

Discontinuing long-term iloprost treatment for Raynaud's phenomenon and systemic sclerosis: a single-center, randomized, placebo-controlled, double-blind study

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K E Y W O R D S

Raynaud's phenomenon, scleroderma, sclerosis, iloprost, randomized study, long-term treatment

A B S T R A C T

Background Iloprost has been reported to reduce Raynaud's phenomenon (RP) and to inhibit progression of systemic sclerosis (SSc).

Objective The aim of our study was to compare monthly iloprost infusions with placebo in patients treated long-term.

Methods Seventeen patients, six with RP and 11 with SSc on monthly treatment with iloprost, received either a 3-hour intravenous infusion of iloprost or an equal volume of placebo once per month for 4 months in a monocentric, randomized, placebo-controlled, double-blind study. Raynaud attacks as measured by diary entries, skin temperature, skin sclerosis, fist closure, mouth opening, and digital ulcers were recorded during the observation period.

Results Whereas mouth opening improved significantly ($p = 0.043$) in the iloprost-treated group, RS improved in both patient groups. However, no significant differences were found in the outcome measures.

Conclusion Although iloprost influences the inflammatory cascade in SSc, no statistical differences were seen in our study, indicating that treatment strategies with iloprost should be modified.

Introduction

Systemic sclerosis (scleroderma) (SSc) is an autoimmune disease of unknown origin affecting multiple organ systems (1). Treatment of SSc is still challenging and should specifically target the pathomechanism of the disorder, including the vascular and the immune systems and the connective tissue (2).

Many vasoactive drugs such as calcium channel blockers, ACE inhibitors, angiotensin-II-receptor antagonists, and sildenafil have proven to reduce Ray-

naud attacks (3–5). Further, bosentan has been reported to be effective in the inhibition of new acral skin ulcers (6).

Iloprost, a stable prostacyclin analogue, is not only an effective vasodilator that reduces Raynaud attacks, but also an inhibitor of the adhesion and activation of thrombocytes that also has an antifibrotic effect (7) through suppression of transforming growth factor (TGF)- β -induced connective tissue growth factor production of scleroderma fibroblasts, which are re-

sponsible for the abundant collagen production. Serum levels of soluble adhesion molecule 1 (sICAM-1), vascular adhesion molecule 1 (sVCAM-1), and E-selectin are elevated in SSc and are a significant marker of microvascular damage correlated with disease activity (8, 9). Iloprost infusions significantly reduced the serum level of all markers (10) for 6 months after the infusions (11). Iloprost may therefore play an important role in the inhibition of the pathways in the pathogenetic process in RP and SSc.

We recently published a review of long-term studies (12). In line with this evaluation, we have treated our RP and SSc patients according to a standardized treatment protocol since 2003, with a 3-hour infusion on 5 consecutive days as initial therapy and a 3-hour infusion once a month regularly as maintenance therapy in the highest tolerated dose of 0.5 to 2.0 ng/kg/min.

The aim of our study was to evaluate whether discontinuation of the monthly iloprost infusion has an effect on the Raynaud attacks. We therefore designed a randomized study to compare the effect of the monthly iloprost infusion with placebo.

Methods

Patients

The trial was approved by the local ethics committee, and all participants gave written informed consent. Seventeen patients (13 women, 4 men) with RP and/or SSc were selected for the study. These patients had been on maintenance therapy with iloprost for 2 months to 10 years with a 3-hour infusion of iloprost once a month. All of these patients had had initial therapy with iloprost on 5 consecutive days with a well-tolerated dose of 0.5 to 2.0 ng/kg/min for 3 hours. The diagnosis of RP was based on the verification of vasospasm by pulse oscillography upon cold provocation with a 10°C water bath. Scleroderma was classified according to the Le Roy criteria and also met the ACR criteria (13).

The demographic data are outlined in Table 1, which also shows risk factors and organ involvement in the investigated patients. Eight patients described their disease as stable at the time of enrollment, two patients reported recurrent flares, six patients reported disease progression, and one had noticed improvement.

