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HIGH-DOSE VERSUS LOW-DOSE D-PENICILLAMINE IN EARLY DIFFUSE SYSTEMIC SCLEROSIS

Analysis of a Two-Year, Double-Blind, Randomized, Controlled Clinical Trial

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Objective. **To test the hypothesis that systemic sclerosis (SSc) patients taking high-dose D-penicillamine (D-Pen) would have greater softening of skin, lower frequency of renal crisis, and better survival than patients taking low-dose D-Pen.**

Methods. **Seventeen centers enrolled 134 SSc patients with early (≤18 months) diffuse cutaneous scleroderma into a 2-year, double-blind, randomized comparison of high-dose D-Pen (750–1,000 mg/day) versus low-dose D-Pen (125 mg every other day). All 134 patients were followed up for a mean ± SD of 4.0 ± 1.1 years to assess the frequencies of new-onset scleroderma renal crisis (SRC) and mortality.**

Results. **Sixty-eight patients completed 24 months of drug treatment. The course of the modified Rodnan skin thickness score in the 32 high-dose and the 36 low-dose D-Pen completers was not different at 24 months: the skin score dropped 4.8 ± 10.3 (mean ± SD) units in the high-dose group and 6.9 ± 8.4 units in the low-dose group ($P = 0.384$ by *t*-test; favoring low-dose D-Pen) from 20.4 ± 10.3 in the high-dose and 19.9 ± 6.6 in the low-dose D-Pen group at study entry. The incidences of SRC and mortality were not different ($P > 0.38$ by Cox proportional hazards and by chi-square test) in the 66 high-dose patients (8 developed SRC and 8 died) compared with the 68 low-dose patients (10 developed SRC and 12 died). Of the 20 adverse event–related withdrawals, 80% occurred in the high-dose D-Pen group.**

Conclusion. **The course of the skin score and the frequencies of SRC and mortality in the high-dose D-Pen group were not different from those in the low-dose D-Pen group. Eighty percent of the adverse event–related withdrawals occurred in the high-dose D-Pen patients. Although this study cannot answer the question of whether low-dose D-Pen is effective, it does suggest that there is no advantage to using D-Pen in doses higher than 125 every other day.**

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Systemic sclerosis (SSc) is a multisystem disorder of connective tissue that is characterized clinically by fibrosis of the skin (scleroderma), by internal organ involvement including the heart, lungs, kidneys, and gastrointestinal tract, and by considerable morbidity and mortality. Its etiology and pathogenesis are unknown, and effective treatment to alter its natural history is lacking.

Because it interferes with the molecular cross-linking of collagen and perhaps because it has immunomodulatory effects, D-penicillamine (D-Pen) was proposed as a potential therapy for SSc. Since 1966, numerous studies reported the clinical usefulness of D-Pen in treating SSc (1–12). These studies were all uncontrolled and employed diverse dosages, durations of therapy, types of patients enrolled, and measures of efficacy. They resulted in a wide spectrum of conclusions, ranging from no discernible effect to an overall 70% favorable clinical response.

In 1982, Steen et al (11) analyzed a large group of patients with early diffuse SSc. In that retrospective study, D-Pen treatment was associated with significant improvement in skin thickness, better survival, and fewer instances of scleroderma renal crisis (SRC) compared with a similar (nonrandomized) comparison group receiving no treatment or other therapies. Twice as many D-Pen patients had ≥25% improvement in skin score. New organ involvement was reduced (particularly renal), and the 5-year cumulative survival rate was significantly higher in those receiving D-Pen.

Since no controlled randomized trial of D-Pen in SSc has been reported, however, its therapeutic role has remained controversial. We examine the efficacy of the conventional dosage of D-Pen (high-dose D-Pen) for SSc patients most likely to benefit from a disease-modifying therapy (i.e., SSc with diffuse cutaneous scleroderma of <18 months' duration) in a randomized, double-blind, prospective, controlled study against an unconventionally low dose of D-Pen (low-dose D-Pen). We hypothesized that patients receiving high-dose D-Pen were more likely to have greater softening of skin, reduced mortality rate, and lower frequency of new-onset SRC than were patients receiving low-dose D-Pen.

PATIENTS AND METHODS

Study design. This trial was a 17-center, parallel, randomized, double-blind, controlled, 24-month-per-patient study of high-dose D-Pen (750–1,000 mg daily) versus low-dose D-Pen (125 mg every other day) for the treatment of patients with recent-onset diffuse cutaneous scleroderma. The trial was conducted from January 1991 through December 1996. In 1996 and again in 1997, we attempted to contact all patients or their relatives or physicians to assess their disease course since leaving the study, particularly as it pertained to the occurrence of SRC and survival.

Patients had to meet American College of Rheumatology (formerly, the American Rheumatism Association) criteria for SSc (13), have diffuse cutaneous involvement (skin thickening proximal to the elbow and/or knee, with or without face and neck involvement) (14), and a duration of SSc ≤18 months from the onset of the first SSc manifestation other than Raynaud's phenomenon. All patients signed a consent form approved by the institutional review board at their center.

Patients were excluded for the following reasons: age <18 or >75 years, pregnancy, presence of another well-defined rheumatic disease or only localized scleroderma, serious organ involvement (i.e., diffusing capacity for carbon monoxide [DLCO] <45% predicted [corrected for anemia but not alveolar volume], serum creatinine ≥2.0 mg/dl, proteinuria >500 mg/24 hours, or intractable malabsorption), another chronic debilitating illness (e.g., cancer), history of a chronic blood dyscrasia, SRC within the preceding 2 months, or intractable congestive heart failure.

