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A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset

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Summary

Background—Several uncontrolled studies in systemic sclerosis have shown that D-penicillamine may cause improvement in skin sclerosis, decrease the rate of new visceral organ involvement, and improve overall survival.

Objectives—To undertake a single-centre retrospective randomly selected cohort study to examine the effects of D-penicillamine treatment on skin and visceral organ involvement in patients with rapidly progressive systemic sclerosis of recent onset.

Methods—Eighty-four patients with diffuse cutaneous systemic sclerosis who had received D-penicillamine within 24 months of clinically detectable onset of skin sclerosis were randomly selected from the systemic sclerosis cohort followed at the Scleroderma Center of Thomas Jefferson University. Employing a previously described severity scale, disease severity and skin involvement were compared from initiation of D-penicillamine to end of study and a correlated matched t-test was used to establish statistical significance.

Results—At a mean $\pm$ SD duration of D-penicillamine therapy of 29.2 ± 5.5 months and at a median dose of 750 mg per day statistically significant improvement in skin ($P < 0.01$) and cardiac, pulmonary and renal involvement ($P < 0.05$) was observed. At last follow-up, 17 (20%) patients were still receiving D-penicillamine, 25 (30%) had discontinued it owing to disease improvement, and 18 (21%) had discontinued it owing to side-effects.

Conclusions—In a population of patients with diffuse cutaneous systemic sclerosis, with progressive disease of recent onset, D-penicillamine treatment at a median dose of 750 mg per day caused a statistically significant reduction in skin involvement and improvement of renal, cardiac and pulmonary involvement.

Keywords

D-penicillamine; scleroderma; systemic sclerosis; tissue fibrosis

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Conflicts of interest

None declared.

Systemic sclerosis is a heterogeneous autoimmune disorder characterized by excessive collagen deposition in the skin and visceral organs, endothelial dysfunction and humoral and cellular immune dysregulation.¹ Organ-specific therapies have substantially decreased morbidity and mortality;^{2–5} however, studies of potential disease-modifying agents have shown negative or contradictory results^{6–12} and at present there is no generally accepted effective disease-modifying treatment for this disorder. Owing to the heterogeneity and rarity of systemic sclerosis, it is difficult to perform prospective, randomized, double-blind placebo-controlled clinical trials at a single centre or institution. Furthermore, it is generally accepted that studies of potential disease-modifying agents in this disorder should be performed with patients with the diffuse cutaneous form (d-SSc) and with recent onset of non-Raynaud symptoms who typically have a more rapidly progressive and severe disease course as compared with patients with the limited cutaneous form of this disorder (l-SSc). While some authors have further narrowed the group of patients with d-SSc on whom clinical studies should be performed, this recommendation has not been universally implemented.¹³

D-penicillamine was first suggested as a potential treatment for systemic sclerosis following the observation that patients with Wilson's disease treated with the drug showed remarkable thinning of the skin accompanied by a reduction of total skin collagen.¹⁴ D-penicillamine has both an immunomodulatory effect,^{15–17} a reason for its past use for the treatment of rheumatoid arthritis, and it also interferes with the formation of intra- and intermolecular collagen crosslinks,^{16–20} causing the accumulation in tissues of immature, uncrosslinked collagen molecules which are more susceptible to proteolytic degradation than normally crosslinked mature collagen. These effects occur only on newly formed collagen as the drug does not interfere with stable collagen crosslinks.²¹

Several uncontrolled studies in systemic sclerosis have shown that D-penicillamine may cause improvement in skin sclerosis, decrease the rate of new visceral organ involvement, and improve overall survival.^{6,7,22–29} In a previous study conducted by one of the authors between 1973 and 1988 at another institution, 69 consecutive patients with rapidly progressive d-SSc of less than 18 months duration received D-penicillamine at a dose of at least 750 mg per day for at least 6 months.⁷ It was found that administration of D-penicillamine resulted in significant improvement in skin sclerosis and in an arrest in pulmonary involvement. The results were similar to those reported previously by Steen *et al.*⁶ However, a recent prospective study comparing low-dose vs. high-dose D-penicillamine failed to show a difference between the two regimens.⁸ Although the results of this latter study have been largely interpreted to indicate that D-penicillamine administration is not effective in the treatment of systemic sclerosis, an alternative interpretation is that D-penicillamine even at low doses can result in disease improvement. Here, we describe the results of a new study which provides support to the notion that D-penicillamine is effective in the treatment of d-SSc of recent onset.