Study design

In this single-center, randomized, placebo-controlled, double-blind study, every patient received an infusion with iloprost upon enrollment (visit -1). One month thereafter (visit 0, baseline), patients were

assigned using a web-based randomization service (www.randomizer.at) to one of the two treatment groups, with either a 3-hour infusion with iloprost or placebo (0.5% sodium chloride solution). The same therapy was given at the visits in the following 4 months (visits 1 to 4). The infusion or a similar volume of placebo was administered through a peripheral vein at the individually tolerated dose.

Inclusion criteria: Male and female patients at least 18 years old with RP with or without SSc already on therapy with iloprost were selected to enter the study. Patients were allowed to continue their individual medications, such as vasoactive substances or immunosuppressive drugs. Women of childbearing age were asked to practice a medically accepted method of birth control and to have a negative pregnancy test on the morning of the day of every infusion. Different researchers were involved: one that used the randomization service, another that prepared the iloprost/placebo infusions, and a third that performed thermography and collected diary data.

Exclusion criteria: Bleeding diathesis or platelet disorder, therapy with anticoagulants, therapy with acetylsalicylic acid within 2 weeks of inclusion, active gastrointestinal ulcer, polytrauma, intracranial bleeding, severe untreated diabetes or hypertension, hyperviscosity, severe coronary heart disease, unstable angina pectoris, myocardial infarction within 6 months, heart failure NYHA II-IV, relevant arrhythmias, pulmonary edema, chronic alcoholism, nicotine abuse, and severe acute infection.

Evaluations

Diary: Patients received a questionnaire in diary form and were instructed to record daily for the study period of 5 months the total number of Raynaud attacks, an estimate of the duration of an average attack, and the duration of the longest attack in minutes. A 10-point, patient-completed scale was used to determine the severity of attacks, in which 0 represented no attack and 10 represented a very severe attack. Patients were asked for subjective symptoms such as numbness, burning, pain, tingling, and hand disability. Patients started the diary at study entry (visit -1) and made daily entries until the study end (visit 4). Diary data between two visits were summarized, yielding monthly aggregations of month 0 (= baseline, comprising data from visit -1 to visit 0) to month 4.

Thermography: Digital temperature was measured by thermography (FLIR Thermacam PM 595, FLIR Systems, Sweden) before and after infusions at every visit starting with study entry (visit -1). Before recording, patients had to acclimate themselves for 15 minutes in a special climatic chamber under stable environmental

Table 1. Demographic findings in patients with Raynaud's phenomenon with and without scleroderma.