Corticosteroids, if taken, had to have been at a stable dosage of ≤10 mg of prednisone (or equivalent) per day for at least 1 month before study entry. D-Pen, azathioprine, cyclophosphamide, methotrexate, chlorambucil, paraaminobenzoic acid, colchicine, or captopril had to be discontinued for at least 1 month prior to entry. Patients could have taken D-Pen in the past, but at a dosage that was ≤375 mg/day for no more than 3 months (maximum cumulative dose <34 gm). Non-postmenopausal or nonsterile patients had to commit themselves to adequate contraceptive measures.

Patients were withdrawn from the study if they were unreliable or noncompliant, had to stop taking study medication for >1 month, became pregnant, or developed side effects considered by the investigator to be clinically significant and requiring discontinuation. During the trial, up to 6 short bursts (≤2 weeks) of prednisone in doses ≤15 mg/day were allowed.

All examinations and analyses were conducted double-blindedly. The treatment codes were not revealed to the investigators until after the data were fully entered and analysis plans were formalized. After the seventieth patient completed the trial, the Data and Safety Monitoring Committee was furnished appropriate masked data to determine whether excessive toxicity or clear-cut drug benefit had occurred in either treatment group.

Drug administration. Eligible participants were issued D-Pen study medication (by the pharmacy of the University of Medicine and Dentistry of New Jersey) using a blocked (groups of 4, by center), randomized schedule from a table of random numbers generated centrally before the trial began. During the study, the drug code was never broken.

The trial used a double-dummy design, such that all patients received 2 bottles of medication, bottle A and bottle B. Patients were randomly assigned to receive either 1) active D-Pen, in 250-mg capsules, in bottle A and placebo D-Pen, in 125-mg capsules, in bottle B, or 2) placebo D-Pen, in 250-mg capsules, in bottle A and active D-Pen, in 125-mg capsules, in bottle B. The dose from bottle A was one 250-mg capsule daily

for the first 2 months, 2 capsules daily for the second 2 months, 3 capsules daily for the next 3 months, and 4 capsules daily thereafter, for a total of 24 months. The dose from bottle B was one 125-mg capsule every other day throughout the 24-month trial.

Medication was interrupted (at least temporarily) if any of the following occurred: white blood cell count <3,500/mm^3, platelet count <100,000/mm^3, proteinuria >1,000 mg/24 hours (24-hour urine collections were prompted by finding ≥2+ proteinuria on dipstick), serum creatinine ≥2.0 mg/dl or occurrence of SRC, adverse experience considered by the investigator to be clinically significant, requiring drug discontinuation (e.g., occurrence of myasthenia gravis), or pregnancy.

If adverse effects requiring interruption of medication occurred, the effects were allowed to abate; thereafter, medication from bottle A was restarted at 1 capsule daily and from bottle B at 1 capsule every other day. Medication from bottle A was then increased by 1 capsule daily at monthly intervals until the daily dose was 1 capsule less than the dose at which the limiting adverse experience occurred. Medication from bottle B remained at 1 capsule every other day. If the patient was not able to tolerate at least 2 capsules of the medication from bottle A daily and 1 capsule of that from bottle B every other day, the patient was withdrawn from the study. Any patient who stopped taking study medication for >1 month, for any reason, was withdrawn from the study.

Diagnostic tests. At baseline and every 3 months, all patients had an evaluation of the degree and extent of SSc skin thickening, using the modified Rodnan skin thickness score technique (15): skin thickness was assessed clinically in each of 17 body surface areas, using a 0–3 scale, where 0 = normal, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness (maximum score of 51).

At baseline and every 6 months, other tests were performed: active handspread, fist closure, and maximum oral aperture, assessed as previously described (15); Health Assessment Questionnaire (HAQ) (16); serum creatine kinase (CK), as % of upper limit of normal; manual muscle testing; tenderness and swelling in the wrist, metacarpophalangeal, elbow, and knee joints (8 joints); contractures of the wrists, elbows, and knees (6 joints); palpable tendon rubs (6 areas); serum creatinine; and routine urinalysis. Every 6 months after entry, a physician's global assessment was made about the patient's status compared with entry. A 7-point Likert scale was used: 3 levels of worsening, no change, or 3 levels of improvement.

At baseline and every 12 months, the following were performed: pulmonary function tests (DLCO, forced vital capacity [FVC], forced expiratory volume in 1 second, and total lung capacity in milliliters and percent predicted [17–19]); posteroanterior chest radiograph (for heart size and chronic interstitial fibrosis); and 24-hour urine for creatinine clearance and protein content.

Pulmonary involvement required a DLCO ≤70% predicted, FVC ≤75% predicted, or chronic interstitial changes on chest radiograph. Renal involvement required a serum creatinine ≥1.4 mg/dl or the occurrence of SRC. SRC was determined to be present by the patient's physician–investigator if renal insufficiency (serum creatinine ≥2.0 mg/day in the absence of another defined cause) and/or malignant hypertension occurred with a blood pressure ≥160/110 mm Hg on at least 2 occasions at least 12 hours apart accompanied by persistent urine abnormalities or evidence of microangiopathic hemolytic anemia. Because D-Pen can cause excessive proteinuria and because 24-hour urine collections are often incomplete, neither proteinuria >300 mg/24 hours nor low creatinine clearance was a reliable criterion of SSc renal involvement. Muscle involvement required a CK ≥200% the upper limit of normal or proximal muscle strength ≤4/5. Joint involvement was present if the joint tenderness count was ≥1. Cardiac involvement required a history or presence of congestive heart failure, cardiac arrhythmia requiring medication, pericarditis or moderate-to-large pericardial effusion, or cardiomegaly (radiologist's interpretation or by cardiothoracic ratio >0.5 measured on posteroanterior chest radiograph by the study investigators).