Patients and methods

We undertook a retrospective analysis, randomly selecting a cohort of patients who had rapidly progressive systemic sclerosis of recent onset and who received treatment with D-

penicillamine for at least 3 months, from a large population of patients followed at the Scleroderma Center of our institution between 1987 and 2002. With this cohort of randomly selected patients, we examined the effects of D-penicillamine on the extent and severity of skin involvement employing the modified Rodnan skin score²⁹ (MRSS) and on an estimate of total body surface (TBS) involvement employing the rule of nines.³⁰ We also examined the effects of the drug on the severity of visceral organ involvement, employing some of the categories of the severity scale developed by Medsger *et al.*^{31,32}

The Thomas Jefferson University Scleroderma Center cohort of patients with systemic sclerosis includes 769 patients evaluated and followed between 1987 and 2002 fulfilling the criteria of the American College of Rheumatology (formerly the American Rheumatism Association) classification criteria for systemic sclerosis.³³ Three hundred and ninety-two patients were classified as having d-SSc and 377 were classified as having l-SSc based on the criteria of LeRoy *et al.*³⁴ Patients seen at our institution with d-SSc who have a progressive course in their disease are placed on D-penicillamine with an escalating dose, starting from 250 mg daily and increasing by 250 mg daily every 2 weeks to reach a maximum dose of 1250 mg daily if this is tolerated. Other medications concomitantly used for patients with rapidly progressive d-SSc include low-dose prednisone (< 20 mg daily), calcium channel blockers and low-dose aspirin. Of the 392 patients with d-SSc, 50 did not receive D-penicillamine because of long duration from initial diagnosis, previous use of D-penicillamine, use of other medications or enrolment in therapeutic studies not involving D-penicillamine. From the 342 patients 150 patients were randomly selected using a computer randomization program to avoid inherent selection biases. From these 150 patients who received D-penicillamine, the following inclusion and exclusion criteria were used to define the study population further. Inclusion criteria were: (i) time of onset of skin sclerosis to initiation of D-penicillamine 24 months; (ii) extent of skin sclerosis at initiation of D-penicillamine involving the trunk and/or arms and legs proximally to the elbows and/or knees, respectively; (iii) no previous treatment with D-penicillamine or other potential antifibrotic or immunosuppressive agent; and (iv) systemic sclerosis with progressive skin involvement (this was defined based on data provided by the patient and/or the referring physician as to the progression of skin involvement). Exclusion criteria were: (i) skin involvement confined to face or acral regions of the body; and (ii) chemically induced scleroderma, diffuse fasciitis, mixed connective tissue disease and overlap syndromes. From the group of patients who met the inclusion and exclusion criteria, 84 patients who received at least three consecutive months of D-penicillamine therapy were selected on whom to perform the statistical and comparative analyses.

Study entry was the initiation of D-penicillamine treatment and end of study was either the last time the patient received D-penicillamine, or if the patient was still receiving D-penicillamine, the last recorded visit. The extent and severity of skin involvement was assessed by an MRSS evaluating by palpation skin thickness in each of 17 body surface areas using a 0–3 scale (0, normal; 1, mild thickness; 2, moderate thickness; 3, severe thickness). The maximum score in this assessment is 51.²⁹ Extent of body surface affected (TBS) was assessed by the rule of nines employing a burns victim diagram.³⁰ The Medsger systemic sclerosis severity scale was employed to assess extent and severity of the disease.^{31,32} All were recorded at study entry and at end of study. The Medsger severity scale is a

scale describing the severity of organ involvement in patients with systemic sclerosis and, thus, it provides a global assessment of disease severity in populations participating in clinical studies both at a single point and longitudinally.