RS/ Scl (years)	Age	Sex	Rayn- aud (years)	Scl (years)	Course of disease	External risk factors	Lung involv.	Esoph. involv.	Auto- antibodies	Skin ulcer/ calcinosis	Vasoac- tive drugs	Immuno- supp./ antiprolif. drugs	Iloprost (months)	Total dose/ day (µg)	Dose (ng/kg/ min)
RP	64	M	1		Stable	No	No	No	No	No/no	Yes	No	2	11	0.84
RP ⁱ	37	F	1		Progressive	No	No	No	ANA, Scl 70, RF	No/no	Yes	No	2	10.8	1.05
RP	56	M	6		Stable	Cold exposition, vibration traumata, talcum	No	No	ANA, Ro/SS-A, La/SS-B	No/no	No	No	49	11.6	0.78
RP	48	F	3		Stable	Cold exposition	No	No	ANA, CENP-B, RF	No/no	Yes	No	12	10.6	0.8
RP ⁱ	39	F	1		With flairs	Cold exposition	No	No	No	No/no	Yes	No	5	9	0.58
RP	50	F	4		Stable	Cold exposition	No	No	ANA	No/no	No	No	17	7.2	0.6
Scl ltd	72	F	2	1	Stable	No	PAH	Yes	ANA, Scl-70	No/no	No	Yes	13	10.6	0.94
Scl ltd	64	F	8	7	Progressive	No	Fibrosis, e.i. PAH	Yes	ANA, CENP-B	No/no	Yes	No	43	13.2	1.12
Scl diff	55	F	12	12	With flairs	No	PAH	Yes	CENP-B	Yes/yes	Yes	No	72	10	0.81
Scl ltd	67	F	13	10	Progressive	No	E.i. PAH	Yes	ANA, CENP-B	No/no	Yes	No	20	9.8	0.87
Scl diff	60	F	4	4	Stable	Silicon implantation	Fibrosis	No	ANA	Yes/yes	Yes	Yes	36	11.6	0.84
Scl ltd	72	F	10	10	Improved	No	Fibrosis	Yes	RF	Yes/no	No	No	96	12	1.1
Scl ltd	65	M	11	11	Progressive	Cold exposition, vibration traumata	Fibrosis, e.i. PAH	No	ANA, Scl 70	No/no	No	No	123	13	0.96
Scl diff	55	F	9	9	Stable	No	Fibrosis, PAH	Yes	ANA, Scl 70	No/no	Yes	Yes	70	10	0.7
Scl ltd	72	F	10	8	Progressive	No	Fibrosis	Yes	ANA, U1-RNP, RNP-Sm, Sm	Yes/no	Yes	Yes	47	13.2	1.46
Scl ss	63	F	13	6	Stable	Cold exposition	PAH	Yes	ANA, U1-RNP, La/SS-B	No/no	Yes	No	96	9	0.56
Scl diff	54	M	1	1	Progressive	No	discrete fibrosis	Yes	ANA, U1-RNP	No/no	Yes	Yes	2	10.2	0.56

Note: 1 = undifferentiated scleroderma; antiprolif = Antiproliferative; cm = centimeter; diff = diffuse; esoph = esophagus; e. i. = exercise-induced; f = female; immunosupp = immunosuppressive; involv = involvement; ltd = limited; m = male; min = minutes; NA = not applicable; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon; SSC = systemic sclerosis; Scl = scleroderma; Scl ss = scleroderma sine scleroderma.

conditions (temperature: 21 ± 1 °C, humidity: $48 \pm 2\%$). Temperature was visualized using a color scale between black and white. Black represented the coolest area and white the hottest area. For documentation, temperature was measured in two circular areas (radius 18 and 15 mm) on the proximal and the distal interphalangeal joint of the coolest finger of each hand. The temperatures of both areas of both hands were averaged.

Scores in scleroderma patients

Modified Rodnan score: The extension and severity of skin involvement were determined using the modified Rodnan score (13, 14).

Ischemic lesion score: The ischemic lesion score was determined as the sum of the scores for the extent, depth, and total number of ischemic lesions on each finger and toe. The extent was rated as follows: 0 = no lesion, 1 = lesion measuring less than 0.2 cm, 2 = lesion measuring 0.2 to 0.4 cm, and 3 = lesion measuring more than 0.4 cm. Depth criteria were as follows: 0 = no lesion, 1 = fissure, 2 = superficial ulcer, and 3 = deep ulcer.

Fist closure was measured as the distance in millimeters between the tip of the third finger and the distal wrist fold. The measures of the left and right hand were averaged. Mouth opening was measured as the distance in millimeters between the upper and lower central incisors. For safety reasons, blood pres-

sure and heart rate were measured before, during, and after the infusion.

Statistical analyses

Data were entered into a computerized database and analyzed. Age, temperature, and parameter changes are reported as mean (standard deviation, SD), and for all other continuous variables the median is used (range: minimum-maximum). For counts and categorical data, frequencies are displayed with percentages in parentheses. To determine the statistical significance of group differences, the Wilcoxon rank-sum test was used; for changes within groups we used the Wilcoxon signed rank test. To assess the thermography data, an analysis of variance (ANOVA) with repeated measures was performed. To adjust the alpha level in multiple comparisons, we used the Bonferroni correction. All computations were carried out using the statistical package SPSS for Windows version 14®. A *p* value of < 0.05 was considered significant.