Safety tests included complete blood cell counts and dipstick urine protein performed every 2–4 weeks and a chemistry panel performed every 3 months.

Statistical analysis. The following analyses were conducted on the primary outcomes of all 134 patients who took

Table 1. Baseline characteristics (continuous variables) of the 134 study participants*

Variable	D-Pen treatment group, mean ± SD	
	Low-dose (n = 68)	High-dose (n = 66)
Demographic		
Age, years	43 ± 13	45 ± 12
If taking prednisone, dosage at entry, mg/day	7.3 ± 2.7	7.6 ± 2.3
Laboratory		
Hematocrit, %	39 ± 4	39 ± 4
WBC, ×1,000/mm^3	8.4 ± 2.3	8.4 ± 2.3
Platelets, ×1,000/mm^3	344 ± 109	338 ± 98
ESR, mm/hour	25 ± 19	23 ± 15
Global		
HAQ Disability Index (0–3.0 scale)	1.0 ± 0.7	1.0 ± 0.6
Heart		
Cardiothoracic ratio	0.46 ± 0.05	0.48 ± 0.09
Joints		
Joint tenderness count (0–8 joints)	1.6 ± 2.5	1.5 ± 2.2
Kidney		
Serum creatinine, mg/dl	0.87 ± 0.19	0.90 ± 0.19
Creatinine clearance, ml/minute	92 ± 32	94 ± 30
Lung		
Forced vital capacity, % predicted	85 ± 18	81 ± 15
FEV_1, % predicted	91 ± 19	86 ± 16
TLC, % predicted	89 ± 17	88 ± 14
DLCO, % predicted	76 ± 20	75 ± 17
Muscle		
Serum CK, % upper limit of normal	77 ± 89	86 ± 154
Skin		
Skin score (range 0–51)	20.9 ± 7.4	21.2 ± 8.7
Oral aperture, mm	45.4 ± 9.5	45.2 ± 10.6
Right hand extension, mm	176 ± 24	173 ± 33
Right fist closure, mm	28.0 ± 19.8	22.6 ± 21.6

* D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day); WBC = white blood cells; ESR = erythrocyte sedimentation rate (Westergren); HAQ = Health Assessment Questionnaire; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide; CK = creatine kinase.

Table 2. Frequency of baseline characteristics (discrete variables) of the 134 study participants*

Variable	No. (%) in D-Pen treatment group	
	Low-dose (n = 68)	High-dose (n = 66)
Historical information		
Demographic		
Sex (females/males)	55/13	49/17
Skin thickening in previous 3 months		
New areas of thickening	46 (68)	54 (82)
Worsening of involved areas	53 (78)	56 (85)
Unchanged	15 (22)	10 (15)
Improved	2 (3)	4 (6)
Medications at entry		
NSAID	26 (38)	27 (41)
ACE inhibitor	5 (7)	6 (9)
Diuretic	11 (16)	9 (14)
Calcium channel blocker	23 (34)	25 (38)
Prednisone	20 (30)	20 (30)
Joint		
Morning stiffness	42 (62)	37 (56)
Joint pain on motion	54 (79)	53 (80)
Lung		
Dyspnea	24 (35)	19 (29)
Muscle		
Muscle pain	25 (37)	22 (34)
Muscle weakness	27 (40)	17 (26)
Peripheral vascular		
History of Raynaud's phenomenon	57 (84)	59 (89)
Skin		
Digit tip ulcers	21 (31)	19 (29)
Physical examination		
Joint		
Tendon friction rubs	26 (38)	23 (35)
Peripheral vascular		
Digital tip ulcer	8 (12)	7 (11)
Skin		
Truncal skin thickening	59 (87)	55 (83)
Skin ulcer elsewhere	10 (15)	11 (17)
Joint contractures	42 (62)	33 (50)
Digital pitting scars	21 (31)	28 (42)
Laboratory findings		
Urine protein >300 mg/24 hours	1 (1)	3 (3)
Creatinine clearance ≤70 ml/minute	19 (30)	13 (20)

* D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day); NSAID = nonsteroidal antiinflammatory drug; ACE = angiotensin-converting enzyme.

≥1 dose of study medication (a modified intent-to-treat paradigm in which the last observation on a patient was "brought forward" to the final analysis) and on the 68 patients who completed the 24-month study (completers). Differences in skin score and other continuous variables were compared within and across treatment groups by use of the Student's 2-tailed *t*-test (paired and unpaired, as appropriate). The number of "responders" (final skin score ≥25% lower than baseline skin score) in each treatment group were compared by chi-square test and analysis of variance, as were the number of "nonresponders" (final skin score ≥25% higher than baseline skin score). The frequencies of death and SRC and of new occurrence of heart, lung, muscle, and joint involvement in patients at risk were compared across treatment groups using chi-square tests. The duration of SSc from entry to occurrence or ascertainment of death and SRC was compared using Cox proportional hazard and Kaplan-Meier analyses. Continuous data are shown as mean ± SD, unless otherwise stated. Differences were not significant unless specifically stated.