Percentages and means $\pm$ SD were used to describe the cohorts' demographics. A correlated matched t-test was used to compare study entry and study end data. During analysis, it was observed that the extent of skin involvement continued to increase for a variable length of time (4–7 months) following initiation of D-penicillamine therapy. Therefore, for the MRSS and TBS scores of skin involvement instead of comparing the data at study entry with the data at study end, the maximal TBS and MRSS scores were compared with the corresponding scores at the end of study to provide a more accurate assessment of the effect of D-penicillamine on the extent and severity of skin involvement.

Results

We randomly selected 150 patients from all the patients with d-SSc who received D-penicillamine. From these 150 randomly selected patients, 91 met the inclusion and exclusion criteria. From this group of 91 patients, 84 patients received D-penicillamine for at least 3 months (Fig. 1). None of the patients had received D-penicillamine or other immunosuppressive agents prior to study entry. The demographic data and other relevant clinical information of the 84 patients are shown in Table 1. The mean $\pm$ SD age at initiation of D-penicillamine was 48.7 ± 3.0 years and the mean $\pm$ SD duration of treatment with D-penicillamine was 29.2 ± 5.5 months at a median daily dose of 750 mg. Clinically detectable skin alterations were first noted in this population at a mean $\pm$ SD of 7.1 ± 1.0 months prior to study entry. Serological studies performed at study entry showed a positive test for antinuclear antibodies (ANA) in 78 (93%) patients, with 35 (42%) showing a speckled pattern, 26 (31%) a nucleolar pattern and 17 (20%) a homogeneous pattern. Only 16 (19%) patients were anti-Scl-70 positive and only two (2%) were anticentromere antibody positive. At initiation of D-penicillamine treatment the mean $\pm$ SD extent of TBS affected by clinically detectable sclerodermatous involvement was $30.9 \pm 4.2\%$ and the MRSS was 19.9 ± 2.1 . Maximum skin involvement occurred at a mean $\pm$ SD of 5.01 ± 2.2 months after study entry and reached a maximal mean $\pm$ SD TBS skin involvement of $40.4 \pm 4.3\%$ and a maximal mean $\pm$ SD MRSS of 25.0 ± 2.3 . The mean $\pm$ SD skin involvement assessed by the MRSS was reduced from 25.0 ± 2.3 at maximal involvement to 13.9 ± 2.5 at end of study, and the TBS involvement was reduced from a peak of 40.4 ± 4.3 – $18.1 \pm 4.09\%$. Both reductions reached statistical significance (Table 2). The first signs of clearly detectable skin improvement were noted at a mean $\pm$ SD of 10.6 ± 2.4 months following D-penicillamine initiation. In 12% of patients this was achieved with a dose of D-penicillamine of 500 mg per day or less, in 70% at a dose of 750 mg per day and in 17% at a dose of 1000 mg per day or above, with a maximum dose of 1250 mg per day in 9% of patients. Nineteen (23%) patients did not have skin improvement. The extent and severity of skin involvement as assessed by TBS involvement and MRSS for each individual patient in the cohort at initiation of D-penicillamine therapy, at peak (maximal) skin involvement and at end of study are shown in Figure 2.

Based on the Medsger severity scale, the general systemic sclerosis severity at study entry was mild in 33 patients (39% of the cohort). However, there was end-stage organ involvement in 15 (18%) patients. Thirty-seven (44%) patients had moderate or severe lung disease at study entry. The initial pulmonary function study showed a mean $\pm$ SD carbon monoxide diffusion capacity (DLCO) of $68.6 \pm 5.6\%$ of predicted, a total lung capacity of $90.1 \pm 5.1\%$ of predicted and a forced vital capacity of $89.6 \pm 4.2\%$ of predicted. Cardiac and renal involvement was as an average mild in the population at study entry. Peripheral vascular disease was mild in 57 patients (68%) and severe in 14 (17%), gastrointestinal involvement was mild in 41 (49%) and absent in 36 (43%) and muscle involvement was mild in 24 (29%) and absent in 60 (71%) of the cohort (Table 3). At end of study there was statistically significant improvement in pulmonary, renal and cardiac involvement (Table 3; $P < 0.05$ for all three systems). In contrast, peripheral vascular involvement worsened at the end of study although the difference did not reach statistical significance. Muscular and gastrointestinal involvement showed slight improvement without reaching statistical significance. Despite the improvement in pulmonary, renal and cardiac involvement, the mean severity score did not decrease to a lower level on the scale.

