Differences in presentation of younger and older systemic sclerosis patients in clinical trials

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ABSTRACT

Objective. *To compare the characteristics of younger and older subjects with diffuse cutaneous systemic sclerosis (SSc) entering clinical trials.*

Methods. *Subjects were participants in three randomised interventional trials that shared relative uniformity of demographics and disease characteristics. Only subjects with diffuse cutaneous systemic sclerosis were evaluated. To maximise possible differences, the lowest (age<38 years) and highest quartiles (age>53 years) were used, and a total of 264 diffuse cutaneous SSc (dcSSc) subjects were identified. For the comparison between the two age groups, generalised linear mixed or linear models with adjustment for population norms, demographics and medications were employed to assess differences attributable to subject age.*

Results. *After adjustment for population norms and study effects, differences in diastolic blood pressure, alkaline phosphatase, AST, and creatinine phosphokinase (CK) were found between the two age groups. After further adjustment for demographics, disease duration and medications, older SSc patients still had significantly higher alkaline phosphatase (11 U/L higher), and lower CK (76 U/L lower) than younger patients (p<0.003 for all). All other variables were not significantly different in the two age groups.*

Conclusion. *Clinical baseline differences exist between younger and older patients with SSc. However, after adjustment for population norms and potential confounders, including medications, only differences in alkaline phosphatase (only 11U/L) and CK (76 U/L) remain. Overall, older patients with SSc in clinical trials seem to be more similar to younger patients than was previously thought.*

Introduction

Systemic sclerosis (SSc) is a heterogeneous disorder with important differences in the pace of development and severity of clinical and pathologic features. Effective therapies are lacking. Recently there have been several randomised controlled trials in which a sizable population of scleroderma patients has been studied (1, 2). Although these trials have specific inclusion and exclusion criteria, it remains possible that basic demographic and/or clinical features within the trial populations might influence outcomes and therapeutic responses. One such feature is patient age.

Differences between younger and older SSc patients are often difficult to study given the number of patients needed to undertake such a study and the inherent recruiting difficulties in studies of uncommon disorders. In one prospective cohort study, 7 of the 9 Hungarian SSc patients in the elderly onset group showed rapid progression of SSc with early involvement of the cardiac, pulmonary, and renal organ systems (3). In addition, previous analyses have suggested that older SSc patients tend to have more lung, kidney, and heart involvement and that onset of SSc at an older age predicts poorer prognosis and has been associated with decreased survival (4-7). Another study showed that SSc patients who were older than 40 years at diagnosis had a greater 10-year mortality compared to patients who were 16–40 years old (8). However, little is known about how much of these changes with age are secondary to aging per se versus secondary to the SSc disease process. Differences between older and younger patients would have implications for prognosis and treatment.

Our study attempts to evaluate whether baseline laboratory and clinical differences between younger and older SSc

patients enrolled in clinical trials are secondary to SSc or the aging process.

Materials and methods

Patients

Participants were subjects in one of three SSc randomised controlled clinical trials conducted from 1991 to 2006: the study of oral cyclophosphamide versus placebo in SSc interstitial lung disease (1); the study of recombinant human relaxin versus placebo in diffuse cutaneous SSc (dcSSc) (2); and the dose comparison study of D-penicillamine for dcSSc (9). These studies were multi-centre, double-blind and placebo-controlled (cyclophosphamide and relaxin) or with very low control doses *versus* standard doses (D-penicillamine). The cyclophosphamide trial (1) included both diffuse and limited SSc patients with active interstitial lung disease and randomised them to either placebo or oral cyclophosphamide. The relaxin trial (2) randomised moderate to severe but stable dcSSc patients to either placebo or relaxin by subcutaneous infusion. The D-penicillamine trial enrolled early dcSSc patients and randomised them to high versus very low dose D-penicillamine.

These studies were chosen from a group of five available studies collated through the Sclerodermas Clinical Trials Consortium (http://www.sctc-online.org). We excluded 2 trials from our analysis in order to avoid pooling subject populations that were too heterogeneous or lacked a number of key clinical outcomes of interest. We excluded a trial of oral tolerisation to type 2 bovine collagen as compared to placebo which specifically excluded patients on NSAIDs and steroids, thus resulting in recruitment of a group of patients inherently different from the other trials (10). We also excluded a partially placebo-controlled trial of methotrexate due to lack of potentially influential variables, *e.g.* blood pressure (11).

A total of 535 eligible patients were identified in the three analysed trials. To increase uniformity, only diffuse disease patients were included in this analysis. Although the patients in the three studies were not precisely the same, we found that most demographics and disease characteristics across the studies were not statistically different and, importantly, all three trials collected all variables of interest. All patients fulfilled ACR classification criteria for systemic sclerosis (12) and had dcSSc based on the presence of skin involvement in anatomic locations proximal to the elbows and knees (13). Because the present analysis deals with baseline characteristics, we adjusted for study in the event of possible imbalance in study characteristics. Disease duration was measured as time from first non-Raynaud's symptom. When the patients were split into quartiles of age, the youngest quartile (n=132) consisted of ages less than 39 while the oldest quartile consisted of ages greater than 53 (n=132). These two quartiles were chosen to maximise age-related differences while achieving balance in sample size.