Results

Patients

All 17 patients with RP with or without SSc assessed for eligibility were included and all completed the study. The study period lasted from April to November 2006. The baseline characteristics were similar in the iloprost and the placebo groups (Table 2).

Table 2. Baseline data.

Variable	Treatment			
	Iloprost <i>n</i> = 10		Placebo <i>n</i> = 7	
Sex: m/f – N ⁰ (%)	3 (30%)	7 (70%)	1 (14%)	6 (86%)
Age (yrs) – mean (SD)	57.8	(11.67)	59.1	(10.08)
Underlying disease: SSc/RP – N ⁰ (%)	6 (60%)	4 (40%)	5 (71%)	2 (29%)
Diagnosis				
Raynaud phenomenon – N ⁰ (%)	4	(40.0%)	2	(28.6%)
Scleroderma diffuse – N ⁰ (%)	2	(20.0%)	2	(28.6%)
Scleroderma limited – N ⁰ (%)	4	(40.0%)	3	(42.9%)
Number of Raynaud attacks/day – median (range)	1.06	(0.1–3.0)	1.37	(0.0–2.5)
Duration of Raynaud attacks – median (range)	11.72	(2.0–304.3)	14.98	(3.3–1440.0)
Severity of Raynaud attacks – median (range)	1.83	(1.1–5.0)	2.33	(0.9–5.1)
Digital temperature (°C) – mean (SD)	29.5	(3.42)	29.2	(3.23)
Rodnan score of SSc patients – median (range)	15.5	(1–40)	11.0	(0–19)
Fist closure of SSc patients (mm) – median (range)	4.78	(3.3–7.0)	5.30	(3.0–5.5)
Mouth opening of SSc patients (mm) – median (range)	2.65	(2.0–4.0)	3.50	(2.8–5.5)

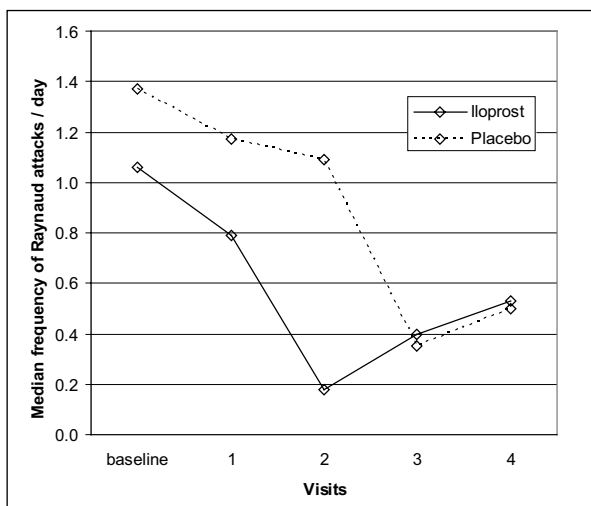


Figure 1. Median number of Raynaud attacks per day.

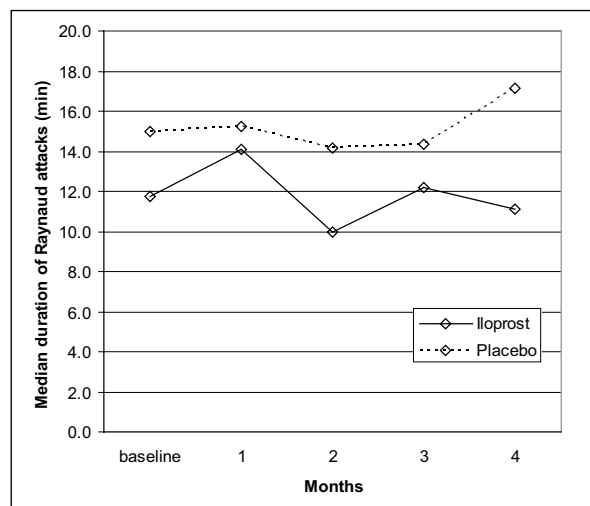


Figure 2. Median duration per Raynaud attack.