At last follow-up, 17 (20%) patients were still receiving D-penicillamine, 25 (30%) had discontinued it owing to disease improvement, and 18 (21%) had discontinued it owing to side-effects related to the medication which included proteinuria ($n = 7$), skin rash ($n = 4$), neutropenia ($n = 3$) and pemphigus ($n = 2$). One patient (1%) discontinued D-penicillamine owing to the development of scleroderma renal crisis and four patients (5%) were lost to follow-up. Nineteen patients (23%) had died at last follow-up after the end of the study: 15 from respiratory failure, two from cardiac events, one from scleroderma renal crisis and one from metastatic cancer.

Discussion

Systemic sclerosis is a heterogeneous disease ranging from limited skin involvement with slow progression of cutaneous and internal organ involvement, to diffuse skin involvement with rapid progression of skin and internal organ involvement.¹ Organ-specific therapies have substantially decreased the morbidity and mortality of the disease; however, there is a general agreement that effective disease-modifying therapy is not available. D-penicillamine has been extensively studied in numerous retrospective studies as well as in a single double-blind placebo-controlled clinical trial.^{6-8,22-28} Most retrospective studies have suggested that in selected populations of patients with systemic sclerosis, this agent causes improvement in skin involvement and reduction in mortality and organ-specific morbidity.^{6,7,22-28} In contrast, in the single double-blind placebo-controlled study in which a high and a low dose of D-penicillamine were compared, there was no statistically significant difference in skin scores between the two groups, although both groups showed improvement in skin involvement as assessed by the MRSS. However, there was a threefold greater number of patients dying of progression of the disease while they were taking the drug in the low-dose as compared with the high-dose group, although this difference did not reach statistical significance.⁸ A key difference is that the patients in the observational studies,^{6,7,28} including the one presented here, were patients with early progressive disease,

while in the single prospective study⁸ the patients had early disease that was stable and not progressive.

It is well accepted that disease modification is more important for the diffuse form of the disease and clinical studies of disease-modifying agents are performed solely with patients with d-SSc. The purpose of the present study was to revisit the use of D-penicillamine in systemic sclerosis and to describe a 15-year experience with this therapy at our institution. The present study included only patients with progressive d-SSc of recent onset. The autoantibody picture of our patients was interesting and meaningful. Only 19% of patients were anti-Scl-70 positive, 31% had a nucleolar ANA pattern (which carries a worse prognosis), and another 42% had just a speckled pattern, many of whom are likely to have a positive RNA polymerase III autoantibody, which is typical of patients with the most severe skin involvement.

In this carefully selected and followed cohort, the use of D-penicillamine showed a clear therapeutic benefit. There was statistically significant improvement in several aspects of disease severity, including a statistically significant improvement in extent and severity of skin involvement as assessed by MRSS and extent of TBS involvement, as well as improvement in lung, kidney and heart involvement when D-penicillamine was used at a median dose of 750 mg daily and for a mean $\pm$ SD of 29.2 ± 5.5 months.

In comparison with the recent low-dose vs. high-dose D-penicillamine study our patients were naïve to the use of D-penicillamine or other potential antifibrotic or anti-inflammatory agents at study entry. The previous use of such agents in some patients included in the low-dose vs. high-dose D-penicillamine study may have obscured the potential benefit of D-penicillamine on disease severity. Another important difference between the two studies is that while patients with severe lung disease were included in our study, these patients were excluded from the low-dose vs. high-dose D-penicillamine study in which a DLCO of $< 45\%$ was one of the exclusion criteria.