Sample size calculations. For sample size/power calculations, we assumed that the average skin score at entry would be ~20 with a standard deviation of ~8, an effect size of 5 (a difference thought by most investigators to be clinically meaningful), and an alpha of 0.05. Sample size and power calculations (20) for death and SRC in 134 subjects were based on data from Steen's 1982 study (11): 1) for death, we assumed a hazard ratio of 4 (4 times more deaths in the low-dose group), an alpha of 0.05, and a minimum of 22 deaths; 2) for SRC, we assumed a hazard ratio of 4, an alpha of 0.05, and a minimum of 18 SRC occurrences.

RESULTS

Patient characteristics. One hundred thirty-four SSc patients signed the consent form, completed the entry examination, and took ≥1 dose of study medication. At baseline, the 66 patients taking high-dose D-Pen and the 68 patients taking low-dose D-Pen were similar in demographics, concomitant or past medications, and

Table 3. Frequency of visceral involvement in the 134 study participants at baseline*

Variable	No. (%) in D-Pen treatment group	
	Low-dose (n = 68)	High-dose (n = 66)
Lung (n = 133)	39 (57)	33 (51)
FVC, FEV_1, or TLC ≤75% predicted†	18 (27)	18 (28)
DL_{CO} ≤70% predicted†	29 (43)	24 (38)
Interstitial fibrosis (by chest radiograph)†	7 (10)	8 (12)
Heart (n = 133)	8 (12)	19 (29)‡
Pericarditis, arrhythmias, CHF†	1 (1)	2 (3)
Cardiomegaly (chest radiograph)†	8 (12)	19 (29)‡
Kidney (n = 134)	0 (0)	0 (0)
Serum creatinine ≥1.4 mg/dl†	0 (0)	0 (0)
Scleroderma renal crisis†	0 (0)	0 (0)
Joint (joint tenderness) (n = 134)	24 (35)	27 (41)
Muscle (n = 131)	11 (16)	11 (17)
Muscle strength ≤4/5†	8 (12)	6 (9)
CK ≥200% of upper limit of normal†	4 (6)	6 (10)

* D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day); FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; DL_{CO} = diffusing capacity for carbon monoxide; CHF = congestive heart failure; CK = creatine kinase.
† Variable used to determine involvement in that viscera. See Patients and Methods for definition of visceral involvement.
‡ $P = 0.015$ versus low-dose group, by chi-square test.

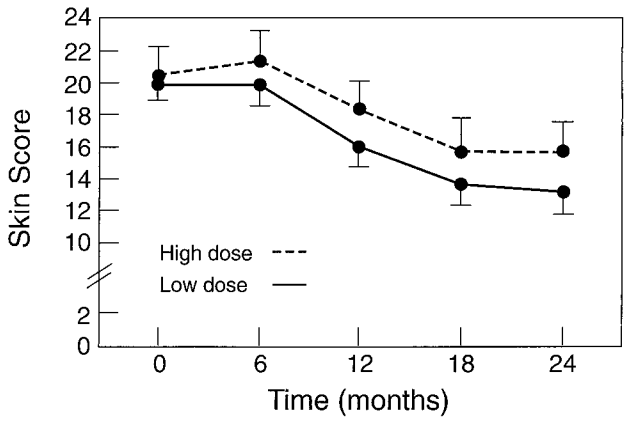

Figure 1. Course of the mean modified Rodnan skin thickness scores in the 36 patients taking low-dose D-penicillamine (D-Pen) and the 32 patients taking high-dose D-Pen who completed the 24-month trial. Skin scores in the low-dose group did not decline significantly until 12 months ($P < 0.003$); those in the high-dose group did not decline significantly until 18 months ($P < 0.006$). Between the 2 dosage groups, these changes were not significantly different at any time during the 24-month trial.

cutaneous and visceral involvement, except for cardiac involvement (selected data displayed in Tables 1–3). Enlarged heart was detected in 8 of the low-dose group (12%), in contrast to 19 of the high-dose group (29%) ($P = 0.015$, by chi-square test). Prior to entry, only 7 patients had received D-Pen (mean ± SD cumulative dose 11.8 ± 7.9 gm) and only 5 had received methotrexate (mean ± SD cumulative dose 37 ± 21 mg). No patient had received cyclosporine, cyclophosphamide, azathioprine, or other immunomodulator prior to study entry.

Primary outcomes. *Skin score.* Although skin scores were obtained in all patients who continued to take the study medication, the full series was obtained only in the 68 patients who completed 24 months of the study medication (Figure 1 and Table 4 show the 68 completers). Mean baseline skin scores for low-dose and high-dose D-Pen were not significantly different (19.9 versus 20.4, respectively). Significant decreases in skin scores occurred by 12 months in the low-dose D-Pen group ($P < 0.003$), but not until 18 months in the high-dose D-Pen group ($P < 0.006$) (Figure 1). By 24 months, the mean skin score decreased by 6.7 units in the low-dose group ($P < 0.001$) and by 4.9 units in the high-dose group ($P = 0.012$, by paired *t*-test). The mean change score during 24 months in the low-dose group (−6.7 units) was not statistically different from that in the high-dose group (−4.9 units) ($P = 0.384$, by *t*-test).

The percentages of responders were not significantly different between groups: 25 (70%) taking low-dose versus 17 (53%) taking high-dose D-Pen ($P = 0.167$, by chi-square test). During the trial, 18 of the 68 completers (26%) had skin scores which at some point rose ≥25% over their baseline (10 in the low-dose group and 8 in the high-dose group). By the end of the trial, the skin scores had returned to within 25% of baseline in 8 subjects, remained elevated ≥25% above baseline ("nonresponder") in 7 subjects, and decreased to ≤25% of baseline ("responder") in 3 subjects.

