

Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis and the quality of life: a new therapeutic protocol

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Objectives. To evaluate the clinical efficacy and the effects on the quality of life of iloprost, a prostacyclin analogue, used according to a new protocol in patients with Raynaud's phenomenon secondary to systemic sclerosis.

Methods. In this randomized study, we treated 30 patients with iloprost, given by intravenous infusion, at progressively increasing doses (from 0.5 to 2 ng/kg/min) over a period of 6 h each day for 10 days in two consecutive weeks, with repeated cycles at regular intervals of 3 months for 18 months. The results were compared with those obtained in 30 other patients who received the same drug but with different dosing schemes.

Results. The total average daily duration of the attacks, the average duration of a single attack and the average daily frequency of the attacks were reduced significantly in all treatment groups, but the comparison between the groups demonstrated significant differences between patients treated with the new protocol and the others at later times (12 and 18 months). The effects on the quality of life in the group treated with the new protocol, evaluated with the Short Form-36, demonstrated a marked improvement regarding both the scale relating to the physical aspect of the illness and, especially, the scale relating to the mental aspect.

Conclusions. In patients with systemic sclerosis, cyclic intravenous iloprost infusion is efficacious in the treatment of Raynaud's phenomenon. The protocol that we used, compared with others, not only has favourable clinical effects but also leads to a marked improvement in the quality of life.

KEY WORDS: Systemic sclerosis, Raynaud's phenomenon, Iloprost, Quality of life.

Systemic sclerosis (SSc), as is well known, is a condition of the connective tissue, characterized by obliterative vascular lesions that affect, above all, the small vessels, and the involvement in the advanced stages of various organs and apparatus [1–3].

In most cases, the precocious clinical manifestations are acrovascular and manifest themselves as Raynaud's phenomenon; in more advanced phases, there are necrotic and/or ulcerative ischaemic lesions [4]. Often Raynaud's phenomenon precedes, perhaps by several years, the clinical onset of the illness [5–7]. Its physiopathological mechanism is still not clear [8], but some factors are clearly evident: structural and functional alterations of the endothelium with reduced production of nitric oxide and prostacyclin [9–11]; activation of white cells with the release of free O₂ radicals [12, 13]; and platelet activation, with an increase in viscosity and aggregation.

The treatment of systemic sclerosis, in particular the vascular manifestations, includes the following objectives: the reduction of vasospastic phenomena; improvement in vascular permeability, counteracting endothelium dysfunction and leucocyte migration; control of the haemorrhological component, also by an anti-platelet action; the prevention of visceral involvement; and improvement in the quality of life.

Many substances may be used to achieve these aims. Among these, a synthetic form of prostacyclin, iloprost, is the most promising as it is able to carry out numerous actions, as reported in Table 1 [14–17].

Several studies have shown the effectiveness of iloprost in the treatment of the vascular manifestations of SSc using different but equally effective protocols [18–22]. Because there is no standard protocol, we need a therapeutic one that is distinguished by its effectiveness in improving the quality of life, because we are concerned with chronic patients treated day by day throughout their life [23, 24].

The objective of this study was to evaluate the validity of a new protocol, taking into consideration not only the clinical efficacy of the drug with respect to the vascular manifestations of SSc, but also its effects on the quality of life.

Methods

Study design and treatment

The protocol provides for the intravenous administration, by means of a peristaltic pump, of iloprost at progressively increasing doses (from 0.5 to 2 ng/kg/min) for 6 h a day. The treatment proceeds for 10 days for two consecutive weeks (5 consecutive days + 2 days of interruption + 5 consecutive days) with repeated cycles four times a year at regular intervals of 3 months.

Thirty patients suffering from SSc with secondary FR were treated during a 2-yr period with the protocol described above (group A). They were compared with 30 other patients with a similar disease who had received different dosing schemes of the

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TABLE 1. Pharmacological effects of iloprost

Inhibition of platelet adhesiveness and aggregation, interacting with receptors of prostacyclin
Inhibition of proliferation of smooth muscle cells of the media
Profibrinolytic activity
Vasodilator effect, with consequent improvement of the microcirculatory flow
Inhibition of chemotaxis and activation of white cells
Reduction of expression of adhesion molecules
Reduction of production of superoxide anion by leucocytes
Inhibition of the platelet-leucocyte interaction
Stimulation of formation and growth of collateral circulation
Restoration of the equilibrium between the system regulating microvascular flow and the microvascular defence system, with a reduction in endothelial permeability and inhibition of the vasoconstrictive activity of thromboxane A ₂ , serotonin, leukotrienes and endothelins

drug, administered by the same means: 15 of them were given an infusion each month (group B1), according to one of the more commonly used protocols, and the others were given 20 consecutive infusions every 6 months (group B2), according to a protocol that we have used in the past.

