LETTERS TO THE EDITOR

Intermittent Iloprost Infusion Therapy of Pulmonary Hypertension in Scleroderma—A Pilot Study

Str—Systemic sclerosis (SSc, scleroderma) is characterized by disturbed microcirculation, which may lead to pulmonary hypertension (PH), a serious internal organ manifestation for which effective treatment does not exist today. However, a beneficial effect has been reported from treatment with continuous i.v. infusion of prostaglandins [1].

The prostacyclin analogue iloprost has a half-life of 13 min [2], which is longer than that of the biological substance, and an oral bioavailability of 13% [3], making future oral administration possible. It is reported to have mainly three pharmacodynamic properties: inhibition of platelet aggregation, vasodilatation and cytprotection [4]. Despite the short half-life, an improvement of peripheral circulation has been reported up to 6–9 weeks after infusion [5]. The reported long-term effect on peripheral circulation of intermittent treatment by iloprost prompted us to examine the effect of this regime on mild and moderate PH.

Eight SSc patients (six women and two men), who fulfilled the classification criteria developed by the American College of Rheumatology [6], participated in the study (Table I). Five patients had diffuse systemic sclerosis (dSSc) and three patients had limited systemic sclerosis (ISSc) [7].

Iloprost (Ilomedin), 0.1 mg active drug, was added to 500 ml NaCl and given i.v. by use of an infusion pump during 6 h, on three consecutive days, with 6 week intervals on four occasions. Infusion rates of 0.5–2.0 ng/kg/min were used. On days 2 and 3, the infusion rate was increased from 0.5 to 1 ng/kg/min with 0.25 ng/kg/min every 60th min. On day 1, the infusion rate was increased from 1 to 2 ng/kg/min or to the highest tolerated dose. The peripheral blood pressure was measured twice per hour. If any adverse event such as headache, hypotonia and/or nausea occurred, the infusion rate was reduced stepwise. Other vasodilating drugs, except for ACE inhibitors, were excluded on the infusion days. None of the patients had oral warfarin due to PH. Iloprost treatment was given during the cold season of the year (October–March).

The systolic pulmonary artery pressure (PAPsyst) was determined by Doppler cardiography as previously described [8], and evaluated by the same cardiologist before and after 24 weeks. PH was defined as >32 mmHg. A change in PAPsyst >5 mmHg was regarded as significant.

PAPsyst decreased in three patients by 9, 11 and 13 mmHg, whereas it was stable (±5 mmHg) in the remaining five patients (Fig. 1). The poorest response was found among smokers (Table I). Five patients noticed improvement of Raynaud’s phenomenon, i.e. less severe and less frequent vasospastic attacks, and 3/5 patients reported peripheral wound healing. All patients reported considerable subjective improvement in their well-being. Seven patients experienced headache and five nausea and/or diarrhea during the infusions.

Previously described long-term continuous prostacyclin infusion therapy is both time consuming and expensive, but gains longer lifetime in patients awaiting lung transplantation [9]. Because of the reported long-lasting effect of intermittent iloprost infusion on peripheral circulation, we examined the effect of this regime on PH in SSc. Since at the start of the study there was no previous experience of the treatment of PH in SSc with intermittent iloprost, our treatment approach was based on the already described regimen in patients with Raynaud’s phenomenon secondary to SSc [5].

A beneficial effect of intermittent iloprost infusion on PH in SSc was recently reported by Bartram et al. [10]. The greater reduction of the pulmonary pressure among their patients may be explained by a shorter disease duration, a higher percentage of patients with ISSc without pulmonary fibrosis (80% compared to 38% in our study) or by the different treatment regime. It remains to be shown whether another treatment

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<th>Table I Clinical features of eight SSc patients with mild to moderate pulmonary hypertension</th>
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ISSc, limited systemic sclerosis; dSSc, diffuse systemic sclerosis; VC, forced vital capacity; DLCO, carbon monoxide diffusing capacity, p%; percentage of predicted value; PAPsyst, systolic pulmonary artery pressure.

Biochemical activity was defined as an erythrocyte sedimentation rate >15 mm/h, an orosomucoid level >1.1 g/l, and/or a C-reactive protein level >12 mg/l.

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approach with a different selection of patients can yield better results in lowering PAPsyst.

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Resolving Familial Mediterranean Fever Attacks with Interferon Alpha

Sir—Attacks of familial Mediterranean fever (FMF) can be decreased by colchicine and this drug also possibly prevents amyloidosis, the most serious complication of the disease. Ten to 20 per cent of the patients continue to have painful attacks despite colchicine therapy, however. We recently treated a patient with FMF and chronic hepatitis whose uncontrolled attacks with colchicine therapy completely resolved after interferon α treatment.

A 40-yr-old man was referred to our gastroenterology department because of persistently elevated liver enzymes for the last 6 months. He had had typical attacks of FMF with abdominal pain and fever since the age of 16 yr. The disease was also present in his grandfather, one sister and a nephew. These relatives were symptom free with colchicine therapy and had no liver function abnormalities. Our patient began treatment with colchicine in 1976 and initially he used the drug intermittently. Because his attacks continued to occur twice a week, he was advised to take 1.5 mg/day of colchicine regularly. For the previous 6 months, he had been taking 2 mg of colchicine per day without any decrease in the number or severity of attacks. On presentation to us, his ALT was 132 IU/l, AST 94 IU/l, alkaline phosphatase 90 IU/l, GGT 83 IU/l, total protein 6.6 g/dl, albumin 4.5 g/dl and total bilirubin 1.0 mg/dl. His upper abdominal ultrasonography was normal. HBsAg and HBeAg were positive, and HBV DNA was 16 pg/ml. A liver biopsy was performed and chronic hepatitis with moderate activity was found.

Interferon α (Intron A, Schering Plough) was started at 10 million units three times a week. Immediately after the first dose, his FMF attacks disappeared completely. He is at the sixth month of treatment and did not have an attack until now. His liver enzymes began to fall during the first month of treatment and at the sixth month his ALT was within normal limits. The patient has stopped taking colchicine for the last 4 months on his own initiative, against our recommendations.

The pathogenesis of FMF attacks is poorly understood. Increased levels of tumour necrosis factor (TNF) α and decreased inhibitors of complement fragment C5a and interleukin-8 may individually or concurrently cause the inflammation [1, 2]. Interferon α has some anti-inflammatory properties but, interestingly, although the actions of interferon α on TNF are not as evident as those of interferon gamma, it was shown to increase TNF and TNF receptors in recent studies [3]. Thus, the mechanism of