A modified intent-to-treat analysis of skin scores was also conducted on all 134 patients. The baseline skin score in the 68 low-dose D-Pen patients (mean ± SD 20.9 ± 7.4) was not significantly different from that in the 66 high-dose D-Pen patients (21.2 ± 8.7) (Table 1). Skin scores in the low-dose D-Pen group decreased by 3.5 ± 9.1 units (mean ± SD), and by 2.0 ± 10.1 units in the high-dose D-Pen group ($P = 0.36$, by *t*-test comparing change scores between treatment groups). Thirty patients taking low-dose D-Pen (44%) were responders, compared with 25 patients taking high-dose D-Pen (38%) ($P = 0.54$, by chi-square test).

Scleroderma renal crisis and survival. While still taking study medication, 4 patients died (3 in the low-dose group and 1 in the high-dose group) and 10 developed SRC (8 in the low-dose group and 2 in the high-dose group; $P = 0.095$, by chi-square test). Of the 10 patients who developed SRC while still taking study medication, 7 had taken D-Pen for <100 days, a duration thought to be too short for D-Pen to have been active in preventing SRC. Survival and SRC were also ascertained a mean ± SD of 4.0 ± 1.1 years after entry in 133 patients (intent-to-treat). The frequency of new-onset SRC and of mortality were not different in the 66

Table 4. Course of skin scores in the 36 patients taking low-dose D-Pen and the 32 patients taking high-dose D-Pen who completed the 24-month trial*

	D-Pen treatment group			
	Low-dose (n = 36)		High-dose (n = 32)	
	Mean ± SD	*P*	Mean ± SD	*P*
Baseline	19.9 ± 6.6		20.4 ± 10.3	
6 months	19.8 ± 8.0		21.3 ± 11.0	
12 months	16.0 ± 8.3	<0.003	18.2 ± 11.2	
18 months	13.3 ± 7.3	<0.000	15.7 ± 11.5	<0.006
24 months	13.2 ± 8.7	<0.001	15.5 ± 11.4	<0.012

* *P* values are for change from baseline within treatment group, by single-comparison *t*-test. D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day).

Table 5. Prevalence of organ involvement at baseline and frequency of new-onset organ involvement during the trial in the 68 patients who completed the 24-month trial*

Involvement	No. of patients affected at baseline		New onset during 24 months in patients at risk, no. affected/ no. at risk	
	Low-dose D-Pen (n = 36)	High-dose D-Pen (n = 32)	Low-dose D-Pen	High-dose D-Pen
Lung	16	19	5/20	3/13
Heart	3	8†	5/33	5/24
Kidney (chronic)	0	0	3/36	2/32
Muscle	2	4	7/34	7/28
Joint	13	15	7/23	8/17

* See Patients and Methods for definition of involvement. D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day).
† $P = 0.038$ versus low-dose group.

patients taking high-dose D-Pen (8 SRC, 8 deaths) compared with the 68 patients taking low-dose D-Pen (10 SRC, 12 deaths) ($P = 0.63$ by Cox proportional hazard and $P = 0.69$ by chi-square test for SRC; $P = 0.42$ by Cox proportional hazard and $P = 0.38$ by chi-square test for death). Kaplan-Meier analysis revealed no differences between the 2 patient groups, some of whom were followed up for as many as 6.3 years. The 5-year cumulative survival in all study patients was 85%.

Because past studies suggested that D-Pen may take several months to "become effective," a tertiary analysis was conducted in a manner similar to that above for SRC and mortality in the 117 patients who took the study drug for at least 100 days. This analysis showed no significant differences in deaths or SRC for those patients: 10 deaths in the low-dose group versus 5 in the high-dose group ($P = 0.23$, by chi-square test); 6 SRC in the low-dose group versus 5 in the high-dose group ($P = 0.89$, by chi-square test).

Secondary outcomes. *New organ involvement.* The prevalence of organ involvement at baseline for the 68 completers is displayed in Table 5. All new-onset organ involvement occurred equally in the 2 treatment groups during the 24-month trial.

Course of selected disease variables. None of the selected disease variables changed significantly during the 2-year study (Table 6), with the exception that right and left handspread declined significantly ($P < 0.022$ and $P < 0.013$, respectively, by paired t-test) in the high-dose group but not in the low-dose group.

Physician's global assessment. For ease of computation, the responses in the 7 categories were divided into 2 groups: all categories of "worsened" and "no change" were pooled into one group ("not improved"), and all categories of "improved" were pooled into another group ("improved"). Among the completers, 19 of the 32 patients in the high-dose group (59%) and 31 of the 36 in the low-dose group (86%) "improved" ($P < 0.013$, by chi-square test, favoring the low-dose D-Pen group). Of the 66 patients who withdrew, 15 withdrew before having their first global assessment (7 in the high-dose and 8 in the low-dose group), while 51 completed at least 1 global assessment (>6 months). Nine of the 27 patients who withdrew from the high-dose group (33%) and 6 of the 24 who withdrew from the low-dose

Table 6. The course of continuous variables in the 68 participants who completed the 24-month trial*

