Letters to the Editor

Possible role of iloprost (stable analog of PG12) in promoting neoangiogenesis in systemic sclerosis.

Sirs,

In Systemic Sclerosis (SSc) fibrosis is principally due to involvement of microcirculation with capillary necrosis, arteriolar intimal proliferation which result in irreversible local ischemia. Acidosis, ischemia, fibrosis promote neoangiogenesis, but this observation is rare (1). The simplest technique to observe microvascular bed in vivo is nailfold videocapillaroscopy, used in monitoring microangiopathy and assessing severity in SSc (2). The therapy of SSc is not yet encoded, but currently vasodilator drugs such calcium channel blockers or prostacyclin analogs, as iloprost, are associated to conventional therapies, in fact iloprost is able to control vasospastic attacks, to improve carbon monoxide diffusion (DLCO) and fibrosis, to decrease pulmonary hypertension (PH) and perhaps cutaneous fibrosis (3). Moreover iloprost modulating coagulative cascade and adhesion molecules (4) is useful in treatment of chronic and acute peripheral ischemia (5), but data about the potential capacity of iloprost to stimulate neoangiogenesis in vivo in humans are indefinite (6). We report a preliminary observation of the gradual development of peripheral neoangiogenes is, detected by videocapillaroscopy, in four female sclerodermic patients (age mean 58 years), treated with iloprost (Endoprost - Italiana, Italy), in continuous infusion starting with six hours for five days, followed by two days every six weeks at mean dosages of 4 ng/kg/min (range 2-5 ng/kg/min), consecutively for three years. All patients presented Anti-Nuclear Antibodies and Scl70, Raynaud's phenomenon with digital ulcers; modified Rodnan Skin Score (mRSS) was 18, the lung diffusion of alveolar CO (DLCO) was reduced (mean 60%) and a mild secondary pulmonary hypertension (mean pulmonary arterial pressure (PAP) detected by echocardiographic method was 35 mm Hg) was present. They underwent a basal nailfold videocapillaroscopy (Videocap DS-Medigroup Italy) at 200x on all fingers of both hands and monitored yearly during therapy. In association, all patients took 75 mg/day of acetilsalycilic acid and nifedipine 10 mg/day. A small control group was enrolled, consisting of 6 female patients matched for age, sex, severity of disease, who refused iloprost therapy and were treated with nifedipine (30-40 mg/day) and acetilsalycilic acid (75 mg/day).

After three years, in the iloprost group a improvement of peripheral vasularization was observed by capillaroscopy, with an increase in the capillary number, a mild regression of avascular areas and pericapillar oedema. Some morphological changes in capillary shape were also detected: a decrease in the number of megacapillars, regression of some morphologic anomalies and improvement of blood flow detected by Doppler, that can hypothesize a partial regression of the scleroderma spectrum activity of a capillaroscopic pattern (Fig. 1). In the control group, the capillaroscopic pattern was unchanged. In the iloprost group, a mild improvement of symptoms was observed with in the DLCO (72% mean 60-75%), in the decrease of PAP (mean 30 mmHg) and in the number of vasospastic attacks and development of ulcers, and an improvement of mRSS (mean 14 vs 18). In the control group only a mild decrease in PAP (mean 32 mm Hg) and vasospastic attacks was observed (statistical significant only a trend).

We can hypothesize that the therapeutic properties of iloprost that could justify our data are associated to its activity in modulating Vascular Endothelium Growth Factor (VEGF) secretion; in fact Konttinen showed in SSc a reduction of neoangiogenesis by a lack of expression of α2-β3 integrines that mediate neoangiogenesis by secretion of VEGF (7). Pola et al., showed in murine angiogenesis that iloprost induces neoangiogenesis activating Peroxisome Proliferator-Activated ReceptorS (PPARs) located in the endothelial cell nucleus that enhance transcription and secretion of VEGF (8, 9). Moreover, iloprost aging on ERK pathway (that enhances fibrosis induced by endo-thelin-I and Fibroblast Growth Factor β inhibits mitogenic and proliferative activities of vascular smooth muscle [10]. Nevertheless, our preliminary observations need further clinical, standardized and controlled studies to be confirmed.

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Fig. 1. Legend: hands nailfold videocapillaroscopy in four patients affected by diffuse systemic sclerosis at the baseline and after three years of iloprost therapy. We noted a development of neoangiogenesis and a partial regression of features typical of capillaroscopic scleroderma pattern spectrum (megacapillars, avascular areas, oedema).
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References