Erectile Dysfunction in Systemic Sclerosis: Effects of Longterm Inhibition of Phosphodiesterase Type-5 on Erectile Function and Plasma Endothelin-1 Levels

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ABSTRACT. ***Objective.*** To investigate the effects of prolonged inhibition of phosphodiesterase type-5, using once-daily long-acting phosphodiesterase type-5 inhibitor (tadalafil) on erectile function and biomarkers of endothelial function in male patients with systemic sclerosis (SSc) and erectile dysfunction (ED).

Methods. In an open-label study, 14 nonconsecutive male patients with SSc with different degrees of ED were enrolled into the study irrespective of their clinical response to tadalafil, and received once-daily tadalafil 10 mg for 12 weeks. Primary endpoints were variations from baseline of penile arterial inflow [peak systolic velocity (PSV, cm/s); measured with dynamic color duplex ultrasound] and the erectile function domain score (measured with the International Index of Erectile Function questionnaire). Secondary endpoints were variations from baseline of morning erections (determined by modified question 13 of the Structured Interview on Erectile Dysfunction® questionnaire) and plasma concentrations of endothelin-1 (ET1).

Results. The PSV and the erectile function domain score were significantly improved by once-daily tadalafil (from 21.3 ± 6.4 to 30.0 ± 7.0 cm/s and from 13.0 ± 6.8 to 17.0 ± 9.0 vs baseline, respectively; $p < 0.05$). Question 13 scores decreased dramatically after treatment compared with baseline (from 2.2 ± 0.2 to 0.8 ± 0.5 arbitrary units; $p < 0.001$), and plasma ET1 levels decreased (from 24 ± 15 to 9.8 ± 7.4 pg/ml; $p < 0.05$).

Conclusion. In men with SSc-related ED, once-daily tadalafil improved both erectile function and vascular measures of cavernous arteries. Increases in morning erections and decreases in plasma ET1 levels were found, which may play a potential role in preventing progression of penile fibrosis and erectile dysfunction. (First Release July 1 2007; J Rheumatol 2007;34:1712–7)

Key Indexing Terms:
ENDOTHELIUM
PENILE DUPLEX ULTRASOUND
TADALAFIL
INTRACAVERNOUS INJECTION

Systemic sclerosis (SSc) is a connective tissue disorder of vascular alterations and immunological activation leading to progressive, widespread fibrosis of organs such as skin, lungs, gastrointestinal tract, heart, and kidneys[1,2]. The prevalence of erectile dysfunction (ED) in men with SSc may be as high as 80%[3], and it can be considered (like pulmonary hypertension and Raynaud's phenomenon) a manifestation of endothelium damage[4-8].

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We investigated the extent of penile vascular damage in male patients with SSc by assessment of duplex ultrasonography features of cavernous vasculature. Our study showed that damage of the penile cavernous arteries occurs in almost all patients, regardless of clinical symptoms, and it is characterized by both fibrotic and vascular alterations, as shown by the presence of hyperechoic spots (fibrotic changes) and low peak systolic velocities [(PSV) vascular changes][9]. In a subsequent study, we investigated penile thermal properties in men with ED and SSc, using infrared functional imaging technology, and found alterations in almost all scleroderma patients as a consequence of microcirculation abnormalities[10].

Several studies have shown the efficacy of phosphodiesterase type-5 (PDE-5) inhibitors in the treatment of ED related to diseases such as atherosclerosis, diabetes mellitus, and hypertension. Preliminary studies involving animal models and data from open-label uncontrolled trials concerning patients with pulmonary arterial hypertension, as well as small randomized controlled studies in those patients with idiopathic pulmonary arterial hypertension, suggest that PDE-5

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inhibitors are beneficial in the treatment of pulmonary arterial hypertension[11-19].

We investigated the efficacy and tolerability of longterm therapy with tadalafil (a long-acting PDE-5 inhibitor) once daily in male patients with SSc-related ED and its potential influence on penile arterial and systemic endothelial function.

