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Does Iloprost Interfere with the Inflammatory Cascade in Systemic Sclerosis?

In this issue (p. 245–249) Philipp Rehberger and co-workers report on the long-term impact of a 5–7-day course of iloprost infusion on endothelial-cell-associated soluble adhesion molecules and growth factors in 13 patients with systemic sclerosis. Serum levels of sE-selectin, sVCAM-1 and sICAM-1 were increased before therapy and were significantly reduced by the treatment. sE-selectin and sVCAM-1 remained significantly reduced until 6 months after treatment. Endothelin-1 (ET-1) concentrations were subject to marked inter-individual variations, but also decreased significantly after therapy and were still reduced after 13 weeks. Additionally, 12 of the 13 patients reported a reduction in the frequency and severity of Raynaud’s phenomenon and 6 out of 7 patients reported a reduction in the size of digital ulcers. Patients received 5–6-h intravenous infusions of iloprost 0.5–2.0 ng/kg/day (50 µg/day).

Iloprost, a stable prostacyclin analogue, down-regulates adhesion molecules and causes vasodilatation. Furthermore, it has the following effects: inhibition of adhesion, aggregation and activation of thrombocytes, blood flow, vessel permeability, antithrombotic, fibrinolytic, and anti-fibrotic activity by suppression of tissue growth factor (TGF)-β, inhibition of neutrophil chemotaxis, and down-regulation of the endothelin gene expression (1). In clinical use iloprost has reduced the frequency and severity of attacks of Raynaud’s phenomenon, and has also been used to treat digital necroses in patients with systemic sclerosis and peripheral occlusive arterial disease, thrombangitis obliterans, frost-bite, venous ulcers, pulmonary hypertension and even aseptic osteonecrosis.

The pathogenesis of systemic sclerosis remains unknown, albeit interaction among lymphocytes, endothelial cells and fibroblasts appears to be involved in the process (2). The function and distribution of adhesion molecules are crucial factors in controlling the perpetuating inflammatory process. A multi-step cascade involves the recruitment of lymphocytes, their migration to endothelial cells, and their interaction with adhesion molecules. Selectins mediate the rolling of lymphocytes to endothelial cells, thus providing co-stimulatory signals for cytotoxic T-lymphocyte activation. This is followed by the activation of integrins, which provokes the attachment of lymphocytes to blood vessel walls, and lymphocyte binding to ICAM-1, followed by diapedesis of lymphocytes. The increased expression of sE-selectin and elevated sICAM-1 levels in patients with systemic sclerosis, as shown by Rehberger et al., might reflect the grade of activation of endothelial cells.

ET-1 is one of the most potent vasoconstrictors leading to Raynaud’s phenomenon. It also induces proliferation of fibroblasts. Serum VCAM levels have been shown to correlate with the extent of skin sclerosis and serum TGF-β levels. Elevated VCAM levels were found to be an indicator of capillary damage in systemic sclerosis (3).

Therefore, the significant decrease in serum concentrations of sE-selectin, sVCAM-1, sICAM-1 and ET-1 after a 5–7-day course of treatment with iloprost, and the subsequent reduction in the investigated adhesion molecules and growth factors for several weeks to months, prove the fact that iloprost interferes with the initial inflammatory process in systemic sclerosis and might have a long-term impact on the morbidity of disease.

The presented data are important because they show that treatment with iloprost influences pathogenetic mechanisms in systemic sclerosis, a disease associated with limited treatment options.

REFERENCES


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Not to be Forgotten: Cutaneous Langerhans’ Cell Histiocytosis in an Adult

Campanati and coworkers (p. 299–301) describe an interesting differential diagnostic case: an elderly patient who developed large, diffuse erythematous inflammatory plaques resembling psoriasis inversa, impetiginized eczema or intertrigo. A skin biopsy revealed a lymphohistiocytic infiltration consisting of histiocytes with large kidney-shaped nuclei and abundant pink cytoplasm. A diagnosis of Langerhans’ cell histiocytosis (LCH) was made. LCH is best known in neonates and young children, since the vast majority of LHC patients are children under 10 years of age. LCH can range from limited involvement that spontaneously regresses to progressive multiorgan involvement. Letterer-Siwe disease (LSD) is the disseminated multisystemic form of LCH and often, the course of LSD is rapid and fatal. However, LCH is also found in adults of all ages, although less often. Most adult patients will survive LCH but in some cases, the disease may run a progressive course and can be life threatening. Why do the Langerhans’ cells proliferate is not known, and since LCH is so rare, very little research has been directed into its cause and treatment.

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