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ORIGINAL ARTICLE

Personalized Physical Therapy Versus Usual Care for Patients With Systemic Sclerosis: A Randomized Controlled Trial

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Objective. **To compare a physical therapy program to usual care of systemic sclerosis (SSc) patients on disability.**
Methods. **A 12-month followup, parallel-group randomized controlled trial involving a modified Zelen design was conducted in 4 tertiary-care hospitals. Patients were enrolled if they had a disability rating ≥0.5 on the Health Assessment Questionnaire disability index (HAQ DI) or symptoms of decreased mouth opening or limited range of motion of at least 1 joint. The experimental intervention (n = 112, of which 110 were analyzed) was a 1-month personalized supervised physical therapy program provided by trained care providers followed by home sessions. The comparator (n = 108, and all 108 were analyzed) was usual care that could include ambulatory physical therapy. The primary outcome was the HAQ DI score.**
Results. **There was no statistically significant difference in disability at 12 months (HAQ DI score between-group difference −0.01 [95% confidence interval (95% CI) −0.15, 0.13]; $P = 0.86$). Disability was reduced at 1 month for patients in the physical therapy group (HAQ DI between-group difference −0.14 [95% CI −0.24, −0.03]; $P = 0.01$); at 6 months the HAQ DI score between-group difference was −0.12 (95% CI −0.23, 0.01); $P = 0.054$. There was a statistically significant difference for hand mobility and function, and for pain, at 1 month. Microstomia was lower in the physical therapy group at 1, 6, and 12 months (between-group difference at 12 months 1.62 [95% CI 0.32, 2.93]; $P = 0.01$). No differences in adverse effects were observed.**
Conclusion. **A personalized physical therapy program did not reduce disability at 12 months but had short-term benefits for patients with SSc.**

INTRODUCTION

No disease-modifying treatment exists for systemic sclerosis (SSc), and its management is predicated on identifying organ-specific disease manifestations and initiating targeted therapies (1). Visceral involvement is responsible for reduced life expectancy (2–5), and damage to skin, tendons, joints, and blood vessels leads to impairment and disability (6). Impairments, activity limitations, and participation restrictions are mainly caused by mouth microstomia, skin retraction, hand deformation, joint motion limitations, and visceral involvement, particularly pulmonary fibrosis, and hypertension (7,8).

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Significance & Innovations

- This is the first multicenter randomized controlled trial comparing usual care to a supervised and personalized physical therapy program for patients with systemic sclerosis that includes long-term followup and has adequate sample size/power.
- The physical therapy program, in comparison to usual care, did not reduce disability at 1-year followup for patients with systemic sclerosis but did provide short-term benefits.

As in other chronic diseases affecting joints or pulmonary function, physical therapy may help reduce disability in SSc patients (9,10). However, as in many rare diseases, evidence-based rehabilitation interventions that meet the specific needs of patients are not available for SSc. Few clinical trials are available, and most of those that are lack methodologic rigor and have a limited number of patients (11–16). Recent guidelines for SSc management (1) highlighted the potential importance of rehabilitation interventions in disease management but could not make any recommendations for or against these interventions because of a lack of evidence. Moreover, SSc has a wide range of clinical phenotypes, and a simple one-size-fits-all physical therapy program may not be appropriate; standardized and personalized programs may be better adapted to the disease. Such programs are not easy to design, and the technical difficulty is worsened by the rarity of the disease and the few experts in physical therapy for SSc.

We developed a specific standardized physical therapy program supported by a type of software to generate an individualized standardized supervised physical therapy program according to a standardized individual impairment patient's report. The primary aim of this study was to assess the impact of this supervised standardized and individualized physical therapy program followed by daily home sessions at 1 year in SSc patients on disability.

PATIENTS AND METHODS

Study design. We conducted a 2-group multicenter parallel-group randomized controlled trial (RCT) with a modified Zelen design (17,18) in 4 tertiary-care hospitals. The modified Zelen design involved 2 steps. In the first step, patients were invited to participate in a cohort study aimed at assessing disability in SSc. In the second step, patients were randomized into 2 groups. Patients randomized to the usual care arm were assessed at baseline, and at 1, 6, and 12 months. Patients randomized to the experimental arm were informed that they were randomized and that if they agreed, they would receive a standardized, individualized physical therapy program. They signed a second consent form.

Patients refusing the physical therapy program were evaluated as specified in the first consent form, at baseline and at 1, 6, and 12 months, but were analyzed in the physical therapy group. Thus, patients randomized to the control group were not aware of the presence of an alternative therapy and therefore were less likely to experience "resentful demoralization," which could bias the trial results by artificially increasing the effect of the treatment (18). The study was approved by the Institutional Review Board of Cochin Hospital (no. CPP2233), and all participants gave written informed consent.

Study participants. Study participants were recruited from 3 internal medicine departments (in Paris and Lille, France) and 1 rheumatology department (in Strasbourg, France) in 4 tertiary-care hospitals by referral from their physicians (internists or rheumatologists, all experts in SSc).