Side effects of treatment were rare. In the iloprost group one patient had epistaxis and dizziness and one patient a headache; in the placebo group, one patient had a headache.

Diary

Number of Raynaud attacks: The number of patients showing no attack at all during an entire observation interval increased from baseline to the end of the study. At baseline, all 10 patients (100%) in the iloprost group reported attacks whereas 7/10 patients (70%) were free of attacks at month 4. In the placebo group, 6/7 patients (86%) reported attacks at baseline but 5/7 patients (71%) at month 4. The median number of Raynaud attacks per day at baseline was 1.06 (range: 0.1–3.0) in the iloprost group and 1.37 (0.0–2.5) in the placebo group and decreased to 0.53 (0.0–1.2) in the iloprost group and 0.50 (0.0–3.0) in the placebo group at month 4 (Figure 1). The changes in the two groups (mean -0.70 [SD: 0.85] for iloprost; -0.48 [SD: 0.90] for placebo) did not differ significantly from each other ($p = 0.601$).

Duration of Raynaud attacks: The median duration of an attack in the 10 iloprost patients (100%) at baseline was 11.72 (range: 2.0–304.3) minutes and in the seven patients (70%) with attacks at month 4, 11.11 (3.3–250.7) minutes (Figure 2). In the placebo group, the median duration of a Raynaud attack was 14.98 (range: 3.3–1440.0) minutes in the six patients (86%) with attacks at baseline and 17.16 (range: 3.0–1440.0) minutes in the five patients (71%) with attacks at month 4. The changes in the two groups (mean -10.08 [SD 19.78] for seven iloprost patients; -0.76 [SD 3.71] for five placebo patients) did not differ significantly ($p = 0.432$).

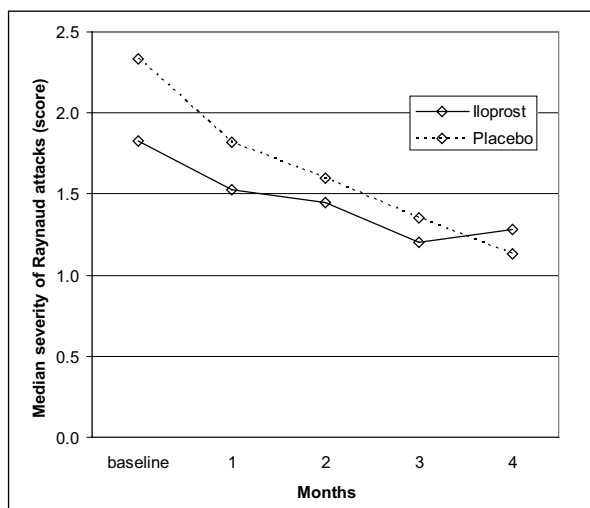


Figure 3. Median severity per Raynaud attack.

Median severity: The median severity of a Raynaud attack at baseline was 1.83 (range: 1.1–5.0) points in the 10 (100%) iloprost patients and 2.33 (range: 0.9–5.1) in the six (86%) placebo patients with attacks, which decreased to 1.28 (range: 0.9–4.5) for the seven (70%) iloprost and 1.13 (range: 0.3–5.0) for the five (71%) placebo patients with attacks at month 4 (Figure 3). The changes in the two groups (mean -0.02 [SD 0.77] points for seven iloprost patients; -0.05 [SD 1.03] for five placebo patients) did not differ significantly ($p > 0.999$).