MATERIALS AND METHODS

Selection of patients. We studied 14 male patients with limited or diffuse SSc as defined by Le Roy, *et al*[1] that satisfied the American College of Rheumatology criteria, associated with erectile dysfunction defined by a score < 21 on the International Index of Erectile Function[20] (IIEF-5; questions 1, 2, 3, 4, 5 and 15), having a history of ED within the previous 6 months, and having no evidence of pulmonary hypertension, defined as a value of pulmonary arterial systolic pressure > 30 mm/Hg measured by transthoracic echocardiography[21]. Subjects over 50 years of age or younger than 18, who were active smokers, had atherosclerosis, ischemic cardiopathy, arterial hypertension or hypogonadism, or who were receiving parenteral prostanoids, androgens, nitrates or nitric oxide-donor drugs within the previous 3 months were excluded. The protocol was approved by the local ethics review committee, and written informed consent was obtained from all patients.

Study design. The study was carried out for 12 weeks, from January 2006 to March 2006. SSc patients (n = 14) with moderate to severe ED received 10 mg tadalafil daily in an open-label fashion, irrespective of their prior clinical response to tadalafil. At baseline and after 12 weeks, patients received clinical and laboratory evaluation of erectile function (IIEF-5 and duplex ultrasonography assessment of penile blood flow) and measurement of plasma concentrations of endothelin-1 (ET1). Primary endpoints were variations from baseline of the erectile function domain score on the IIEF questionnaire and of basal inflow PSV on duplex ultrasound. Secondary endpoints were variations from baseline in morning erections as scored using the Structured Interview on Erectile Dysfunction questionnaire (Q13-SIEDY®) and plasma levels of ET1.

Erectile function evaluation. The penile blood flow study consisted of evaluation of cavernous artery flow by a dedicated machine (Philips HDI 5000, Philips Medizin Systeme, Hamburg, Germany) using a broadband linear array transducer and color-power Doppler ultrasonography software as described[22]. Flow measures included PSV, end diastolic velocities, and the resistance index after an intracavernous injection with 10 μg prostaglandin E_1 (PGE_1) and subsequent audiovisual sexual stimulation at 5, 10, 15, and 20 min. Readministration of 10 μg PGE_1 plus 1 mg of the nonselective α-blocker phentolamine was performed when necessary to maximize the erectile response and give better diagnostic sensitivity[23]. The degree of erection after maximal cavernous relaxation was estimated subjectively by visual rating of a different investigator (RB) who was unaware of the flowmetric results, according to a graded scale: type 0: no response; type 1: full tumescence ± no sustained rigidity, angle on the abdominal plane > 90°; type 2: sustained partial erection ± valid for intromission, angle = 90°; and type 3: sustained full erection, angle < 90°; and according to patient's self-assessment compared with his home evaluation[23]. Arteriogenic and corporeal venoocclusive dysfunction were defined by the presence of altered inflow in the cavernous arteries (PSV < 30 cm/s) or normal inflow, but persistent high diastolic inflow (end diastolic velocities > 5 cm/s and resistance index < 0.90) determined by duplex ultrasound after 20 min from maximal pharmacostimulation, respectively. Moreover, additional evaluation of erectile function was based on scores obtained on questions 1, 2, 3, 4, 5, and 15 on the IIEF questionnaire.

Erectile function at entry is reported in Table 2, with all patients exhibiting a moderate to severe degree of ED (mean score 13). The result of a modified Question 13 of the SIEDY questionnaire regarding morning erections ["In the last three months, did it ever occur to you to wake up with an erection?"; with relative scoring (0 = yes, regularly; 1 = more frequently than before; 2 = occasionally; 3 = never)] was designated as a secondary endpoint to evaluate improvements obtained by the patients during the once-daily tadalafil treatment[24].