The patients were randomized with an allocation sequence obtained using a random-number table (sealed envelopes).

The study used a prospective, controlled, open design with parallel groups, and was performed between February 2003 and March 2005. It complied with the Consolidated Standards of Reporting Trials (CONSORT) statement [25]. The protocol was approved by the appropriate ethics committee of the University Hospital P. Giaccone of Palermo.

Patients

We enrolled patients suffering from SSc, with either diffuse or limited skin disease, with secondary Raynaud's phenomenon (RP). The diagnosis of SSc was made according to criteria described by Le Roy *et al.* [3]. The diagnosis of RP was based on a history of episodic digital pallor and/or cyanosis in response to cold exposure or emotional stress, and was confirmed by capillaroscopic examination. Males and females were included and all patients were at least 18 yr old. Also, they had to have an average of at least eight Raynaud's attacks per week.

Exclusion criteria were pregnancy, the presence of platelet alterations, the occurrence of AMI, unstable angina, strokes and TIA within the past three months, surgical sympathectomy in the last 12 months, and the presence of RP connected to other pathologies.

Calcium antagonist drugs, α -blockers and other vasodilators used for the treatment of RP were suspended at least a month before the infusion period, while angiotensin-converting enzyme inhibitors and calcium antagonists used for the treatment of accompanying arterial hypertension were maintained with the same dosing scheme for the duration of the study.

All patients were informed about the nature and aim of the study, and provided written consent to their participation in the study.

Procedures, outcomes and measurement

All patients were submitted to clinical and instrumental evaluation to define their characteristics and any possible subtypes. Patients with serious organ damage were excluded.

On admission, all subjects underwent a medical examination and also answered a questionnaire on personal and medical items,

TABLE 2. Patients' characteristics at baseline

	Group A	Group B1	Group B2
Number of patients	30	15	15
Age, yr: mean (s.d.)	39 (21)	40 (21)	39 (20)
Sex: no. of females (%)	25 (83)	12 (80)	12 (80)
Smokers: no. (%)	13 (43)	8 (53)	7 (46)
Clinical history			
Time since appearance of illness: yr (s.d.)	6 (3)	5 (4)	6 (4)
Weekly frequency of the attacks: no.	>8	>8	>8
Clinical features			
Ulcers: no. (%)	6 (20)	3 (20)	3 (20)
Oesophagus alterations: no.	1	—	1
Myocardial alterations: no.	—	—	—
Pulmonary hypertension: no.	—	—	—
Renal alterations: no.	—	—	—
Laboratory features			
Immunological alterations: no. (%)	24 (80)	13 (86)	13 (86)
Increase in ANA: no. (%)	20 (66)	9 (60)	8 (53)
Increase in ACA: no. (%)	19 (63)	8 (53)	8 (53)
Increase in anti-Scl 70 antibodies: no. (%)	4 (13)	2 (13)	3 (20)
Increase in anti-RNP antibodies: no. (%)	7 (23)	4 (26)	2 (13)
Capillaroscopic changes: no. (%)	26 (86)	13 (86)	14 (93)

including age, past medical history and the use of medications. Digital cutaneous lesions were recorded before the start of the study. Patients underwent: capillaroscopy, barium oesophagography, echocardiography, myocardial scintigraphy, chest radiography, high-resolution renal sonography; and laboratory tests comprising determination of immunoglobulins (Ig) A, G and M, testing for autoantibodies ANA, ACA, anti-double-stranded DNA, anti-Scl70 (anti-topoisomerase), anti-SSA, anti-SSB, anti-SM, anti-RNP and anti-Jo1.

Table 2 shows the baseline characteristics of the patients.

The clinical outcomes were the duration, number and severity of Raynaud's attacks, which were recorded in a diary kept by the patients. Each patient had to record the number of crises each day, as well as the duration of each attack and its severity on a visual analogical scale 10 cm long.