Variable	Low-dose D-Pen (n = 36)			High-dose D-Pen (n = 32)		
	Baseline	12 months	24 months	Baseline	12 months	24 months
DLco, % predicted	77.0 ± 19.8	79.6 ± 18.9	74.1 ± 20.3	74.3 ± 15.1	76.2 ± 16.8	73.8 ± 21.1
FVC, % predicted	88.0 ± 19.0	90.7 ± 17.7	92.0 ± 20.1	80.7 ± 17.9	85.0 ± 17.5	85.6 ± 17.4
HAQ Disability Index (0–3.0 scale)	0.91 ± 0.60	0.89 ± 0.69	0.72 ± 0.59	1.07 ± 0.57	0.98 ± 0.72	0.94 ± 0.73
Creatinine clearance, ml/minute	88 ± 30	83 ± 25	87 ± 26	96 ± 34	88 ± 25	85 ± 23
Tender joint count (0–8 joints)	1.47 ± 2.36	1.14 ± 2.03	0.74 ± 1.69	1.63 ± 2.12	1.97 ± 2.53	1.34 ± 2.50
CK, % of upper limit of normal	66 ± 87	53 ± 55	57 ± 55	104 ± 211	45 ± 29	57 ± 38
Weight, kg	70.7 ± 16.4	70.3 ± 15.7	70.3 ± 14.2	69.6 ± 14.9	69.2 ± 16.2	71.0 ± 16.5
Left handspread, mm	187 ± 21	182 ± 25	183 ± 25	183 ± 32	176 ± 31	174 ± 33†
Right handspread, mm	182 ± 24	178 ± 27	181 ± 27	179 ± 35	171 ± 35	169 ± 34‡
Left fist closure, mm	25 ± 18	24 ± 21	20 ± 17	22 ± 21	22 ± 19	18 ± 19
Right fist closure, mm	27 ± 20	23 ± 20	19 ± 15	22 ± 22	22 ± 18	19 ± 20
Oral aperture, mm	48 ± 11	49 ± 9	51 ± 9	49 ± 11	49 ± 11	50 ± 10

* D-Pen = D-penicillamine (low-dose = 125 mg every other day; high-dose = 750–1,000 mg/day); DLco = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HAQ = Health Assessment Questionnaire; CK = creatine kinase.
† $P = 0.013$ versus baseline, by paired t-test; $P = 0.179$ comparing change scores in high-dose versus low-dose D-Pen groups, by analysis of variance (ANOVA).
‡ $P = 0.022$ versus baseline, by paired t-test; $P = 0.048$ comparing change scores in high-dose versus low-dose D-Pen groups, by ANOVA.

Table 7. Reasons for withdrawal and course of skin score and HAQ in 68 participants who withdrew from the study*

	No. of patients	Months taking drug, mean ± SD	Skin score					HAQ Disability Index		
			Study entry	Final	Change	No. of responders	No. of nonresponders	Study entry	Final	Change
High-dose D-penicillamine (n = 34)										
Administrative (total)	17	9.4 ± 8.0	21.0 ± 8.3	23.5 ± 13.6	2.5 ± 10.3	4	7	1.10 ± 0.58	1.31 ± 0.87	0.21 ± 0.57
Treatment failure	8	7.4 ± 5.3	23.4 ± 11.5	32.6 ± 12.5	9.3 ± 8.8†	0	6	1.44 ± 0.45	1.77 ± 0.80	0.33 ± 0.63
Patient refusal to continue	6	9.5 ± 10.2	19.0 ± 4.5	17.3 ± 5.9	−1.7 ± 2.6	2	0	0.85 ± 0.64	1.10 ± 0.68	0.25 ± 0.39
Other (moved [n = 1], maximum improved [n = 2])	3	14.6 ± 9.6	18.7 ± 1.2	11.7 ± 13.3	−7.0 ± 14.0	2	1	0.67 ± 0.26	0.50 ± 0.87	−0.17 ± 0.71
Adverse events (total)	16	7.0 ± 4.6	22.4 ± 4.9	21.3 ± 7.5	−1.1 ± 8.1	5	4	0.78 ± 0.64	0.76 ± 0.73	−0.02 ± 0.33
Proteinuria >1.0 gm/24 hours	7	7.2 ± 3.8	21.1 ± 5.0	20.9 ± 7.7	−0.3 ± 7.0	2	1	1.02 ± 0.74	0.90 ± 0.90	−0.11 ± 0.28
Rash	3	4.7 ± 2.0	22.0 ± 6.2	18.3 ± 6.5	−3.7 ± 4.5	1	1	0.58 ± 0.47	0.64 ± 0.56	0.05 ± 0.16
Other (low platelets [n = 2], flu symptoms [n = 1], stomatitis [n = 2], myasthenia gravis [n = 1])	6	7.8 ± 6.5	24.0 ± 4.6	23.3 ± 8.3	−0.7 ± 11.1	2	2	0.60 ± 0.60	0.65 ± 0.67	0.04 ± 0.46
Death while taking study drug	1	1.2	29.0	29.0	0	0	0	2.65	2.65	0
Low-dose D-penicillamine (n = 32)										
Administrative (total)	25	10.7 ± 7.0	20.9 ± 8.3	21.2 ± 10.2	0.2 ± 8.2	4	5	1.14 ± 0.77	1.27 ± 0.89	0.13 ± 0.52
Treatment failure	12	11.3 ± 6.6	23.5 ± 9.4	23.9 ± 11.3	0.4 ± 11.2	3	4	1.38 ± 0.55	1.55 ± 0.72	0.18 ± 0.72
Patient refusal to continue	9	11.7 ± 7.5	18.6 ± 7.3	18.9 ± 9.4	0.3 ± 4.3	1	1	0.82 ± 0.78	0.92 ± 0.89	0.10 ± 0.32
Other (moved [n = 1], illness [n = 2], noncompliance [n = 1])	4	6.3 ± 30	18.5 ± 6.2	18.5 ± 8.4	0.0 ± 2.2	0	0	1.16 ± 1.20	1.22 ± 1.27	0.06 ± 0.13
Adverse events (total)	4	10.0 ± 10.7	25.8 ± 8.6	20.3 ± 13.1	−5.5 ± 6.6	2	0	1.41 ± 1.26	1.78 ± 0.72	0.38 ± 0.62
Proteinuria >1.0 gm/24 hours	1	22.1	27.0	14.0	−13.0	1	0	2.75	2.625	−0.125
Other (low platelets [n = 1], flu symptoms [n = 1], stomatitis [n = 1])	3	6.0 ± 8.6	25.3 ± 10.5	22.3 ± 15.2	−3.0 ± 5.2	1	0	0.96 ± 1.08	1.50 ± 0.54	0.54 ± 0.64
Death while taking study drug	3	6.4 ± 3.4	27.0 ± 2.7	33.7 ± 11.0	6.7 ± 12.4	0	1	1.33 ± 0.69	1.54 ± 1.05	0.21 ± 0.36