Plasma ET1 concentration. Plasma ET1 concentration was measured by a specific radioimmunoassay (Peninsula Laboratories, Belmont, CA, USA) as described[24a]. In brief, ET1 was extracted from samples with a C-18 column (Sep-PaK column) after acidification with 0.2 ml of 0.01 sodium hydrogen phosphate buffer, 0.05 M NaCl, 0.1% bovine serum albumin, and 0.01% NaN. After incubation of samples and standards with the antiserum for 24 h at 4°C, 1200 mCi of ^{125}I-endothelin was added to reaction mixtures, and incubated again for 24 h at 4°C. Subsequently, 100 ml of diluted goat antirabbit IgG serum (Peninsula Laboratories) were added to the samples and samples were incubated 2 h at 20°C. After centrifugation at 1700 g for 2 min and removal of the supernatant, the residual pellet activity was counted using an automatic gamma counter (LKB-Wallac, Turku, Finland). The recovery of the extraction procedure with respect to standard was 90%. According to Tremann factor's instruction, the antibody crossreacts 100% with human, rat, porcine, canine, bovine, and mouse ET1 and 7% with ET2 and ET3, respectively, but not with atrial natriuretic factor, angiotensin I or II, ACTH, or vasopressin. Concentrations of ET1 were expressed as pg/ml. The deviation of this assay was 1 pg/ml and crossreactivity was 100%.

Statistical analysis. Sampled data were inserted in our scleroderma patient database and analyzed with dedicated software. Continuous variables were expressed as mean ± standard deviation (SD). A Kolmogorov–Smirnov normality test was carried out: variables not showing normal distribution were compared by nonparametric tests, those showing normal distribution were compared by the Student t test (independent samples t test and paired samples t test). A significance < 0.05 was chosen for all the tests.

RESULTS

The features[25] of the study population are shown in Table 1.

Erectile function evaluation. The effects of once-daily tadalafil treatment on erectile function are summarized in Table 2. The treatment significantly improved IIEF-5 scores compared to baseline ($p < 0.05$). During intracavernous injec-

Table 1. Baseline features of the study population (n = 14).

Age, yrs	41 ± 6
Disease duration, yrs	4.7 ± 5
Raynaud's duration, yrs	8.4 ± 4
Diffuse/limited SSc	9/5
Concurrent therapies, %	
Calcium channel blockers	71 (10/14)
Corticosteroids	35 (5/14)
Cyclophosphamide	143 (2/14)
Severity Index Activity Scale[25] score	3.5 ± 2.5

Table 2. Evaluation of tadalafil treatment on erectile function.

	Baseline	12 Weeks	p
IIEF05	13 ± 6.8 (9.4–16.5)	17 ± 9 (12.2–21.7)	< 0.05
PSV, cm/s	21.3 ± 6.4 (17.9–24.6)	30 ± 7 (26.3–33.6)	< 0.05
EDV, cm/s	3 ± 4	2.7 ± 4.6	NS
Resistance Index	0.88 ± 0.22	0.9 ± 0.2	NS
GAQ (Yes/No) (%)	4/14 (28)	12/14 (85)	< 0.05

IIEF-5: International Index of Erectile Function version 5; PSV: peak systolic velocity; EDV: end diastolic velocity; GAQ: "In the last three months, did the treatment improve your erections?"

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tion of alprostadil, penile pain, mild in intensity, was reported in 30% of subjects (N = 4) and did not cause discontinuation from the color Doppler ultrasound investigation. No patient reported prolonged erections (more than 2 h duration) or priapism during the intracavernous injection test. According to color Doppler ultrasound results, almost all patients showed significantly improved penile hemodynamics from baseline in terms of PSV values (Table 2, Figure 1). This latter increase was paralleled in most patients (N = 8; 60%) by an upgrade of clinical evaluation of erection after intracavernous injection (from type 1 to type 2 or type 2 to type 3 erection, data not shown). Interestingly, almost all treated patients (N = 12, 85%) reported persistent improvements of morning erections as evaluated by the Q13 score of the SIEDY questionnaire compared with baseline (from 2.2 ± 0.2 to 0.8 ± 0.5 arbitrary units; $p < 0.001$), which were maintained after 15 days' withdrawal (data not shown), and an overall satisfaction as assessed by the Global Assessment Questions (GAQ) "yes" responses after daily treatment compared with baseline. The 2 nonresponders were patients with severe scores for SSc and penile vascular damage at baseline due to penile fibrosis. Data for each patient's PSV and IIEF-5 results are shown in Figure 1.