Eligibility criteria were adults (≥18 years old) with a diagnosis of SSc according to the American College of Rheumatology (19) or Leroy and Medsger criteria (20), with a disability rating of ≥0.5 on the Health Assessment Questionnaire disability index (HAQ DI; range 0–3, with higher scores indicating more severe disability) (21) or symptoms of decreased mouth opening or limited range of motion of at least 1 joint. Exclusion criteria were disabling comorbidities, cognitive impairment, participation in a clinical trial in the previous 3 months, and inclusion in a standardized physical therapy program in the previous 6 months.

Randomization. The randomization process was centralized at the coordinating office, which had no involvement in enrollment, followup, or assessment of participants. An independent statistician created a computer-generated randomization list (with permuted blocks of unequal sizes) stratified by center and disease severity. The coordinating office randomly assigned the patient to the physical therapy program or to usual care and reported the randomization to the physical medicine and rehabilitation departments that contacted the patient for a consultation. During the consultation, patients were informed of their randomization to the physical therapy intervention, and if they agreed, they would receive a standardized, personalized physical therapy program.

Interventions. *Standardized supervised physical therapy sessions: development of the program.* The objectives of the program were to increase the range of motion of impaired joints, increase muscle strength and aerobic capacity, and decrease mouth microstomia, skin retractions, limitations in activities, and restrictions in participation. This standardized supervised program of physical and occupational therapy was developed during a pilot study involving 50 patients, 2 physicians in physical medicine and rehabilitation, 1 physical therapist, and 1 occupational therapist, all familiar with SSc (for study and program details, see Supplementary Appendix A and Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract). The objectives were to select physical and occupational therapy exercises and dynamic and resting splints after assessing their utility and acceptability. For several exercises and for splints, we also wanted to determine objective criteria to propose to patients according to their impairment to develop an algorithm for generating an individualized program. Exercises were stratified by patient objectives (range of motion, strength, aerobic capacity, and activity limitations) and disease localization (mouth and face, shoulders,

elbows, wrists, fingers, hips, knees, or global) and were chosen after consensus was reached between the physician and the physical and occupational therapists. This step resulted in a supervised standardized program of 6 physical therapy sections, 13 occupational therapy exercises, 3 types of splints, and a standardized individual impairment report that could be tailored to the patient with the help of a homemade software program for some exercises and the adapted splints. (See Supplementary Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract.)

Teaching the program. To standardize the physical therapy program in the 4 centers, the physicians and physical and occupational therapists who helped develop the physical therapy program organized a 1-day teaching session in the 3 other centers. The teaching session began with a morning workshop of slide presentations to present the standardized supervised program (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract). In an afternoon workshop, the exercises and splints were presented first to the care providers delivering the intervention and then to patients during treatment sessions. The slide presentations were provided to each center, along with a contact number for questions. Overall, 2 physicians in physical medicine and rehabilitation, 3 physical therapists, and 1 occupational therapist in each of the 3 associated rehabilitation centers attended the sessions.

Delivery of the program. The supervised program consisted of the trained physiotherapists and occupational therapist in each center presenting 3 weekly sessions of 3 hours each for 4 weeks (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract). The content of the program was designed according to the patient's impairment. Impairments were assessed by a physician in physical medicine and rehabilitation. The assessment was standardized, with 15 items corresponding to each anatomic site that could be altered by SSc (hip, knee, hand, wrist, elbow, shoulder, mouth, and skin), which led to the generation of a standardized individual impairment report (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract). The results of the report were entered into a homemade software program to generate the individualized part of the physical therapy program. The hand and joint range-of-motion and face exercises, the aerobic training exercises, and the 3 types of splints were the variable parts of the program. The part of the program that was not individualized and systematically delivered to patients was muscle strengthening, respiratory exercises, functional rehabilitation, and occupational therapy (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract).

Standardized and personalized home exercise sessions. During the supervised sessions, the physical therapist proposed and elaborated on a standardized and personalized home program to the patient according to the patient's supervised program. Patients were told to perform exercises at home for 30 minutes daily. The maximum number of exercises was fixed at 8 in order to increase adherence and quality of realization. The exercises were selected from the supervised physical and occupational therapy programs (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23098/abstract). The patient received a take-home document with a clear explanation of the selected exercises that included a telephone number for support. Patients wearing splints during the supervised program were asked to wear dynamic splints for 2 hours a day in 30-minute sessions and rest splints at night.

Patients in the usual care group were treated as usual as prescribed by their physician (internist, rheumatologist, or general practitioner), with no restrictions on physiotherapy.