Thermography

The mean digital temperature, measured in each case before the administration of the infusions, increased from the baseline (visit 0) from 29.5°C [SD

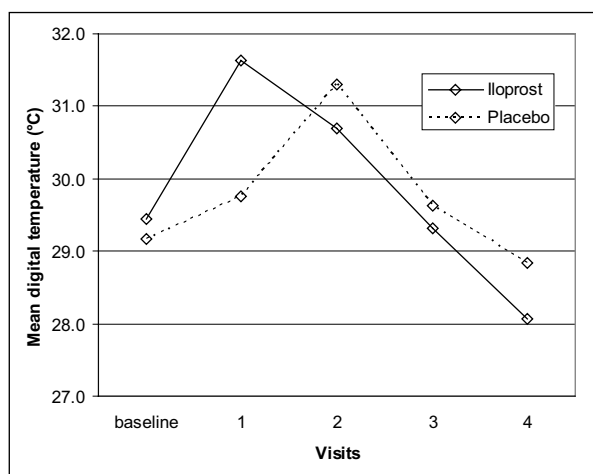


Figure 4. Mean digital temperature before infusions.

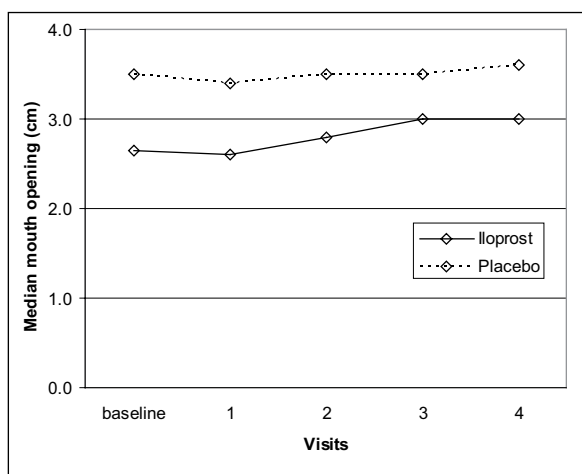


Figure 5. Median value for mouth opening (cm) in scleroderma patients.

3.42] to 31.6°C [SD 2.95] at visit 1 in the iloprost group and then decreased to 28.1 °C [SD 3.44] at visit 4 (Figure 4). In the placebo group, the digital temperature increased from baseline (29.2°C [SD 3.23]) to visit 2 (31.3°C [SD: 3.34]) and then decreased to visit 4 (28.8°C [SD 3.79]). The ANOVA results showed a significant effect of the temperature over time ($p = 0.006$) with no differences between the two groups.

Scores

Scleroderma patients: The Rodnan scores in SSc patients, six of whom were treated with iloprost and five with placebo, varied greatly in both groups among patients and ranged at baseline from 1 to 40 in the iloprost group and from 0 to 19 in the placebo group, but the values showed no statistically significant difference for any patient throughout the entire study period. At study end, the modified Rodnan score ranged from 2 to 35 in the iloprost group and from 0 to 17 in the placebo group.

The ischemic lesion score (ILS) varied between 0 and 35 in the iloprost and between 0 and 20 in the placebo treated group with no relevant difference among the groups within the observation period. Similarly, fist closure showed no statistically significant changes in the verum and placebo group (data not shown).

Mouth opening: The median values for mouth opening differed considerably even at the beginning of the study in both the iloprost and placebo groups. Mouth opening increased between baseline and visit 4 in the iloprost group by 0.47 (SD 0.38) cm, indicating a statistically significant change ($p = 0.043$); in the placebo group the increase of 0.06 (SD 0.92) cm was not statistically significant (Figure 5).

Discussion

In this study, the number of patients with Raynaud attacks and the severity of the attacks decreased, and no worsening of the disease was observed in either group. There was a trend that iloprost reduced the number of Raynaud attacks, but statistical analyses gave no significant difference in the number, duration, or severity of Raynaud attacks or temperature before and after infusion in patients with RP with or without SSc. Mouth opening improved significantly in the iloprost-treated SSc patients but no difference in the Rodnan and ischemic lesion scores or in fist closure was seen during the observation period.