ET1 evaluation. Baseline plasma ET1 levels (24 ± 15 pg/ml) were elevated compared to healthy controls (6.5 ± 2.4 pg/ml; $p < 0.05$), but the mean value at Week 12 decreased by more than 60% (from 24 ± 15 pg/ml to 9.8 ± 7.4 pg/ml) with a significant decline in almost all patients (Figure 2). Moreover, the level of the reduction appears to correlate with the baseline level (data not shown).

Safety. All adverse events experienced by patients (headache 7% and myalgia 7%) were transient and mild in intensity, and no patient withdrew from the study protocol because of side effects.

DISCUSSION

Lally and Jimenez[26] were the first to describe the association of SSc with erectile dysfunction. Subsequent studies have demonstrated that the prevalence of ED in men with SSc, at various disease stages, may be up to 80%, and its incidence seems to be more frequent than in other connective tissue diseases.

We observed severe vasculogenic ED in almost all scleroderma patients[27] as demonstrated by the presence in pulsed-Doppler analysis of severely impaired mean PSV in contrast to a mild venous leakage, and verified by mean end diastolic velocities and normal intima-media thickness and acceleration time. Matching these results with grades for IIEF-5, we were able to observe changes of penile vascular properties even in

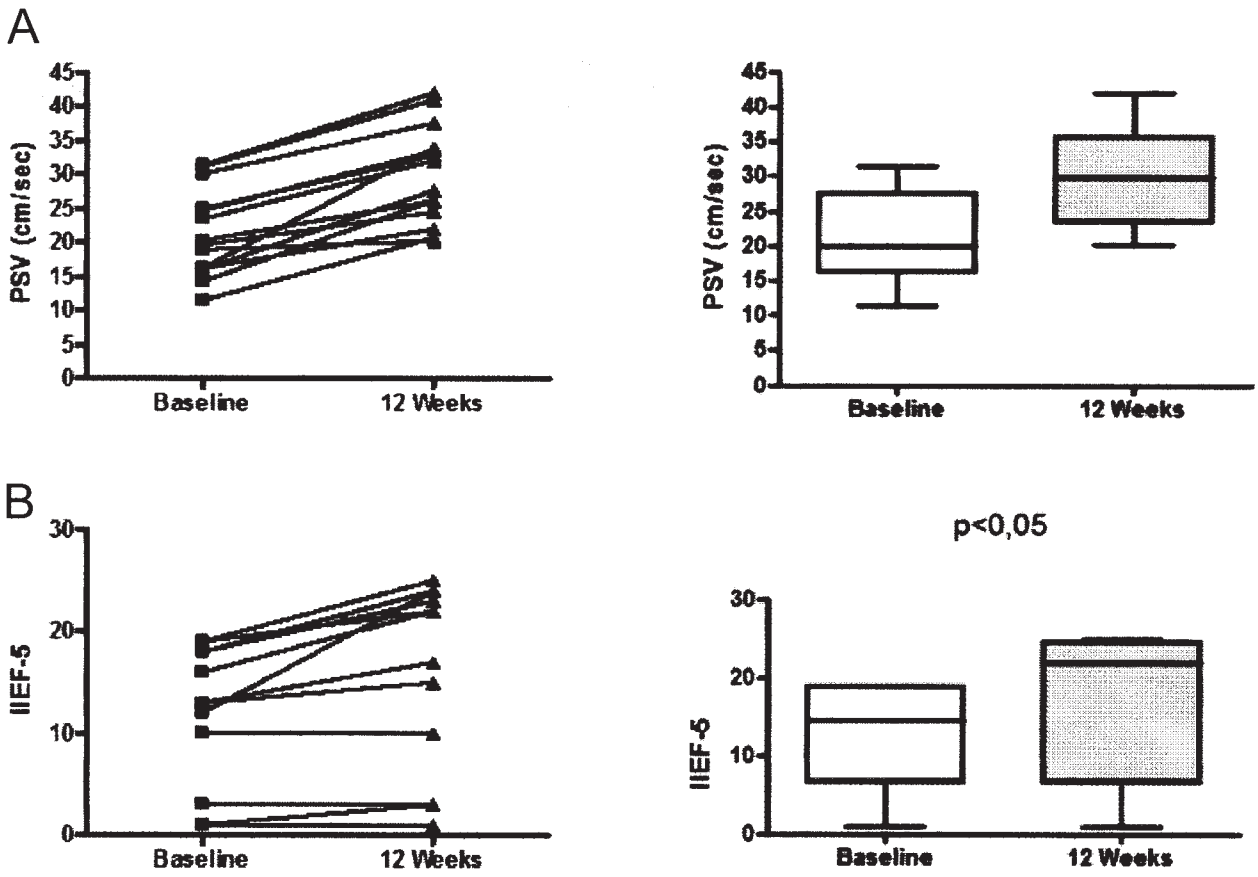

Figure 1. Data for patients' peak systolic velocity (PSV) and International Index of Erectile Function (IIEF-5) results show improvement from baseline in both PSV (cm/s; A) and IIEF-5 scores (arbitrary units; B).

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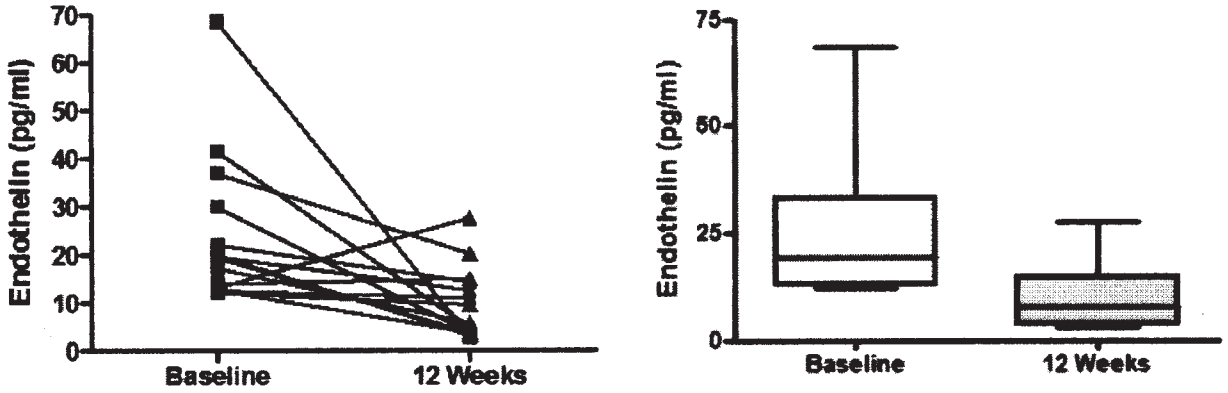

Figure 2. Differences of plasma endothelin concentrations from baseline to Week 12. Left panel shows values in each patient. Right panel shows comparison of the distribution of the mean difference in plasma endothelin concentration from baseline to Week 12 ($p < 0.05$).

the absence of clinical symptoms. Subsequently, we evaluated penile thermal properties of scleroderma patients using infrared functional imaging technology to obtain additional information about microcirculation functions. In that pilot study we saw that patients' penile temperature appeared to be lower than that of healthy controls[10].