Outcomes

We were interested in the domains of SSc of greatest importance to patients: skin, lung, renal, gastrointestinal, musculoskeletal function and functions of daily living. Hence, we examined the modified Rodnan Skin Score (14), maximum oral aperture, both systolic and diastolic blood pressure, pulmonary function test results (FVC, DLCO), and the Health Assessment Questionnaire-Disability Index (HAQ-DI) (15). We also evaluated serum creatinine, creatine kinase (CK), haemoglobin, albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Covariates

We examined medication categories considered to have potential impact on our outcome variables. These categories included NSAIDs (except low dose aspirin), corticosteroids, ACE-inhibitor or angiotensin receptor blockers (ARB), calcium channel blockers or pulmonary hypertension medication such as prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. We also included prior use of agents with putative disease modifying effects, including methotrexate, azathioprine and others less than or equal to 4 weeks prior to entry into the trial.

Statistical analysis:

To maximise the likelihood of discerning baseline differences between the younger and older SSc patients, we analysed the highest and lowest age quartile of the patients in these three trials using three types of analyses. Analysis using all data demonstrated similar results and the highest and lowest age quartile data are presented here for simplicity and clarity.

First, generalised linear mixed models (16) including a study effect were initially used to compare the youngest and oldest age quartiles for continuous and categorical variables. Because age differences were not part of the primary analysis in the original trials, we treated age as an exploratory analysis so no adjustments were made for multiple comparisons.

Next, we examined whether the observed differences between the age groups were due to the aging process or disease effects. We chose outcome variables that had $p<0.10$ for the age effect in the initial models for inclusion in the second analysis step. In the second step we adjusted the variables of interest with age and gender specific values for the normal population from the National Health and Nutrition Examination Surveys (NHANES) III database (17) (serum creatinine, albumin, and blood pressure) or with reference values from the literature (albumin, CK, AST, alkaline phosphatase, and HAQ-DI) (17-19). In both cases we subtracted the reference values from the observed values. The NHANES reference values were obtained for each ethnicity and gender by fitting a 3rd order curve model on each clinical outcome variable in the NHANES III survey data versus age. A 3rd order curve model (20) was selected to take into account any possible non-linearity between age and the outcome variable. Values for the HAQ-DI and CK were adjusted with values found in the literature (18, 19) by subtracting the values for each age and ethnic group of SSc patients from the reference values and then dividing by the standard deviation, if the standard deviation was reported. If the standard deviation was not available, then the adjusted values were

obtained by subtracting the reference values from the values of SSc patients. These final adjusted values were then included in the generalised linear model as a separate dependent variable.

Lastly, we applied generalised linear mixed models with various covariates for the adjusted clinical outcome variables. We evaluated whether the outcome variables were significantly different in the two age groups after adjustment for disease duration, race, gender, body mass index (BMI), medication use, and study effect (given that data from 3 different clinical trials were included), using SAS Proc GENMOD (SAS Release 9.1 The SAS Institute, Cary, NC, USA).

Results

We performed our analyses on the 264 diffuse SSc patients who were either more than 53 (range: 54-83) or less than 39 (range: 19-38) years old. The mean age in the older and younger groups were 61.7 and 32.3 years of age, respectively.

Analysis with adjustment for study effect

The differences between younger and older SSc patients are presented in Table I where data are shown with only adjustment for study effect. Older SSc patients had a significantly higher BMI (26.7 *vs*. 24.8 p=0.0001), and a greater proportion of older patients were Caucasian as compared to younger patients (86% *vs*. 62%, p=0.0001).

Older SSc patients were significantly more likely to be taking aspirin (17% *vs*. 6%, p=0.0001), ACE-inhibitor or ARB (23% *vs*. 6%, p=0.0001). Younger patients were significantly more likely to be on calcium channel blockers or pulmonary hypertension medications (38% *vs*. 30%, p=0.0001). The percentage of patients taking NSAIDs, putative DMARDs, or corticosteroids was not significantly different between the two age groups.

After adjustment for population norms with values available from the literature, mean differences from the general population norms between the two age groups disappeared for albumin, creatinine, and HAQ-DI. However, differences remained in diastolic BP, alkaline phosphatase, AST, and CK. For diastolic blood pressure, the mean difference between the younger SSc patients and age-matched population norms in the younger group was 3.5mmHg *versus* 0.5mmHg mean difference in the older group comparisons, (p=0.0001). For CK, there was a 92 U/L mean difference in the younger group *versus* the older group (175 U/L *vs*. 83U/L, respectively) (p=0.0001).

Table I. Baseline differences between older and younger age groups.