Outcomes. The primary outcome was the HAQ DI score (21) at 12 months. Secondary outcomes were HAQ DI scores at 1 and 6 months. Other secondary outcomes assessed at 1, 6, and 12 months were disability assessed by the SSc HAQ (range 0–3) (22) and the McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) (range 0–30, with higher scores indicating more severe disability) (23); global hand mobility, assessed by the Kapandji index (range 0–50 for each hand and global score 0–100, with higher scores indicating better mobility), giving a score for opposition of the thumb and flexion and extension of long fingers (24); hand function, assessed by the Cochin Hand Function Scale (CHFS) (range 0–90, with higher scores indicating more severe hand disability) (7); microstomia, assessed by the maximal interincisor distance in millimeters, measured with a rigid decimeter scale; joint pain and patient satisfaction with health status, assessed by a 100-mm visual analog scale; health-related quality of life, assessed by the physical and mental scores of the Medical Outcomes Survey Short Form 36 (7); skin involvement, assessed by modified Rodnan skin thickness score (range 0–51, with higher scores indicating more severe skin involvement) (25); and aerobic capacity, assessed by forced expiratory volume in 1 second. The patients recorded compliance with exercise and wearing of splints in a weekly diary. All outcomes were evaluated by a specifically trained outcome assessor at baseline and at 1, 6, and 12 months. The assessor was blind to group status at baseline. When necessary, patient-reported outcomes were collected by phone, or questionnaires were mailed to patients.

Development of a propensity score to model compliance with the home program. In a post-hoc analysis, we evaluated the beneficial effect of the physical therapy program for patients adhering to the home exercise program using propensity scores. We developed a propensity score to model compliance with the home program by adherence with home exercises (assessed at month 12 and defined as at least 20–30 minutes of the home program at least 5 or 6 days per week) in the physical therapy group (for whom we observed the compliance status) and then used that model to estimate the probability of compliance in the usual-care group. Variables included in propensity scores were sex, disease severity, previous physical therapy, ongoing self-care program at inclusion, pulmonary hypertension, baseline pain, and modified Rodnan skin thickness score, CHFS, and HAQ DI scores.

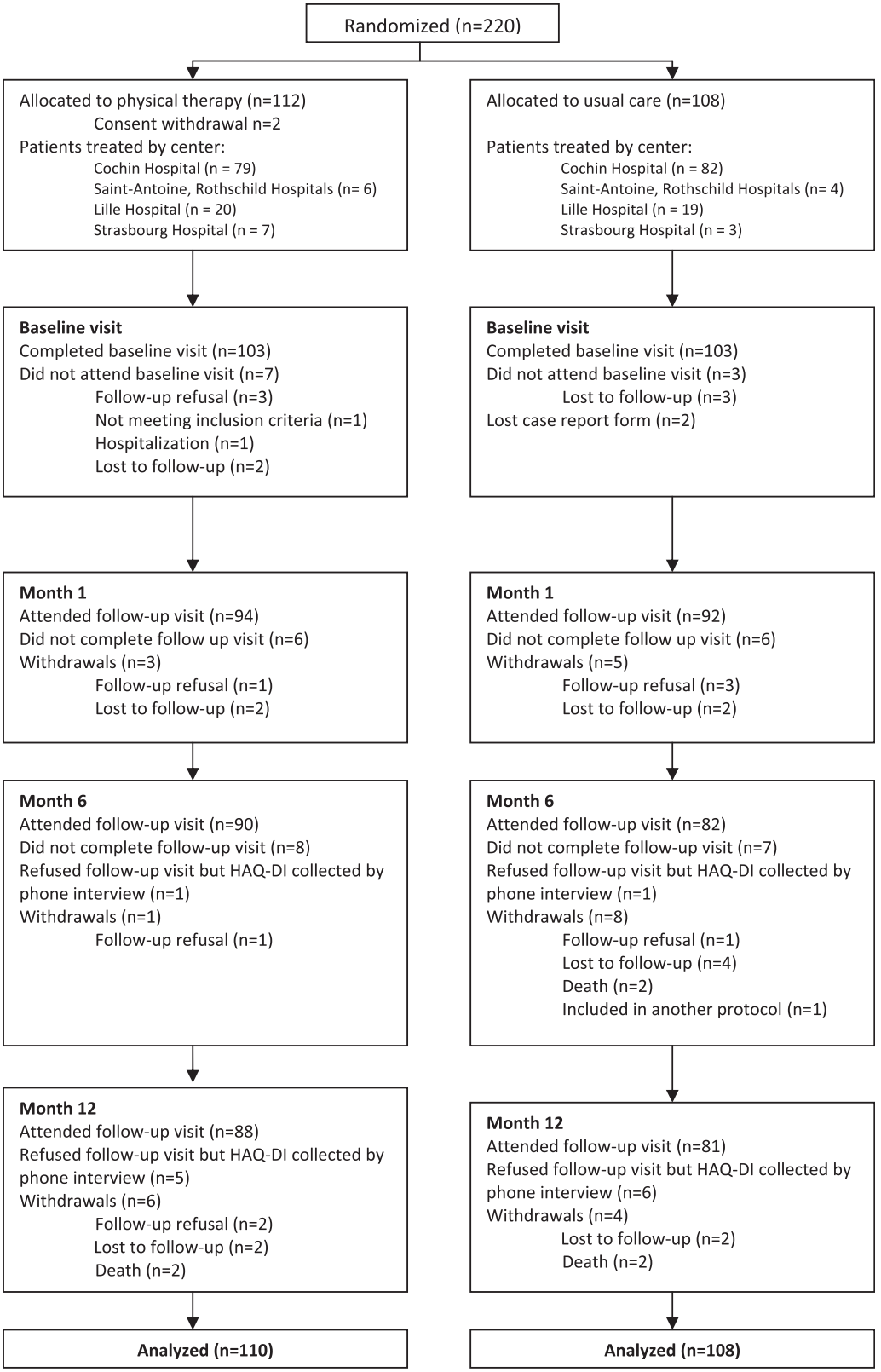

Figure 1. Flow of patients in the study. HAQ-DI = Health Assessment Questionnaire disability index.

