Statin Found to Improve Raynaud's in Scleroderma

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Atorvastatin raised the number of circulating endothelial precursors in a pilot study of 14 patients with systemic sclerosis, significantly improving the symptoms of Raynaud's phenomenon, reported Dr. Masataka Kuwana of Keio University, Tokyo, and associates.

Compared with healthy control subjects, patients with scleroderma had a markedly reduced number of circulating endothelial precursors (CEPs), and their CEPs tended to have an impaired maturation potential when stimulated by angiogenic factors.

Dr. Kuwana and associates theorized that "insufficient mechanisms of vascular repair, due to defective vasculogenesis, contribute to the pathogenic process" underlying scleroderma patients' Raynaud's symptoms, digital ulcers, and gangrene. If so, raising the number of CEPs and stimulating CEP kinetics might improve the vasculopathy.

Statins have been shown to increase CEPs and stimulate their kinetics in patients with coronary heart disease, so the researchers conducted a prospective pilot study to assess whether statins would have the same effect in scleroderma. They assessed 14 women aged 36-75 years (mean age, 57 years), half of whom had diffuse systemic sclerosis and half of whom had limited cutaneous systemic sclerosis. All the patients had Raynaud's phenomenon.

Atorvastatin treatment resulted in a statistically significant 1.7- to 8.0-fold increase in the number of CEPs. The CEP numbers returned to extremely low baseline levels after cessation of atorvastatin, however.

In addition, "reductions in the up-regulated levels of angiogenic factors and vascular endothelial activation/injury markers were observed during treatment," Dr. Kuwana and associates noted.

Raynaud's symptoms improved significantly during treatment, along with patients' activity levels and ratings of disability and pain. No patient developed new ulcers during treatment. These symptoms recurred when therapy was stopped, however, and patients quickly began developing new digital ulcers.

All but one patient completed the 12-week course of once-daily atorvastatin (10 mg) while continuing on their regular medication regimens. None had any adverse events, but one woman withdrew from the study because her total cholesterol level declined excessively, to less than 100 mg/dL, the investigators said (Arthritis Rheum. 2006;54:1946-51). These beneficial drug effects are likely due to the recruitment of CEPs into the periphery and the repair of injured endothelium. Statins may increase both the proliferation and the mobilization of CEPs and may prevent CEP senescence and apoptosis within the bone marrow, the researchers reported.

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"However, it is also possible that the observed clinical changes were mediated through other effects of statins, such as anti-inflammation mechanisms and the improvement of mature endothelial function," Dr. Kuwana and colleagues noted.

Although the number of CEPs increased dramatically with atorvastatin, it never reached the level reported in healthy subjects. Also, atorvastatin failed to improve the impaired maturation potential of the CEPs, the researchers acknowledged. "These observations indicate that although atorvastatin is certainly capable of improving CEP dysfunction in systemic sclerosis patients, its effects are limited.

"In addition to statins, ... drugs that exert potent stimulatory effects on CEP kinetics, such as granulocyte–macrophage colony-stimulating factor and granulocyte colony-stimulating factor, could augment vasculogenesis as a therapeutic intervention for ischemic complications in patients with systemic sclerosis," according to Dr. Kuwana and associates.

CEPs, which are derived from bone marrow, are required for the formation of blood vessels and also contribute to vascular healing at sites of vascular injury or ischemia by working together with existing mature endothelial cells. ■