From an analysis of the daily record sheets, we calculated the following: (i) the total average daily duration of the attacks (TADDA), obtained by dividing the total duration in min of attacks during a given two-week interval (observation period) by the number of diary days; (ii) the average duration of a single attack (ADSA), by dividing the overall duration by the number of attacks during the observation period; (iii) the average daily frequency of the attacks (ADFA), by dividing the total number of attacks during the interval considered (2 weeks) by the number of diary days; and (iv) the severity of the attacks, measured on a visual analogical scale; this was designated the Raynaud's condition score (RCS) and was calculated as the arithmetic average of the daily scores during the interval considered (2 weeks).

Tests were made on all the groups under treatment before the start (T0), and after 3 months (T3), 6 months (T6), 12 months (T12) and 18 months (T18).

The effects on the quality of life were evaluated by means of the Short Form-36 (SF-36), taking into account eight parameters according to a scale from 0 to 3 (physical activity, physical health, physical pain, social activity, emotive state, mental health, general health, and vitality) [26–28]. The findings relative to the test were done at times T0, T6, T12 and T18 in the various groups.

The tolerability of the drug was studied by means of clinical parameters, making note of any symptoms present in the patient and measuring arterial pressure before, during and at

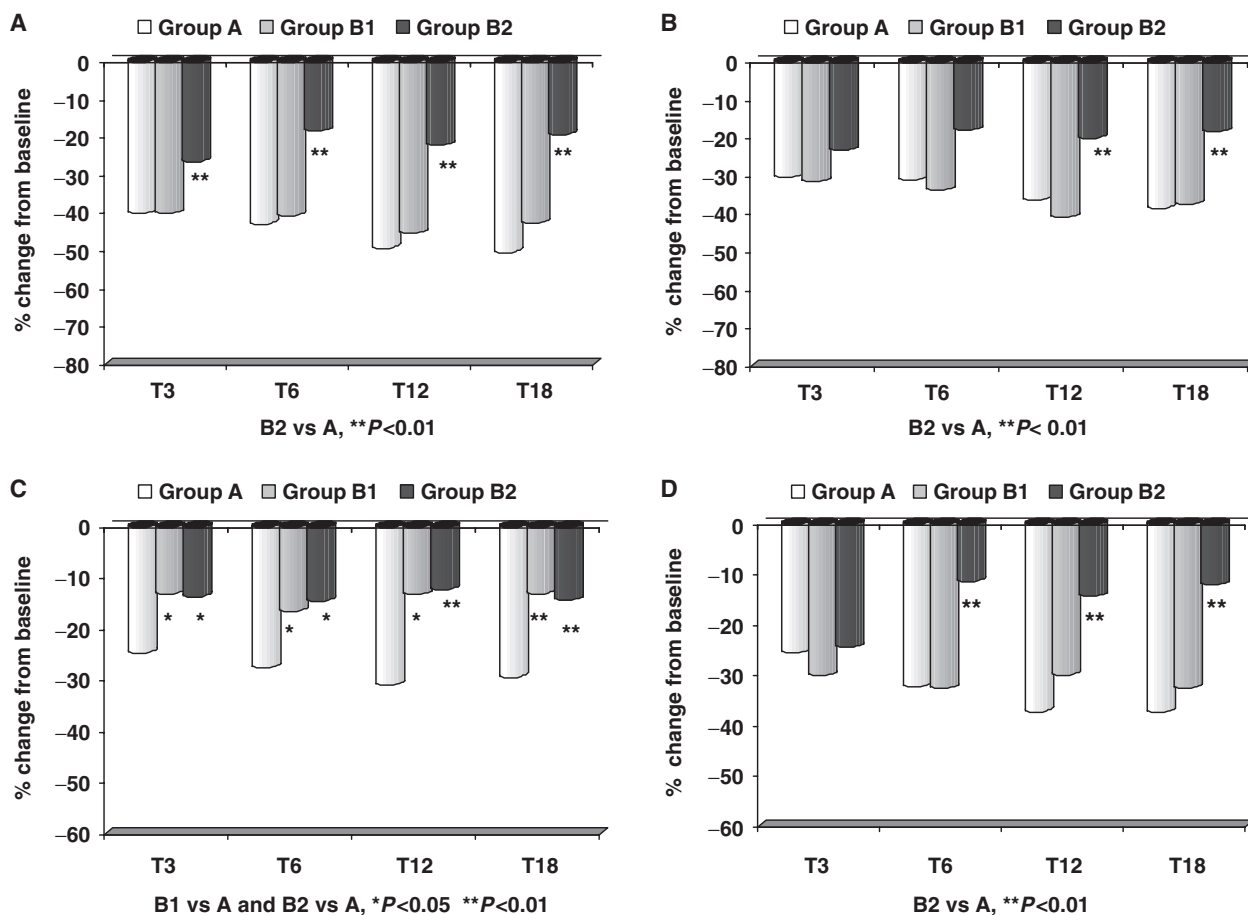


FIG. 1. Changes from baseline in (A) total average daily duration of attacks (TADDA), (B) average duration of single attacks (ADSA), (C) average daily frequency of attacks (ADFA) and (D) severity of attacks (RCS).

the end of each infusion, as well as with laboratory parameters. In this way the main haematochemical and haemocoagulative parameters were determined at the beginning and end of each infusion cycle, and at regular 6-month intervals.

Sample size and statistical analysis

To detect a decrease of 20% in the mean total duration of daily attacks (a reduction considered to be clinically relevant), the number to be included was 14 subjects per arm (α , 0.05; β , 0.10).

Because we compared two standard regimens (groups B1 and B2), we included twice the number of patients in the experimental arm.

Statistical analysis was performed on the data using the Statview Program (Abacus Concepts).

