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Cardiovascular risk and prostanoids in systemic sclerosis

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ABSTRACT

Objectives. *Systemic sclerosis (SSc) is characterized by Raynaud's phenomenon and frequent cutaneous ulcers. In patients resistant to oral treatments, i.v. prostanoids are usefully employed. Some anecdotal reports underlined the potential risk to develop cardiovascular ischemic complications in prostanoid-treated SSc patients.*

Methods. *Fifty SSc patients (group 1: 44 female and 6 male, mean age 60.4 ± 13.8SD) undergoing long-term prostanoid therapy (iloprost or alprostadil) and 42 control patients (group 2), treated with only oral drugs, were retrospectively evaluated for the cardiovascular risk and incidence of ischemic events.*

Results. *Ischemic cardiovascular complications, i.e., myocardial infarction or stroke, were recorded in a significantly higher number of patients undergoing prostanoid treatment compared to controls (group 1: 7/50, 14% vs. group 2: 1/42, 2.4%; p=0.041). Interestingly, these events were significantly more frequent in the subgroup of patients with high cardiovascular risk (group 1: 6/10, 60% vs. group 2: 1/19, 5.2%; p=0.0026).*

Conclusions. *The present study suggests a possible role of prostanoid treatment in the pathogenesis of ischemic cardiovascular complications in SSc patients non-responders to oral vasodilators and high cardiovascular risk.*

Since prostanoids represent the first choice treatment of the most severe scleroderma ischemic cutaneous lesions, cardiovascular risk should be carefully evaluated in all patients before therapy.

Introduction

Systemic sclerosis (SSc) is an immune-mediated disease of unknown aetiology characterized by diffuse microangiopathy and excessive fibroblastic activity with collagen deposition, involving the skin, lungs, heart, kidneys, and gastrointestinal tract (1, 2). Cutaneous and visceral organ involvement can largely affect the patient's quality of life and often the overall prognosis.

Cardiac involvement in SSc is recorded in approximately 20-25% of patients (3, 4). The most prevalent clinical manifestations are conduction defects and ventricular diastolic dysfunction secondary to myocardial fibrosis. Moreover, a coronary artery vasospastic phenomenon has also been described, and it has been suggested that this alteration may cause myocardial ischemia with angina symptoms as well as reperfusion injuries, leading to the development of myocardial fibrosis (3, 4). In SSc, coronary arteries are generally spared; moreover, the prevalence of cardiovascular ischemic events is comparable to that observed in the general population (3, 4).

In SSc patients, thallium perfusion studies have provided strong evidence that perfusion defects are common and can occur both at rest and in response to cold provocation (5). Myocardial involvement is the consequence of typical scleroderma microangiopathy with the possible contribution of atherosclerotic alterations, particularly in older subjects and/or longer disease duration (6).

Peripheral micro-vascular dysfunction is clinically evident and characterized by Raynaud's phenomenon and digital ulcers. The use of intravenous prostanoids represents the first line treatment of peripheral ischemic manifestations in SSc unresponsive to oral vasodilators (7).

Vasodilatation determined by these molecules could lead to a dipyridamole-like misdistribution of flow, causing ischemic complications in predisposed subjects (8). The present study aimed to evaluate the incidence of cardiovascular events in SSc patients treated with long-term intravenous prostanoids in comparison with patients undergoing oral drugs. Ischemic complications were also correlated with cardiovascular risk calculated before the treatment.

Patients and methods

We retrospectively evaluated the incidence of cardiovascular ischemic complications in 92 SSc patients, consecutively referred to our Rheumatology Unit since 2001. All patients were treated with calcium-channel blockers and 100 mg aspirin for typical ischemic skin ulcers and/or severe Raynaud's

phenomenon (Table I). In fifty patients, unresponsive to oral medications, intravenous prostanoids, namely iloprost or alprostadil were also administered. With regards to cardiovascular ischemic complications, patients treated with prostanoids (group 1) were compared with those undergoing chronic oral treatments only (group 2). Among patients of group 1, 33 were treated with iloprost and 17 with alprostadil.

Prostanoids were administered intravenously on 5 consecutive days; then, 1-2 infusions monthly (mean period of treatment 3.8±1.9 years). Iloprost (Schering AG, Berlin, Germany) was infused at 2.0 ng/kg/minute for 8 hours; while Alprostadil (Schwarz Pharma AG, Monheim, Germany) was infused at 6 ng/kg/minute for 3 hours.