Multiple imputation was used to account for missing data in variables included to calculate propensity scores. The propensity score was then used as a principal score to estimate the compliance average causal effect by comparing the outcome of patients compliant with the home program in the physical therapy group to that in the control group, matched

on the principal score (i.e., those who would have the same probability of complying with the home program if they were assigned to physical therapy) (26). Full matching was used, whereby matched sets of at least 1 compliant treated and 1 control patient were formed so as to minimize the average score distance within matched sets. Matched controls were then weighted to reflect the ratio of treated:control patients in the matched set. Analysis was based on a weighted regression model adjusted for baseline score, disease severity, and center, with robust standard errors to account for weighting (analyses were performed separately for 6 imputed data sets and were then pooled).

Sample size. To detect a mean ± SD difference in HAQ DI score of 0.2 ± 0.5 at 12 months with a 2-sided test at the 5% significance level and a power of 80%, we needed a sample size of 100 patients per group. This number was increased to 110 because of expected loss to followup.

Statistical analysis. All outcomes were quantitative. Differences between groups were analyzed by a linear model with random effects at the patient (intercept and slope) and center (intercept) levels for all outcomes; fixed factors were treatment, time, and interaction between time and treatment. Because disease severity was a stratification factor, an adjustment *was included* in models as a fixed factor. Inference was based on the restricted maximum likelihood solution. The model incorporated all available data for each patient in the analysis provided that baseline data for the outcome were available. It provided a likelihood function for the observed data from which treatment effects and other parameters could be estimated, with no additional steps required to account for missing data (under the hypothesis that missing data were missing at random). Thus, this model compared mean adjusted differences at 1, 6, and 12 months between the 2 groups. For the primary analysis, all randomized patients with baseline HAQ DI scores were included. All tests were 2-sided; a P value less than 0.05 was considered statistically significant. Data analysis involved the use of SAS, version 9.3, and R, version 2.15.1.

RESULTS

Selection of patients and baseline characteristics. In total, 220 patients were included and were randomized to the physical therapy group (n = 112) or usual care group (n = 108) (Figure 1). Patients were recruited from September 2005 to November 2009, and the last followup visit was done in October 2011. We excluded 2 patients in the physical therapy group due to withdrawal of consent. Three patients refused the physical therapy program but were analyzed in the physical therapy group, as specified with a modified Zelen design (17). Table 1 shows the baseline characteristics of the study population; 190 patients completed their assigned interventions, and for 169, we had complete data on outcome measures at 12-month followup.

Primary outcome. We observed no between-group differences in the primary outcome (adjusted between-group difference at 12 months −0.01 [95% CI −0.15, 0.13]; $P = 0.86$) (Table 2 and Figure 2A).

Table 1. Baseline characteristics of patients with systemic sclerosis (SSc) in physical therapy or usual care treatment group*

	Physical therapy (n = 110)	Usual care (n = 108)
Age, mean ± SD years	52.7 ± 14.8	53.1 ± 14.4
Women	95 (86.4)	86 (79.6)
Type of SSc		
Diffuse	53 (48.2)	54 (50.9)
Limited cutaneous	53 (48.2)	50 (47.2)
Limited	4 (3.6)	2 (1.9)
Disease duration, mean ± SD years	6.5 ± 6.5	6.7 ± 8.6
% normal total lung capacity, mean ± SD	91.3 ± 20.3	91.9 ± 19.5
Severity of SSc		
Sclerodactylia	97 (94.2)	100 (96.2)
Microstomia†	71 (68.9)	70 (67.3)
Scleroderma renal crisis	6 (5.5)	3 (2.8)
Pulmonary arterial hypertension‡	11 (10.0)	7 (6.5)
Pulmonary fibrosis	20 (18.2)	19 (17.6)
Trunk skin retractions	24 (21.8)	43 (39.8)
Bowel involvement	12 (10.9)	12 (10.9)
Severe SSc§	56 (51.4)	57 (52.8)
Previous or current treatment for SSc		
Physical therapy	40 (38.8)	42 (40.4)
Calcium-channel blockers	69 (62.7)	69 (63.9)
Angiotensin-converting enzyme inhibitors	37 (33.6)	37 (34.3)
Iloprost	9 (8.2)	10 (9.3)
Bowel transit accelerators	26 (23.6)	28 (25.9)
Antipeptic drugs	78 (70.9)	76 (70.4)
Nonsteroidal antiinflammatory drugs	10 (9.1)	5 (4.6)
Corticosteroids	44 (40.0)	47 (43.5)
D-penicillamine	6 (5.5)	7 (6.5)
Methotrexate	18 (16.4)	10 (9.3)
Cyclophosphamide	11 (10.0)	10 (9.3)
Azathioprine	6 (5.5)	6 (5.6)
Colchicine	21 (19.1)	24 (22.2)
Bosentan	14 (12.7)	12 (11.1)

* Values are the number (%) unless indicated otherwise.
† Interincisor distance <40 mm.
‡ Confirmed by right heart catheterism.
§ Evaluated by the treating physician.