Means and standard deviations were calculated for the total daily duration, single duration, frequency and severity of Raynaud's attacks; the differences were analysed by means of Student's *t*-test for paired data to compare with basal values the results at the various observation times, in each treatment group, and by means of Student's *t*-test for unpaired data to compare the various groups.

Clinical changes were assessed as percentage variations in the clinical parameters and, regarding the effects on the quality of life, the parametric scales of the SF-36 were compared using Student's *t*-test for unpaired data [29].

P values less than 0.05 were considered significant.

Results

All the patients in each group completed all cycles of infusion treatment.

The total average daily duration of the attacks (TADDA), whose basal values did not present differences between the groups, were reduced significantly both in group A and in the control groups. In particular, in group A the percentage reduction settled down to around 40% after 3 and 6 months (39.9 and 43.1%, respectively), becoming more noticeable later (50.0% at T12 and 51.1% at T18). More or less the same values were observed in the patients of group B1 at 3 and 6 months (reductions of 38.2 and 1.3%, respectively); the later results regarding the percentage difference were less relevant with respect to group A (47.2% at T12 and 44.6% at T18). In group B2, on the contrary, the differences in values between the starting times and those further on were less relevant (22.7% at T3, 18.7% at T6, 23.8% at T12, 21.0% at T18) (Fig. 1A). The comparison between the groups demonstrated a statistically significant difference between group A and group B2, especially at T6, T12 and T18 (Table 3).

The average duration of a single attack (ADSA) showed similar behaviour; it was reduced significantly in all groups and at various observation times: the percentage differences with respect to base values were more or less the same in group A (differences ranging between 28.6 and 37.7%) and in group B1 (between 28.2 and 39.0%), but were noticeably smaller in group B2 (between 16.1 and 23.3%) (Fig. 1B). The statistical comparison between the groups at various times shows significant differences at the later times (T12 and T18) between group A and group B2 (Table 4).

TABLE 3. Total average daily duration of attacks (TADDA)

Observation time (months)	Duration (min)		
	Group A (n = 30)	Group B1 (n = 15)	Group B2 (n = 15)
T0	72.3 ± 22.9	73.1 ± 23.6	71.4 ± 22.4
T3	43.4 ± 15.4	43.1 ± 14.6	51.7 ± 15.0
T6	41.1 ± 14.1	42.9 ± 14.5	58.1 ± 17.2**
T12	36.1 ± 11.1	38.5 ± 11.1	54.4 ± 14.8**
T18	35.3 ± 11.0	40.5 ± 10.5	56.4 ± 15.2**

Data are mean ± s.d.

Groups B1 and B2 vs group A: **P* < 0.05; ***P* < 0.01.

