. Endothelins and endothelin receptor antagonists: therapeutic considerations for a novel class of cardiovascular drugs. *Circulation*. 2000;102:2434-2440. 14. Chen SJ, Chen YF, Opgenorth TJ, et al. The orally active nonpeptide endothelin A-receptor antagonist A-127722 prevents and reverses hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling in Sprague-Dawley rats. *J Cardiovasc Pharmacol*. 1997;29:713-725. 15. Ihara M, Noguchi K, Saeki T, et al. Biological profiles of highly potent novel endothelin antagonists selective for the ET_A receptor. *Life Sci*. 1992;50:247-255. 16. Williamson DJ, Wallman LL, Jones R, et al. Hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. *Circulation*. 2000;102:411-418. 17. Clozel M, Breu V, Gray GA, et al. Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist. *J Pharmacol Exp Ther*. 1994;270:228-235.