Cardiovascular risk has been calculated for all patients, classifying them into three levels – low, medium and high risk – according to the method proposed by WHO for patients with arterial hypertension (9). This assessment includes three main categories, namely risk factors for cardiovascular diseases, target-organ damage, and associated clinical conditions. In all cases cardiovascular risk was calculated at the beginning of the follow-up on the basis of the above parameters; successively, all patients' clinical records were carefully evaluated for ischemic events.

Statistical significance was determined by Fisher's exact test and differences were considered significant when p was less than 0.05.

Results

Cardiovascular complications were ob-served in 7 patients from group 1 (5 treated with iloprost and 2 with alprostadil) and in only one from the control group (7/50, 14% *vs*. 1/42, 2.4%; p=0.041, Fisher's exact test) (Table II). Interestingly, in patients treated with prostanoids the ischemic complications were correlated to the level of cardiovascular risk (Fig. 1), particularly in the setting of patients with high risk (6/7). Although this latter was more frequently found at baseline in control patients (group 2: 19/42, 45.2% *vs*. group 1: 10/50, 20%; p=0.013), the prevalence of ischemic manifestations was statistically higher in prostanoid-treated patients compared to controls (group 1: 6/10, 60% *vs*. group 2: 1/19, 5.2%; p=0.0026, Fisher's exact test). Moreover, the analysis of the three main categories used for the calculation of cardiovascular risk excluded significant differences among high risk subsets in both groups. Neither anti-cardiolipine nor anti-β_2-glicoproteine I antibodies were found in our SSc patients developing ischemic events.

Ischemic complications included myocardial infarction or stroke, requiring always hospitalization; they appeared at variable time intervals from the last infusion and during the iloprost in only one patient (Table II). These complications completely recovered, in two cases after percutaneous coronary angioplasty; while the episode of bowel infarction (group 2) was responsible for the patient's death.

No statistically significant relationships between cardiovascular events and patients' age, cutaneous subsets, autoantibody pattern, visceral SSc manifestations, and/or response to the treatment were recorded.

Discussion

The prostacyclin analogues, iloprost and alprostadil, potent vasodilators and inhibitors of platelet aggregation, are used for the treatment of peripheral arterial occlusive diseases (10). Administration of prostanoids, mainly iloprost, is commonly used in SSc patients with severe Raynaud's phenomenon and/or other cutaneous ischemic manifestations (7). The clinical studies with alprostadil also report its effectiveness in SSc vascular complications along with better tolerability compared to iloprost (11).

Table I. Clinico-epidemiological and serological findings of SSc pts treated with and without prostanoids.

	Group 1	Group 2
No. of patients (female/male)	50 (44/6)	42 (40/2)
Mean age ± SD	60.4 ± 13.8	62.0 ± 11.9
Disease duration (years ± SD)	8.9 ± 6.4	8.5 ± 5.7
Cutaneous subsets L/I/D*	42/7/1	39/1/2
Serological subsets Scl70+/ACA+/ANoA**	14/15/11	13/25/8
Skin ulcers	74%	38%
Cardiovascular risk L/M/H***	33/7/10	17/6/19

*limited (L), intermediate (I), diffuse (D); **antitopoisomerase I (scl70) anticentromere (ACA), antinucleolar (ANoA); ***low (L), medium (M), high (H).
Group 1 and 2: treated with and without prostanoids, respectively.

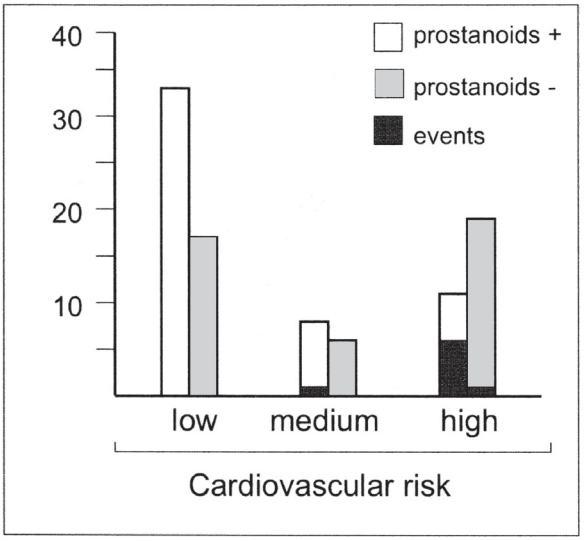

Fig. 1. Incidence of cardiovascular ischemic complications in SSc patients treated with or without prostanoids. A significantly higher number of events were noticed in prostanoid+ compared with control patients (7/50, 14% *vs*. 1/42, 2.4%; p=0.041, Fisher's exact test); moreover, a statistically significant difference between the two groups was also recorded in the setting of patients with high cardiovascular risk (group 1: 6/10 = 60% *vs*. group 2: 1/19 = 5.2%; p=0.0026, Fisher's exact test).