Secondary outcomes: 1-month, 6-month, and 12-month outcomes. At 1 month, reduction in baseline disability by the HAQ DI was greater for the physical therapy than for the usual care group (adjusted between-group difference −0.14 [95% CI −0.24, −0.03]; $P = 0.0096$) (Table 3 and Figure 2A), as was reduced disability by the Scleroderma HAQ (all adjusted between-group differences −0.14 [95% CI −0.23, −0.04]; $P = 0.0051$), reduced disability by the MACTAR (−3.26 [95% CI −4.99, −1.50]; $P = 0.0003$). Reduced microstomia, improved global hand mobility, and reduced hand disability and pain were also observed (Table 3).

At 6 months the between-group difference in HAQ DI scores was −0.12 (95% CI −0.23, 0.01); $P = 0.054$. The reduction in microstomia was greater for the physical

Table 2. Adherence to daily home exercise sessions

Adherence to exercise program (n = 110)	1 month	6 months	12 months
Quantitative adherence			
No. sessions, no. (%)			
Excellent (every day)	NA	20 (24)	33 (43)
Good (5–6 days a week)	NA	8 (10)	10 (13)
Average (3–4 days a week)	NA	26 (33)	15 (20)
Poor (1–2 days a week)	NA	25 (32)	19 (26)
No. patients assessed/total no. patients (%)	NA	79/110 (72)	77/110 (70)
Duration of sessions, no. (%)			
Excellent (>30 minutes)	NA	19 (23)	17 (20)
Good (20—30 minutes)	NA	18 (23)	14 (18)
Average (10–20 minutes)	NA	33 (40)	32 (38)
Poor (<10 minutes)	NA	12 (15)	20 (24)
No. patients assessed/total no. patients (%)	NA	82/110 (74)	83/110 (75)
Qualitative adherence (assessed by a trained physician), no. (%)			
Excellent	NA	3 (4)	16 (19)
Good	NA	33 (40)	22 (26)
Average	NA	31 (38)	33 (39)
Poor	NA	11 (14)	13 (15)
No. patients assessed/total no. patients (%)	NA	81/110 (73)	84/110 (76)
Adherence to wearing splints, no. (%)			
Dynamic extension splints (n = 41)			
Excellent (worn >1 hour 30 minutes/day)	2 (5)	2 (6)	5 (12)
Good (worn 1 hour to 1 hour 30 minutes/day)	9 (25)	11 (29)	11 (28)
Poor (worn <1 hour/day)	23 (57)	19 (51)	12 (30)
Null (not worn)	6 (15)	5 (13)	11 (28)
No. patients assessed/total no. patients (%)	40/41 (98)	37/41 (90)	39/41 (95)
Dynamic flexion splints (n = 40)			
Excellent (worn >1 hour 30 minutes/day)	7 (17)	4 (10)	2 (5)
Good (worn 1 hour to 1 hour 30 minutes/day)	11 (27)	6 (15)	8 (21)
Poor (worn <1 hour/day)	19 (62)	24 (60)	17 (44)
Null (not worn)	2 (5)	5 (12)	11 (29)
No. patients assessed/total no. patients (%)	39/40 (97)	39/40 (97)	38/40 (95)
Rest splints (n = 83)			
Worn at night	76 (92)	60 (76)	50 (65)
Mean ± SD no. nights/week	6.4 ± 1.5	5.5 ± 2.0	5.1 ± 2.3
No. patients assessed/total no. patients (%)	82/83 (98)	79/83 (95)	77/83 (92)

therapy than for the usual care group (1.05 [95% CI 0.03, 2.07]; $P = 0.044$) and there was improved hand mobility (Kapandji index 2.06 [95% CI 0.01, 4.11]; $P = 0.048$).

We observed no between-group differences in most secondary outcomes at 12 months (Table 3). The reduction in microstomia from baseline was greater for the physical therapy than