Limitations of the study were that the treated patient groups were relatively small and highly heterogeneous and that the follow-up period of 4 months was relatively short. The onset, severity, and course of the disease were very different from patient to patient, as was treatment duration with iloprost before enrollment. Furthermore, patients were being treated with various vasoactive and immunosuppressive therapies according to organ involvement and severity of the disease before the study. We did not want to withdraw previous medications for ethical reasons and to rule out unwanted changes in the course of disease.

Several studies have shown the efficacy of iloprost in RP and SSc (7, 15–22). Mazzone et al. observed a significant increase in skin temperature and oxygen saturation after iloprost infusions in two different studies in comparison with sodium chloride infusion and acetylsalicylic acid (17, 19). In other studies, the beneficial effect of iloprost on the microcirculation and the increase in the digital peripheral blood flow lasted for 4 to 9 weeks after infusion (15, 16, 20).

Caramaschi et al. reported that the finger skin temperature increased not only immediately after the infusions but that the effect could be maintained for 1 month, in contrast to our data (23). However, iloprost could not influence skin temperature after cold provocation in their study. Our study was performed during the summer months, when the number of Raynaud attacks is generally diminished; existing differences so might not have appeared to the expected extent. We found that increasing skin temperature was strongly influenced by air temperature rising earlier in the iloprost group as seen in the first 2 months of the study period (Figure 4). At the end of the study period, in a rather rainy August/September at the beginning of the cold season, skin temperature had fallen in both the iloprost and placebo groups.

In a long-term not placebo-controlled study, Biasi et al. treated patients with cyclic 5-day infusions every 3 months for 1 year (18). They found a significant decrease in skin sclerosis and ischemic lesion score. Della Bella et al. (21) compared intravenous iloprost to oral nifedipine given for 5 days and then repeated for 1 day every 6 weeks for 1 year in a prospective, randomized, parallel-group, observer blind trial. The capillaroscopic patterns and skin scores showed significant improvement. Similarly, in contrast to the stable Rodnan score, mouth opening improved significantly in our patients in the iloprost group, which can also be seen as a marker of the extent of facial skin sclerosis and therefore might indicate that iloprost is efficacious.

Filaci et al., however, reported a lack of clinical efficacy for iloprost (25). They compared iloprost infusion therapy with a combination therapy of cyclosporine A and iloprost administered for 5 days every month. A significant improvement of the plicometer skin score and the capillaroscopic parameters was seen only in the combination group.

No long-term studies of more than 1 year have been performed so far, and iloprost has been administered to patients with RP and/or SSc in several studies with different treatment protocols and outcome measurements that preclude direct comparison. Infusion rates of 0.5 to 2.0 ng/kg/min were used for 5 to 8 hours daily. In short-term studies, iloprost was given on 3 to 14 consecutive days. The length of follow-up

in long-term studies varied from 1 to 12 months. Most of the studies were not placebo controlled, although a response to placebo has also been reported in RP (22, 26).

Contrary to our expectations, although the number of patients with Raynaud attacks and the severity of attacks in iloprost-treated patients improved, we did not see significant differences in the outcome measures. The reasons might be too brief an observation period, that the study was performed in the summer months, during which RP tends to improve, or an insufficient treatment regimen with an effective agent. Milio et al. used three different treatment protocols in comparison; the best seemed to be infusions on 5 working days over 2 weeks (10 days), repeated every 3 months taking quality of life and dimensions of attacks into account (26).

The effective dose of iloprost is highly individual and seems to vary in a relatively wide range. A comparative randomized clinical trial did not find any difference in the efficacy of low-dose (0.5 ng/kg/min) and high-dose (5 ng/kg/min) iloprost (27).

To validate the modified Rodnan score, the study period was too short to see changes or to recognize stabilization of disease, although in the inflammatory active disease stage the score could worsen in a short period in spite of treatment. This was not the case in our patients, particularly because four were on additional immunosuppressive therapy.

Thus, although we could not prove a significant effect of iloprost treatment, we think that iloprost might still have a place in the therapeutic armamentarium in RP and SSc with treatment protocols in which dosage, infusion time, and treatment intervals are modified.

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