Table II. Ischemic events in scleroderma patients with and without prostanoid treatments.

Patients	age/sex	Co-morbidities	CV-risk°	Cutaneous subset§	Auto-antibodies#	Prostanoid	Treatment duration (months)	Infusions No.	Ischemic Event	Time after last infusion
1	83F	hypertension	high	L	0	alprostadil	16	30	myocardial infarction	14 day
2	69F	hypertension, diabetes	high	D	ANoA	iloprost	24	24	myocardial infarction	15 days
3	71M	obesity	high	L	Scl-70	iloprost	22	23	stroke	47 days
4	74F	hypertension, obliterans arteriopathy	high	L	Scl-70	iloprost	38	36	myocardial infarction	16 hours
5	63F	–	medium	I	Scl-70	iloprost	50	46	myocardial infarction	4 days
6	55M	obliterans arteriopathy, hypercolesterolemia	high	L	Scl-70	iloprost	20	20	myocardial infarction	during
7	69M	cryoglobulynemia, HCV hepatitis	high	L	ACA	alprostadil	32	30	stroke	2 hours
8	71F	ischemic cardiopathy	high	L	ACA	none	–	–	bowel infarction	–

°CV-risk: cardiovascular risk; §D: diffuse; I: intermediate; L: limited; #ACA: anti-centromere; ANoA: anti-nucleolar; Scl-70: anti-topoisomerase.

The results of this retrospective study suggest that SSc patients with high cardiovascular risk at baseline may have a significantly higher incidence of ischemic complications when treated with prostanoids. However, given the relatively small number of patients included in both groups a clear-cut pathogenetic relationship between hemodynamic effects of prostanoids and cardiovascular complications is difficult to definitely establish.

Hemodynamic effects of iloprost on heart rate, mean blood pressure, coronary vascular resistances were dose-dependent: distinct responses were achieved at a dose of 0.5 ng/kg/minute, while 4 ng/kg/minute induced almost maximal responses (8). In many subjects, side effects such as headache, nausea, and abdominal colics become intolerable when the dose exceeded 4 ng/kg/minute.

After iloprost infusion stopped, hemodynamic responses began to diminish, but up to five weeks later vascular resistances may be still somewhat lower than before treatment (12). Thus, cardiovascular effects of iloprost may continue after the end of infusion (13). In our patients, the sequence of events suggests a role of prostanoids on the ischemic events, particularly for patients 4, 6 and 7 (Table II), while the actual mechanism(s) involved in the remaining four cases are more questionable. However, the statistically higher incidence of these events in prostanoid-treated patients compared to controls, in whom high cardiovascular risk was significantly more frequent, suggests that prostanoids may represent an important pathogenetic co-factor.

A previous observation by Tedeschi *et al*. reported thrombotic events after 1, 5 and 22 days in 3/44 SSc patients undergoing iloprost infusion (14), but these findings were not confirmed by another clinical experience (15).

The present study firstly correlates the appearance of ischemic events in prostanoid-treated patients with the level of cardiovascular risk evaluated before the treatment. Therefore, the calculation of this latter may represent a useful, predictive tool in the therapeutic strategy of SSc peripheral ischemic manifestations.

To date, there are no validated cardiovascular risk charts for rheumatic diseases, and in particular for scleroderma patients. Various available methodologies are able to evaluate the risk only in the general population, whereas WHO guidelines for cardiovascular risk in hypertensive patients (9) seem to be more appropriate. Since this method includes the largest panel of risk factors, it can properly quantify the cardiovascular risk also in SSc patients; similarly to hypertension, SSc is characterized by diffuse vascular damage and possible multiple organ involvement.

Given their multiple therapeutic properties, including the neoangiogenesis promotion (7, 10, 11, 13, 16), prostanoids remain the first choice treatment of the most severe SSc ischemic cutaneous lesions; however, our data indicate that a careful evaluation of cardiovascular risk in all patients before the therapy is mandatory.

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