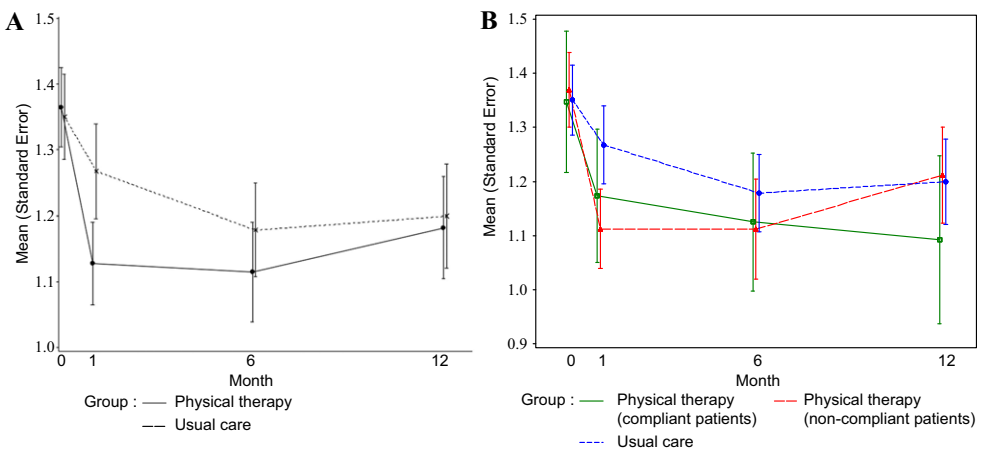

Figure 2. Mean Health Assessment Questionnaire disability index scores over time **A,** by physical therapy and usual care treatment and **B,** by physical therapy compliance and usual care treatment.

Table 3. Adjusted mean change in outcomes from baseline to 1 month, 6 months, and 12 months*

Outcome	Physical therapy	No. patients analyzed	Usual care	No. patients analyzed	Adjusted mean difference (95% CI)†	*P*‡
HAQ DI (range 0–3)						
Baseline§	1.36 ± 0.64	110	1.34 ± 0.67	108		
Month 1	1.13 ± 0.61	93	1.27 ± 0.69	92	−0.14 (−0.24, −0.03)	0.0096¶
Month 6	1.12 ± 0.72	89	1.18 ± 0.65	84	−0.12 (−0.23, 0.01)	0.0539
Month 12	1.19 ± 0.74	93	1.20 ± 0.74	87	−0.01 (−0.15, 0.13)	0.86
Scleroderma HAQ (range 0–3)						
Baseline	1.18 ± 0.55	102	1.23 ± 0.60	101		
Month 1	0.98 ± 0.51	93	1.15 ± 0.61	92	−0.14 (−0.23, −0.04)	0.0051¶
Month 6	0.98 ± 0.58	89	1.05 ± 0.61	85	−0.08 (−0.19, 0.03)	0.13
Month 12	1.09 ± 0.65	93	1.08 ± 0.64	88	0.03 (−0.10, 0.15)	0.69
Microstomia, mm						
Baseline	35.36 ± 8.41	103	35.83 ± 8.11	103		
Month 1	37.48 ± 8.17	93	36.47 ± 8.25	93	1.40 (0.51, 2.30)	0.0021¶
Month 6	37.38 ± 8.45	90	36.47 ± 7.53	83	1.05 (0.03, 2.07)	0.0442¶
Month 12	37.91 ± 8.06	88	36.52 ± 7.76	83	1.62 (0.32, 2.93)	0.0151¶
Kapandji index (range 0–100)						
Baseline	77.97 ± 16.82	103	77.05 ± 19.27	104		
Month 1	82.69 ± 16.12	93	77.51 ± 18.08	93	3.80 (2.07, 5.53)	< 0.0001¶
Month 6	82.54 ± 16.90	90	80.33 ± 17.18	84	2.06 (0.01, 4.11)	0.0490¶
Month 12	81.76 ± 16.65	88	80.00 ± 18.05	83	0.16 (−2.60, 2.93)	0.91
CHFS (range 0–90)						
Baseline	20.05 ± 15.59	102	22.18 ± 18.19	100		
Month 1	14.82 ± 13.47	92	21.20 ± 18.95	91	−3.65 (−6.12, −1.17)	0.0039¶
Month 6	16.60 ± 15.59	89	18.46 ± 17.20	81	−0.77 (−3.57, 2.04)	0.59
Month 12	18.64 ± 16.78	91	20.26 ± 18.69	82	0.48 (−3.05, 4.01)	0.79
Pain (VAS, range 0–100)						
Baseline	37.57 ± 27.73	103	41.04 ± 30.85	104		
Month 1	24.47 ± 22.88	93	41.57 ± 28.40	93	−14.02 (−22.64, −5.39)	0.0015¶
Month 6	28.70 ± 24.85	90	36.23 ± 30.37	84	−5.21 (−14.03, 3.62)	0.25
Month 12	33.80 ± 29.83	88	33.81 ± 31.42	83	1.05 (−7.82, 9.92)	0.82
MACTAR score (range 0–30)						
Baseline	19.03 ± 5.91	103	19.20 ± 6.09	104		
Month 1	13.16 ± 7.18	93	16.35 ± 7.02	93	−3.26 (−4.99, −1.50)	0.0003¶
Month 6	13.63 ± 7.62	90	14.04 ± 7.73	83	−1.10 (−3.00, 0.79)	0.25
Month 12	15.04 ± 7.99	88	15.08 ± 7.39	81	−1.05 (−3.25, 1.16)	0.35
SF-36 aggregate physical health score						
Baseline	34.04 ± 7.74	99	34.30 ± 8.89	99		
Month 1	36.33 ± 8.08	91	35.98 ± 9.37	92	0.57 (−1.41, 2.56)	0.57
Month 6	36.07 ± 8.83	85	36.50 ± 10.46	84	0.49 (−1.68, 2.65)	0.66
Month 12	35.56 ± 9.96	90	36.34 ± 10.02	84	−0.02 (−2.53, 2.50)	0.99
SF-36 aggregate mental health score						
Baseline	39.57 ± 9.87	99	38.95 ± 10.83	99		
Month 1	44.87 ± 10.81	91	41.74 ± 11.54	92	2.16 (−0.58, 4.92)	0.12
Month 6	43.06 ± 11.90	85	40.80 ± 11.22	84	1.17 (−1.78, 4.12)	0.44
Month 12	42.40 ± 11.11	90	41.76 ± 10.55	84	−0.34 (−3.64, 2.95)	0.84
Modified Rodnan skin score (range 0–51)						
Baseline	14.21 ± 8.77	103	16.67 ± 10.55	104		
Month 12	10.98 ± 7.78	86	13.49 ± 8.38	82	−0.19 (−2.14, 1.75)	0.84
Forced expiratory volume in 1 second, liters						
Baseline	2.26 ± 0.62	80	2.16 ± 0.64	82		
Month 12	2.25 ± 0.70	55	2.13 ± 0.59	57	0.08 (−0.04, 0.19)	0.18
Patient satisfaction (VAS, range 0–100)						
Month 12	60.22 ± 25.98	79	61.89 ± 25.70	91	−1.02 (−9.13, 7.10)	0.80