* See text for definitions of responders and nonresponders. HAQ = Health Assessment Questionnaire.
† $P < 0.024$ entry versus final skin score, by paired *t*-test.

group (25%) were classified as "improved" at the time of withdrawal ($P = 0.51$, by chi-square test). Not surprisingly, a larger proportion of patients who completed the 24-month trial were classified as "improved" (50 of 68, or 74%) than the proportion of patients who withdrew (15 of 51, or 30%) ($P < 0.0001$, by chi-square test).

Study withdrawals. The reasons for withdrawals were recorded by the patient's investigator at the time of withdrawal (Table 7). The rate at which patients withdrew (for all reasons combined) from the high-dose D-Pen group was not statistically different from that in the low-dose D-Pen group (life-table analysis not shown). Twenty patients withdrew because of adverse drug events: 16 in the high-dose group (80%) and 4 in the low-dose group (20%) ($P = 0.003$, by chi-square test). Seven of the 16 adverse drug events–related withdrawals in the high-dose group were for proteinuria >1,000 mg/24 hours. Rash and 1 episode of myasthenia gravis were observed only in the high-dose D-Pen group. Thrombocytopenia, flu-like illnesses, and stomatitis were reported slightly more frequently in the high-dose D-Pen group.

Death occurred in 4 patients while taking the study drug: 3 in the low-dose group and 1 in the high-dose group. In the low-dose D-Pen group, 2 patients died of acute SSc cardiac and renal failure, while 1 patient with no clinically obvious visceral involvement died suddenly at home. The 1 high-dose D-Pen death occurred in a patient with acute SSc cardiopulmonary failure. The deaths occurred a mean ± SD of 5.1 ± 3.8 months after study entry and were considered to be related to rapidly progressive SSc rather than the D-Pen treatment.

Twenty patients withdrew for patient-perceived "inefficacy," and 15 patients refused or failed to con-

tinue the study (Table 7). The mean skin score in the 8 patients who withdrew from the high-dose group for reasons of inefficacy (a mean of 7.4 months after entry) increased 9.1 units at withdrawal ($P < 0.024$, by paired *t*-test), while it increased by only 0.4 units in the 12 low-dose D-Pen inefficacy withdrawals (a mean of 11.3 months after entry) ($P = 0.4$, by paired *t*-test). The skin score changes in the high-dose group were not significantly different from those in the low-dose group ($P = 0.07$, by unpaired *t*-test). Similarly, HAQ scores rose in both inefficacy withdrawal groups (0.33 in high-dose D-Pen, 0.18 in low-dose D-Pen, *P* not significant between or within groups). There were no significant changes in skin score or HAQ (baseline to withdrawal) within or between the high- or low-dose groups for other categories of administrative withdrawals.

Drug taking and compliance. The average daily dose of D-Pen (prescribed by the protocol, plus all temporary dosage changes prescribed for adverse events) was 822 mg/day in the high-dose D-Pen group and 120 mg every other day in the low-dose D-Pen group. Pill counts were employed throughout the trial; drug logs were examined in detail for compliance in 35% of the participants. Compliance was 94% for completers, 89% for noncompleters, 91% for the high-dose D-Pen group, and 93% for the low-dose D-Pen group.

Sample size/power. Power calculations for skin score were accurate. Actual skin score was 20 and the standard deviation was 8. With 68 patients completing 24 months, we achieved a power of 0.73 for skin score. A total of 20 deaths occurred (power = 0.87), and a total of 18 episodes of SRC occurred (power = 0.84).

DISCUSSION

This is the first reported randomized, controlled trial of D-Pen for SSc. We recruited SSc patients with early diffuse cutaneous scleroderma, a group with considerable skin thickening, who were projected to develop increasing skin thickening and serious/fatal complications. Since thickening may regress spontaneously later in the disease (14,21), a concurrent control group was needed for comparison. Although we initially considered comparing D-Pen to a placebo, several practical issues led us to choose an unconventional low dose of 125 mg every other day (equivalent to 62.5 mg daily) as the control. First, patients and physicians could be assured that all patients were being treated with an active drug (D-Pen). Second, since the care of patients during the trial was unfunded, it was thought not to be ethical to hold patients responsible for the cost of care while participating in a placebo-controlled trial. Because both groups received active medication in this trial, we thought it ethical to seek reimbursement for medical care and laboratory costs for patient-related care in both groups. Finally, there was the real probability that patients would not be referred to a study comparing a readily available medication (D-Pen) against placebo.