TABLE 4. Average duration of single attacks (ADSA)

Observation time (months)	Duration (min)		
	Group A (n = 30)	Group B1 (n = 15)	Group B2 (n = 15)
T0	20.9 ± 5.7	20.8 ± 6.6	23.4 ± 7.6
T3	14.7 ± 4.7	14.9 ± 5.2	17.9 ± 5.9
T6	14.5 ± 4.5	14.0 ± 5.0	19.2 ± 6.2
T12	13.3 ± 3.9	12.8 ± 4.5	18.7 ± 6.2*
T18	12.8 ± 3.8	13.4 ± 4.4	19.6 ± 6.2*

Data are mean ± s.d.

Groups B1 and B2 vs group A: **P* < 0.05; ***P* < 0.01.

TABLE 5. Average daily frequency of attacks (ADFA)

Observation time (months)	Number of attacks per day		
	Group A (n = 30)	Group B1 (n = 15)	Group B2 (n = 15)
T0	3.5 ± 0.9	3.4 ± 0.7	3.2 ± 0.8
T3	2.9 ± 0.7	2.9 ± 0.6	2.8 ± 0.6
T6	2.8 ± 0.7	2.8 ± 0.6	3.0 ± 0.5*
T12	2.6 ± 0.6	3.0 ± 0.5*	2.9 ± 0.6*
T18	2.7 ± 0.5	3.0 ± 0.5*	2.8 ± 0.6**

Data are mean ± s.d.

Groups B1 and B2 vs group A: **P* < 0.05; ***P* < 0.01.

The average daily frequency of attacks (ADFA) was reduced significantly in all groups with respect to the base values, with a difference of 16.2–23.3% in group A, 12.8–16.5% in group B1 and 6.2–10.3% in group B2 (Fig. 1C). Significant differences were observed between groups A and B2 at T6 and at later times between group A and groups B1 and B2 groups (Table 5).

Finally, regarding the severity of the attacks, measured on a visual analogical scale and identified as RCS, there was a marked improvement in groups A and B1 regarding both the percentage difference from baseline scores (Fig. 1D) and the statistical significances at the different observation times. Group B2, on the other hand, recorded a significant improvement with respect to the basal levels, but there was a less evident reduction in scores such as percentage difference. Moreover, at T6, T12 and T18, there was a statistically significant difference between group A and group B2 (Table 6).

To measure quality of life, we preferred to use the SF-36, which has the advantage over other instruments, such as the Health Assessment Questionnaire (HAQ) and the Systemic Sclerosis Questionnaire (SysQ), of evaluating not only physical health but also mental health, and of minimizing the workload of the subject undergoing the interview, so long as only eight parameters

TABLE 6. Severity of attacks

Observation time (months)	Severity as Raynaud's condition score (visual analogue scale)		
	Group A (n = 30)	Group B1 (n = 15)	Group B2 (n = 15)
T0	4.3 ± 0.5	4.3 ± 0.6	4.1 ± 0.6
T3	3.2 ± 0.5	3.0 ± 0.5	3.1 ± 0.6
T6	2.9 ± 0.5	2.9 ± 0.5	3.7 ± 0.5**
T12	2.7 ± 0.5	3.0 ± 0.4	3.6 ± 0.5**
T18	2.7 ± 0.5	2.9 ± 0.5	3.7 ± 0.5**

Data are mean ± s.d.

Groups B1 and B2 vs group A: **P* < 0.05; ***P* < 0.01.

are considered, without reducing the precision of the findings [30]. Table 7 shows the baseline means for the parameters we considered in the three groups of patients. According to the above-mentioned method, we grouped the eight scales into three classes that represented the physical aspect of the illness, the mental aspect and general health, by summing the scores of the single scales in each class.

Figure 2 shows the percentage variations from baseline of the scale scores constituting the questionnaire and the statistical comparison between the groups. The scale describing the physical aspect of the illness, including physical activity, physical health and physical pain, shows a marked improvement, especially at T12 and T18, in group A, significantly greater than in groups B1 and B2. Similar behaviour is shown by the scales that evaluate general health and vitality. The scales which evaluate the mental aspect show a significant difference between group A and the other two groups, not only at later time points but also at the earlier times; moreover, the percentage changes from baseline were much greater than in the other classes.