The difficulty with recruiting sufficient numbers of patients for systemic sclerosis double-blind, placebo treatment studies often leads to the making of a final conclusion about a potential therapeutic agent based on the results of a single multicentre controlled trial owing to the limited availability of such patients.^{8–11,35} This approach, however, may inherently cause the dismissal of potentially promising therapeutic agents from further study only on the basis of a single trial. We believe the data presented here suggest that the use of D-penicillamine as a disease-modifying therapy of rapidly progressive d-SSc of recent onset merits further study.

Acknowledgments

Although we acknowledge the inherent bias related to our study design and the superiority of randomized, double-blind placebo-controlled trials, the results of the study described here allow the conclusion that treatment of patients with progressive d-SSc of recent onset with D-penicillamine resulted in a statistically significant reduction in skin involvement and improvement of renal, cardiac and pulmonary involvement. The results further suggest that a careful re-evaluation of the potential benefits of D-penicillamine for the treatment of systemic sclerosis needs to be undertaken as no other agents have shown a clear benefit in this disorder and as the only controlled trial for this agent in this disease has not used a true placebo.

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Fig 1. Selection of study population. SSc, systemic sclerosis; l-SSc, limited cutaneous SSc; d-SSc, diffuse cutaneous SSc.

Fig 2.

Extent and severity of clinically detectable skin involvement in each individual patient at initiation of D-penicillamine therapy (study entry), at peak of involvement (maximal involvement) and at end of study assessed by total body surface involvement (a) and modified Rodnan skin score (b).

Table 1Demographic data of patients with systemic sclerosis included in the study ($n = 84$)

Female	60 (71%)
Race	
Caucasian	63 (75%)
African American	14 (17%)
Hispanic	5 (6%)
Asian	2 (2%)
Mean $\pm$ SD age at initiation of D-penicillamine	48.7 $\pm$ 3.0 years
	78 (93%); 26 (31%)
Antinuclear antibody positivity and pattern ^a	N, 35 (42%)
	S, 17 (20%) H
Anti-Scl-70/anticentromere antibody	16 (19%)/2 (2%)
Mean $\pm$ SD duration of D-penicillamine therapy	29.2 $\pm$ 5.5 months
Median dose of D-penicillamine	750 mg daily

^aN, nucleolar; S, speckled; H, homogeneous.

Table 2Extent and severity of systemic sclerosis skin involvement (mean $\pm$ SD)

	Initiation of D-penicillamine treatment	Maximal involvement	At end of study	P-value ^a
MRSS ^b	19.9 $\pm$ 2.1	25.0 $\pm$ 2.3	13.9 $\pm$ 2.5	< 0.01
TBS (%) ^c	30.9 $\pm$ 4.2	40.4 $\pm$ 4.3	18.1 $\pm$ 4.09	< 0.01

MRSS, modified Rodnan skin score; TBS, total body surface involvement.

^a Comparison between maximal involvement and end of study values.^b Assessed as described by Brennan et al.²⁹^c Assessed employing the rule of nines.³⁰

Table 3Disease severity (mean $\pm$ SD) at study entry and at end of study

Category: Medsger severity score ^a	Study entry	End of study	P-value
General	1.71 $\pm$ 0.29	1.7 $\pm$ 0.29	NS
Peripheral vascular	1.09 $\pm$ 0.18	1.22 $\pm$ 0.18	NS
Muscle	0.55 $\pm$ 0.21	0.42 $\pm$ 0.17	NS
GI tract	0.61 $\pm$ 0.17	0.54 $\pm$ 0.13	NS
Lung	1.53 $\pm$ 0.29	1.26 $\pm$ 0.26	< 0.05
Heart	0.30 $\pm$ 0.17	0.19 $\pm$ 0.14	< 0.05
Kidney	0.63 $\pm$ 0.25	0.29 $\pm$ 0.18	< 0.05

^a Assessed according to a modified Medsger systemic sclerosis severity score.^{31,32}

GI, gastrointestinal; NS, nonsignificant.