Our current study shows for the first time that daily exposure to tadalafil improves penile and systemic endothelial function in men with ED and SSc, and that these effects are also evident on erectile capacity, as reported by the erectile function scores, despite the presence of different degrees of penile fibrosis. This improvement was confirmed by the IIEF-5 and GAQ, and by the presence of improved morning erections as scored by modified question 13 of the SIEDY questionnaire. Although it would have been of interest to evaluate the persistence of these benefits in an appropriate monthly followup, persistence of erectile improvement after 15 days' discontinuation of therapy was reported by the patients. Daily tadalafil was well tolerated and no treatment-emergent adverse event was reported during the 12-week period. Observation of improvement in sexual function after once-daily tadalafil treatment is not new[24,28]; however, we are not aware of interventional studies with tadalafil involving male SSc patients with ED where endothelial damage is prominent, as suggested by the presence of high plasma ET1 concentrations at baseline. We are aware of shortcomings of our study, such as the small number of patients and the absence of a control group, that are a consequence of the higher prevalence of women among the scleroderma patient population.

In addition to the beneficial effects of once-daily tadalafil on erectile function, we have shown a significant decrease of plasma ET1 levels. The decrease was present in almost all patients treated and, interestingly, it was greater in those patients with higher baseline levels of ET1. Much evidence has clarified the crucial role of ET1 in vascular damage through its vasoconstrictive effect, and the induction of genes implicated in vascular dysfunction, inflammatory response[29], and tissue remodeling and fibrosis[30,31]. It is well known that the secretion of ET1 is amplified by several factors such as shear stress, thrombin, epinephrine, angiotensin II, growth factors, cytokines and free radical enhancement[32-37]; by contrast, mediators like nitric oxide, cyclic GMP, atrial natriuretic peptide, and prostacyclin reduce the release of endogenous ET1[38-41]. Recently, Aversa and coworkers[24] investigated a cohort of patients with ED in which an alternative 1-month tadalafil dosing regimen was used, and found improvements in both duplex ultrasound and morning erections. They found net changes of surrogate markers of endothelial function, i.e., endothelin, vascular cell adhesion molecules, intercellular adhesion molecules, insulin, and C-reactive protein. Nevertheless, to our knowledge, this is the first study that shows the efficacy of therapy to reduce plasma levels of ET1 in patients with SSc.

Decreases in the corpus cavernosum smooth muscle/connective tissue ratio have been correlated with an increased likelihood of diffuse venous leak and a failure of the venoocclusive mechanism in prospective patient studies. Evidence for such a hypothesis incorporates nocturnal penile tumescence and circadian changes in oxygenation as important mechanisms in maintaining erectile tissue health[42]. The reduction/absence of morning erections reported by our SSc patients with ED may have indicated a reduction in the environmental oxygen tension, to which cells are usually exposed, which may have led to physiological and eventually pathological consequences associated with differential expressions of specific genes that encode for cytokines and growth factors. These genes are thought to play a key role in the regulation of synthesis and assembly of connective tissue proteins, i.e., transforming growth factor-ß1 and platelet derived growth factor[43], that are overexpressed in patients with SSc[44]. Reports on the improvement of morning erections after recommencement of short-acting PDE-5 inhibitor in men with organic ED are frequent[45], but this effect is lost after 2 or 3 days of withdrawal. In our study, administration of daily tadalafil produced a dramatic change of morning erections that was maintained within 15 days after withdrawal (data not

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shown). This suggests a possible rehabilitative action of tadalafil that might be exerted through inhibition of expression of intrapenile profibrotic growth factors, which are caused by chronic hypoxia and absence of nocturnal tumescence episodes.

Our preliminary results on cavernous vasodilatation and ET1 reduction confirm and support our hypothesis that chronic inhibition of phosphodiesterase type-5 could be a valid alternative in treating SSc-related erectile dysfunction. This robust reduction of plasma ET1 concentration moreover suggests a beneficial role in the management of other manifestations of severe endothelial dysfunction, such as pulmonary hypertension and Raynaud's phenomenon.

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