Although the trial was begun prior to the publication of the American College of Rheumatology guidelines for conducting trials of disease-modifying interventions in SSc (22), the trial design incorporated most of the recommendations for such trials: 1) patients with early diffuse scleroderma who were followed up for at least 3 years to determine the occurrences of new organ involvement and mortality; 2) validated, standardized, predetermined outcome measurements (e.g., modified Rodnan skin thickness scoring, serum creatinine, FVC, etc.); 3) randomized test medication administered in a double-blind manner; 4) predefined clinical response criteria (using clinically reasonable measurements with known reliability characteristics) and predefined analysis techniques; 5) quality assurance, data integrity, and frequent contacts with centers to correct missing and unclear data; and 6) cross-checking of entered data against entries in the case report form at least once to correct inconsistencies, out of range values, missing data, etc. In addition, the trial was conducted by a consortium of dedicated, experienced SSc investigators at multiple institutions.

The only baseline characteristic that was different between the treatment groups was cardiomegaly (12% in the low-dose and 29% in the high-dose group). Using univariate and multiple logistic regression, we were able to show that cardiomegaly at baseline was negatively related to response in skin score and positively related to mortality and renal crisis, but not to dosage, even when the model included these other outcomes.

Drug-taking compliance by patients was examined by pill counts locally and at the central pharmacy. The overall compliance rate was not significantly different among groups: >89% in both the high-dose and low-dose groups and for completers and withdrawals. Since the high-dose D-Pen group took a dosage that was >12 times that taken by the low-dose D-Pen group, it is unlikely that the reason the high dosage was not found to be more efficacious than the low dosage was because the doses were not appropriately different in the 2 groups.

Subjects who withdraw for reasons other than adverse events and death are always a concern during data analysis. Since the withdrawing population often

leaves because it is not doing well, its loss could skew the characteristics and outcomes of the remaining group of patients. We took great pains, therefore, in this analysis to examine whether the patient withdrawals in one group demonstrated greater decline in function or increased disease activity at the time of withdrawal compared with the other group (Table 7). Although patients who withdrew from the high-dose D-Pen group because of inefficacy showed a greater degree of worsening in skin scores ($P < 0.024$) and HAQ scores (P not significant) at the time of withdrawal than did those who withdrew from the low-dose group for the same reason, the differences between treatment groups were not significant. The data fail to show that withdrawals occurred preferentially in either group.

In spite of the large withdrawal rate, we are assured with power of 0.73 that high-dose D-Pen is not more efficacious in softening skin than low-dose D-Pen at 2 years. Even though our ability to track skin scores ended after 2 years, our ability to track our other 2 major variables (death and SRC) continued for as long as 6.3 years (mean 4.0 years). During that time, 20 patients died (12 in the low-dose group and 8 in the high-dose group) and 18 developed SRC (10 in the low-dose group and 8 in the high-dose group). This was enough time to be certain (with power ≥ 0.84) that the occurrences of death and SRC in the low-dose and high-dose D-Pen groups were not significantly different.

By initial design, we compared high-dose D-Pen to a very low dose of D-Pen, reasoning that 125 mg every other day would perform little better than a placebo; however, skin scores in both the low-dose and the high-dose D-Pen groups improved significantly during the trial. Even though there was not a dose response seen in the trial (i.e., high-dose D-Pen was not significantly more efficacious than low-dose D-Pen), we cannot rule out the possibility that low-dose D-Pen and high-dose D-Pen are equally efficacious. Therefore, the trial can be criticized for not including a placebo. On the basis of the study design and the data accrued, we cannot dismiss low-dose D-Pen as being ineffective, but we can state that there was no advantage to using high-dose D-Pen over the less toxic low-dose D-Pen among those who received the drug for at least 100 days. The trend in favor of the high-dose D-Pen as it relates to mortality (10 versus 5 deaths) could have been secondary to chance or to effectiveness of high-dose D-Pen but was not significant in any case. The sample size needed to prove a statistical difference when the effect in one group is twice the size of the effect in the second group (compared with the 4 times difference hypothesized) would have required many more patients than we could have recruited.

The trial may also have suffered from center effects. For example, one center had appreciably more instances of scleroderma renal crisis than any of the others. This could be the result of patients with more serious disease presenting at one center in the northeast compared with patients presenting at other centers around the country. In addition, some centers had far fewer patients who completed the trial (i.e., 6 of 21, 1 of 8, and 7 of 19) compared with other centers (i.e., 14 of 18, 6 of 7, and 8 of 10). Although we did not stratify the randomization of D-Pen for use of other medications such as prednisone, our analysis failed to demonstrate any bias in patient groupings by prednisone use at study entry.

D-Pen absorption may be affected by concomitant food, antibiotic, and iron intake (23). This might temporarily affect the absorption of D-Pen, but we believe that these effects were unlikely to affect the long-term average absorption and effect of drug treatment (24). Nevertheless, we had instructed patients to take their D-Pen study medications on an empty stomach in the morning and evening, so long as they could tolerate the study medication on an empty stomach.

On the basis of the trial data analyzed, we conclude: 1) the course of skin score, the occurrence of renal crisis and other organ involvements, and the occurrence of mortality were not different between the low-dose D-Pen and high-dose D-Pen groups; 2) the majority of adverse event–related withdrawals occurred in the high-dose D-Pen group and were largely because of proteinuria; and 3) if D-Pen is to be used to treat SSc, our results suggest that there is no advantage to using dosages higher than 125 mg every other day.

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