* Values are the mean ± SD unless otherwise indicated. 95% CI = 95% confidence interval; HAQ DI = Health Assessment Questionnaire disability index; CHFS = Cochin Hand Function Scale; VAS = visual analog scale; MACTAR = McMaster Toronto Arthritis Patient Preference Disability Questionnaire; SF-36 = Short Form 36.
† Adjusted difference: difference between physical therapy and usual care with 95% CIs obtained by linear mixed-effects models.
‡ From linear mixed-effects models.
§ Two baseline missing values were imputed with a value of 0.5 (1 in each group).
¶ Statistically significant.

for the usual care group (adjusted between-group difference 1.62 [95% CI 0.32, 2.93]; $P = 0.0151$) (Table 3).

Adherence to supervised and daily home sessions. A total of 15 patients (14%) in the physical therapy group did not attend any supervised session. The mean attendance over the 4-week supervised period was 9.3 sessions (median 11 [range 0–12]). Adherence to the daily home sessions part of the program was low (Table 2).

Adverse events. The frequency of adverse effects was similar in both treatment groups. Six participants died during followup (2 in the physical therapy group and 4 in the usual care group). Adverse events related to physical therapy were few: 2 patients reported fatigue during the supervised program, 1 patient reported hip pain after aerobic exercise, and 1 patient reported calf pain 5 days after the end of the supervised program.

Evolution of disease and treatment. At 12-month followup, 35% of patients considered to have SSc had worsened (36% in the physical therapy group and 34% in the usual care group); 25% had a new manifestation of SSc (26% and 23%, respectively), pharmacologic treatments were modified for 61% and 62%, respectively, and 10 and 9 patients, respectively, showed worsened or new digital ulcers.

Post hoc analysis according to compliance with the home program. Figure 2B shows the HAQ DI score (primary outcome) for the post hoc analysis according to home-program compliance (compliant versus noncompliant) with the physical therapy program, and compared with the usual care group. The between-group (compliant group versus usual care group) difference at 1, 6, and 12 months was −0.11 (95% CI −0.28, 0.05), −0.14 (95% CI −0.33, 0.05), and −0.08 (95% CI −0.28, 0.13), respectively (Figure 3). Quantitative and qualitative adherence is shown in Table 3.

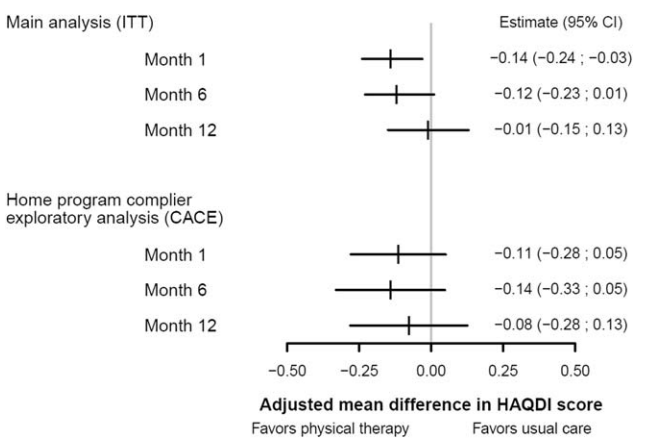

Figure 3. Effect of the supervised physical therapy program on disability. ITT = intent-to-treat; 95% CI = 95% confidence interval; CACE = complier average causal effect; HAQDI = Health Assessment Questionnaire disability index.