No significant differences were observed between the groups undergoing treatment regarding adverse events, which had the same intensity and frequency in all groups, particularly for headaches, nausea and skin rashes. The adverse events reported were not serious enough to interrupt treatment.

We did not observe any significant alteration in the clinical or laboratory parameters in any of the patients.

Discussion

The efficacy of iloprost in the treatment of vascular manifestations of systemic sclerosis, above all RP, has been noted for some time, as reported in numerous studies [18–24].

Endothelial dysfunction and alteration of the normal regulation of the local blood flow that are present in SSc benefit from therapy using iloprost because of its capacity to inhibit platelet and leucocyte activation, and consequently to favour tissue repair. This also explains how the vascular effects and the improvement in the clinical condition of these patients persist for a long time after the end of the treatment, as the vasospasm is correlated to endothelium damage and not exclusively to a functional phenomenon.

Knowing the long-term benefits of treatment with iloprost, the objectives of this randomized study were to establish whether there were differences in the times of efficacy of different dosing schemes and then to establish a protocol for the scheme that had the most favourable effect on the quality of life.

Our data demonstrate that the average daily duration of attacks is significantly reduced regardless of the protocol used, but the persistence of the effects is maximum up to 8–10 weeks, as demonstrated by the different results for the patients of group A and group B1 compared with those of group B2, in which after

TABLE 7. Baseline means and standard deviations of the SF-36 in the three group of patients

	PA	PH	PP	GH	V	SA	ES	MH
Group A	59 ± 10	37 ± 10	45 ± 11	30 ± 11	48 ± 18	68 ± 11	59 ± 9	65 ± 16
Group B1	62 ± 13	36 ± 7	44 ± 14	32 ± 9	47 ± 18	66 ± 15	57 ± 8	63 ± 13
Group B2	60 ± 9	35 ± 9	43 ± 10	31 ± 12	46 ± 17	65 ± 13	55 ± 9	64 ± 11

PA, physical activity; PH, physical health; PP, physical pain; GH, general health; V, vitality; SA, social activity; ES, emotive state; MH, mental health.

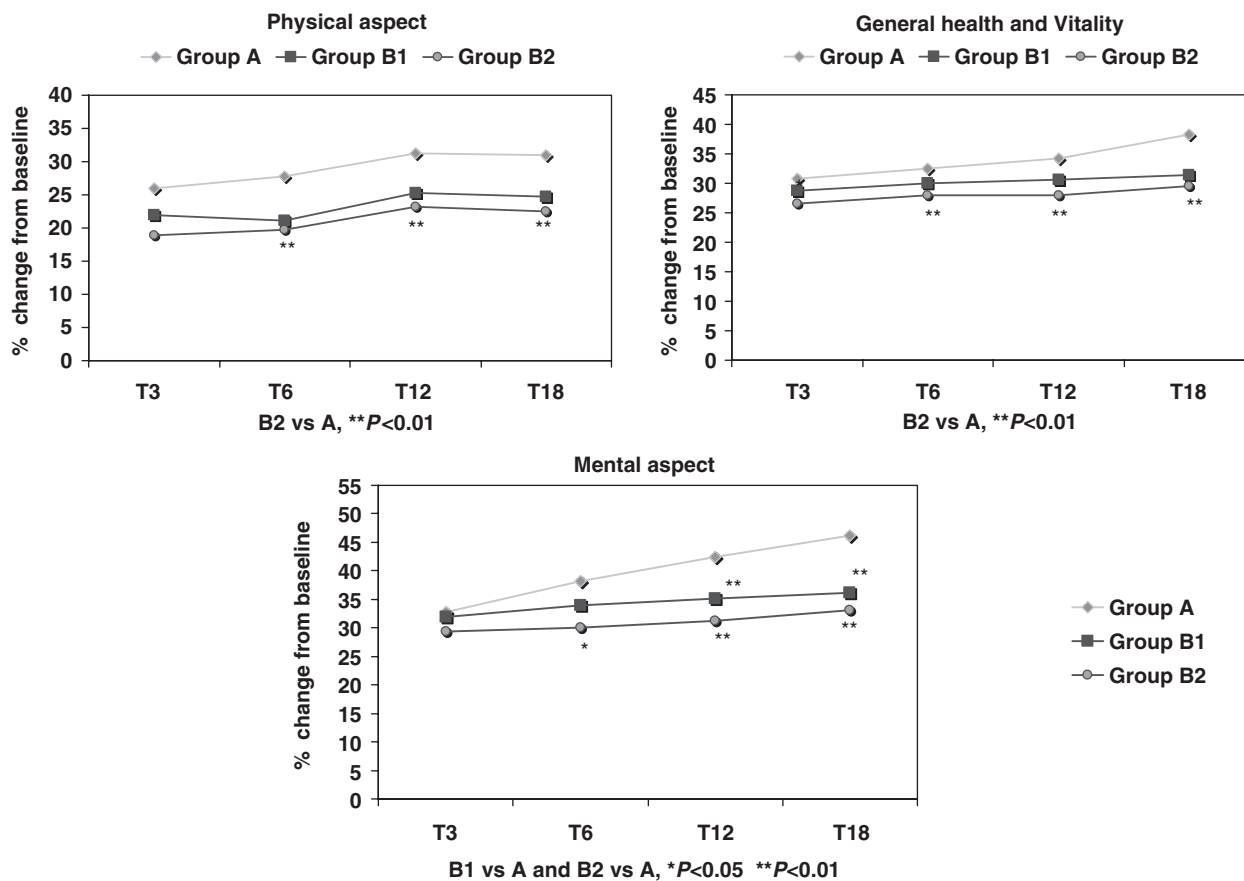


FIG. 2. Change from baseline in main outcomes at different times in the three groups.

6 months there was a reduction in the total average daily duration of the attacks of 18% of the basal values, compared with around 40% in the other two groups. These effects were then consolidated with successive cycles of therapy.

The average frequency of the attacks, which expresses the number of daily crises and was characterized in these patients by notable variability, demonstrates a minor efficacy in the average time of protocol B2 compared with the others. However, after a longer period of time, a difference also emerged between the other two groups to the advantage of group A. This is probably connected to the fact that an overall larger quantity of active substance reduces the chances of an asphyxial crisis, which, once started, lasted just as long in the two groups. This was confirmed by the RCS data, which showed the same severity of attacks in all groups.

Major differences between the various therapeutic protocols are revealed in the evaluations of the effects on the quality of life; this is an important parameter in health-care management. Health is defined not only as the absence of disease but also as a state of comfort: the quality of life of a patient must be considered and measured in the context of a complex system that includes

physical, social and mental aspects. Particularly in patients with SSc, the opinion of the patient is important. The method we used to evaluate the quality of life in patients with SSc was the SF-36, which reflects the opinion of the patient about the severity of the illness and his or her physical and mental well-being; other instruments, such as the questionnaire of Silman [31] and the Systemic Sclerosis Questionnaire (SySQ) [32], are based exclusively on the evaluation of the disability.

The data of our study show that, regarding the physical dimension of the illness and general health, there was an improvement in the patients in group A, with significant differences compared with group B2 especially. On the other hand, for the mental dimension of the illness, which is related mainly to social activity and the emotive state, there was a greater improvement in the group A patients, with significant differences compared with groups B1 and B2.

These results, which reflect greater compliance by the patient, in our opinion, are extremely important if we consider that the state of health of an individual is not only measured in terms of physical well-being but also takes into account the psychic element. This would lead us to prefer our protocol of treatment in patients

suffering from systemic sclerosis, which consists of 10-day cycles every 3 months; we must also consider that judgements about the validity of the effects of a therapeutic intervention must take into account the opinion and the compliance of the patient.

Finally, the monetary cost of treatment using the protocol proposed (A) is the same as that of protocol B2 and slightly greater than that of protocol B1. However, protocol A may have a favourable cost-benefit ratio even though the monetary cost is quite high. The improvement in the quality of life, especially regarding the mental dimension, produced by our proposed treatment protocol, gives it a favourable socio-economic character and leads to a quicker return to work.

<i>Rheumatology</i>	Key messages
	<ul style="list-style-type: none"> • The improvement in quality of life, considered as physical well-being as psychic healthy, is one of the most important objectives of the treatment of systemic sclerosis. • Compliance with the protocol that we used in the treatment of patients with Raynaud's phenomenon secondary to systemic sclerosis was better than compliance with other protocols.

The authors have declared no conflicts of interest.

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