DISCUSSION

This is the first large RCT assessing physical therapy for SSc patients with a long-term followup. A supervised, tailored, 3-times-weekly physical therapy program for 4 weeks followed by a once-daily program performed in the home for 11 months was no different from usual care in reducing the global disability of patients with SSc at 12 months. However, the physical therapy program had a short-term clinically relevant (27) impact on global disability, assessed by the HAQ DI, and statistically significant differences were observed for hand disability, pain, and hand mobility. Furthermore, the program had short- and long-term benefits on maximal mouth opening. Although we cannot exclude that this result could be due to a multiplicity of analyses, the prolonged effect of such mouth exercises on microstomia may be important for patients with SSc: dental care is pivotal in this group because of sicca syndrome but is often problematic because of insufficient mouth opening (28). Last, concerning the HAQ DI for SSc, the minimum clinically important difference has been estimated to be between 0.10 and 0.14 (27). These values are observed at 1 month and 6 months for the physical therapy group.

A recent systematic review of trials of nonpharmacologic treatments for SSc (29) identified 9 RCTs. Only 3 of these were rated as high quality, and the largest one included 53 patients (30). One RCT suggested that a multifaceted oral health intervention improves mouth hygiene, and additional orofacial exercises did not improve mouth opening (31,32); another suggested that a multidisciplinary team-care program improves limitations in activities, mouth opening, and hand grip strength (30); and one suggested that manual lymph drainage improves hand function, reduces activity limitations, and enhances quality of life (33). The maximum followup in these RCTs was 6 months (31,32), the primary end point was at the end of the supervised program, and the type and intensity of the exercise therapy programs were heterogenous. Although the reporting of the exercise therapy programs in these RCTs was not always totally detailed, it seems that our program was more intense. The huge heterogeneity of these studies in terms of exercise program, followup, end point, and outcome measures used make comparison with our results very difficult and hazardous. Finally, the main conclusion of this systematic review was that the body of knowledge regarding nonpharmacologic care in SSc is very limited.

Our supervised program is innovative in that it is both standardized and personalized according to the patient impairments. It allows for focusing the physical treatment on the main impairments and disabilities of the patient and thus designing a personalized medicine approach that is easy to implement. Such a program is important in SSc, a complex disease with multiple clinical presentations. The high attendance rate for the training sessions suggests that 12 sessions of 3 hours each over 4 weeks is acceptable for patients with SSc. This program may be easily transferable to outpatient clinics proposing physical therapy for rheumatic and musculoskeletal disorders even if the physicians and physiotherapists are not familiar with SSc. Training of these caregivers could be helped by the use of DVDs and/or web sites. Finally, adverse events related to physical therapy

were few, and wearing splints was not associated with an increase in digital ulcers.

The daily home exercise program failed to sustain the short-term benefits on disability observed after the supervised tailored program. Poor compliance with the home program can explain these results, and post hoc analysis showed differences in HAQ DI scores between compliant patients in the physical therapy group and usual care group above published values (27) of the minimum clinically important difference at 6 months. Face-to-face procedures, such as regular supervised sessions, or at-distance procedures should be tested to help increase the efficacy of nonsupervised home exercise programs.

Although it is difficult to speculate, it is unlikely that differences observed between the intervention and control groups regarding clinical presentation (renal crisis, pulmonary arterial hypertension, and trunk skin retractions) or treatments (methotrexate and nonsteroidal antiinflammatory drugs) at baseline had an influence on results. Overall, the proportion of patients with diffuse SSc and the clinical severity assessed by trained specialists of the disease were similar in both groups and treatments were well-balanced.

Our study has some limitations. Patients were all recruited from tertiary-care centers. However, these patients are likely to represent the SSc population that may need physical therapy. SSc is a rare and often serious and complex disease, usually managed in highly specialized centers. Although this was a multicenter trial, most patients (almost 75%) were recruited in one center that might have developed special skills and experiences in supervised physical treatments for SSc, which may suggest an overestimation of short-term results. This was a pragmatic trial, and the usual care group had no limitation for physiotherapy use during the followup period. This may have led to masking potential differences between the structured physiotherapy program and no physiotherapy. However, it is very unlikely that patients in the usual care group may have received a physiotherapy program close to or comparable to the one proposed in the physical therapy group. Given the nature of many of the specific interventions of the program (i.e., splinting, strengthening, stretching, aerobic exercise), the outcomes may have been balanced by more impairment-level measures. However, for methodologic reasons, outcomes should be limited, and we decided to prioritize function and disability outcomes, as it is appropriate for this type of trial design and when the assessor has several contacts with patients and we cannot certify that he was blind to group status during the all follow up period. Blinding of patients is frequently difficult or impossible in evaluating complex interventions (34). No credible placebo or sham intervention was possible and, because no curative treatment exists for SSc, patients may have high expectations concerning physical therapy. Therefore, a strength of the study was to adopt a modified Zelen technique to enroll patients in order to avoid "resentful demoralization" in the control group. This technique probably weakens the risk of bias linked to the absence of blinding.

In conclusion, a 1-month personalized supervised physical therapy program followed by home exercise sessions did not reduce disability at 12 months but had short-term benefits for patients with SSc. Long-term benefits for microstomia were observed.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rannou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Rannou, Boutron, Mouthon, Baron, Porcher, Ravaud, Poiraudeau.

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