		Age<39 n=132		Age>53 n=132		
		MEAN	SD[1]	MEAN	SD	p-value[2]
Demographic variables	Age	32.3	4.88	61.7	6.35	--
	Disease duration (years)	2.92	1.69	2.63	1.82	0.58
	BMI	24.8	4.61	26.7	5.24	0.0001
	Race % (white)	62%		86%		0.0001
	Gender % (female)	75%		75%		0.97
Medications	NSAIDs %	38%		40%		0.81
	DMARDs %	4%		9%		0.22
	Aspirin %	6%		17%		0.0001
	Steroids %	26%		32%		0.24
	Ace-inhibitor/ARB %	6%		23%		0.0001
	Calcium channel blockers or pulmonary hypertension %	38%		30%		0.0001
Outcome variables	Modified Rodnan Skin Score (0-51)	21.0	9.7	21.1	10.5	0.71
	Maximum oral aperture (mm)	46.8	10.0	46.9	9.2	0.71
	Systolic blood pressure (mmHg)	113.2	14.5	128.7	19.5	0.0001
	Diastolic blood pressure (mmHg)	68.95	8.8	75.03	11.1	0.0001
	Haemoglobin (g/dl)	12.9	1.3	12.9	1.4	0.79
	Albumin (mg/dl)	3.95	0.47	3.84	0.36	0.003
	Alkaline phosphatase (U/L)	64.7	20.3	72.5	23.6	0.0001
	AST (U/L)	23.0	11.2	25.1	10.9	0.0001
	ALT (U/L)	20.5	17.6	20.5	14.2	0.96
	CK (U/L)	187.3	263.3	122.8	218.4	0.0001
	Creatinine (mg/dl)	0.72	0.20	0.81	0.28	0.0001
	Creatinine clearance (mL/min)	131.2	39.7	94.4	34.7	0.0001
	FVC maximum %predicted	76.8	18.0	79.7	16.1	0.002
	DLCO % predicted	65.1	21.5	60.9	21.2	0.50
	HAQ-DI (0-3)	0.90	0.65	1.05	0.68	0.009
	Global Patient Assessment (0-100)	45.9	26.0	44.1	24.9	0.66

Standard deviation.
p-values from two-group comparison test after adjustment for study effect.

Regression analyses with multiple adjustments

After adjustment for gender, race, BMI, patient medications plus using normative adjustments from the literature, we applied generalised linear mixed models with various covariates for the adjusted clinical outcome variables. Alkaline phosphatase, and CK (Table II) remained significantly different in the two age groups (p<0.003 for each). For instance, after holding all other model variables constant in the models, alkaline phosphatase was 11 U/L higher, and CK was 76 U/L lower in older patients than younger patients. Other outcome variables were not significantly different between the two age groups (results not shown).

In addition, using the above models and adjustments, higher observed CK was significantly associated with non-Caucasian race, NSAIDs, steroid use, younger age and not taking calcium channel blocker or pulmonary hypertension medications (nominal p<0.008 for all). Also, lower observed alkaline phosphatase was significantly associated with Caucasian race, female sex, longer disease duration, use of NSAIDS, steroids, ace-inhibitor/ARB, higher age and not using calcium channel blocker or pulmonary hypertension medications (nominal p<0.03 for all).

Table II. Results of generalised linear models with multiple covariates.

Outcome variables	Age estimate	Race	Gender	Disease duration	BMI	NSAIDS/ COX II inhibitors	Steroid	Ace-inhibitor/ ARB	CCB or pulmonary hypertension medications
Alkaline phosphatase	11*	-5.5*	-2.9*	0.5*	NS	5.3*	3.8*	2.6*	-7.8*
CK	-76*	156*	NS	NS	NS	5.1*	133*	NS	-60*

*p-value <0.05. NS: not significant. The younger age group is set as reference group.

Discussion

The goal of this study was to evaluate baseline characteristics between younger and older SSc trial participants and to assess whether age may need to be accounted in trial design. Many studies (4-7, 21) have described older patients as having more severe disease and poorer prognosis but they do not adjust for age-related differences and tend to describe relatively small numbers of SSc patients. Based on these reports, we had expected to find more differences between older and younger SSc patients in our outcome variables. However, only a few differences remained after adjustment for the effects of aging that are demonstrated in the general population *per se* and after also adjusting for other covariates such as demographics and medications. Older SSc patients were more likely to be Caucasian as compared to younger SSc patients. A previous study also reported that the mean age at diagnosis was lower in the African-American SSc patients – 43.8 years (SD 12.3) – compared to Caucasian patients 55.5 years (SD 15.2) (22). If Caucasian patients have a later age of diagnosis or disease onset (22) and/or African Americans have a lower survival rate, then it is not surprising that Caucasians represent a greater proportion of the SSc patients in the older age group (23). In general, African American SSc patients tend to have more severe disease with progressive interstitial lung disease as compared to Caucasian patients and may have a shorter survival rate (24).

Medication use, usually not accounted for in published studies, was different between the two age groups in our study. The higher percentage of older patients taking aspirin and ACE-inhibitors or ARBs is consistent with the higher prevalence of heart disease and hypertension in older patients. A higher percentage of younger patients were taking either calcium channel blockers or pulmonary hypertension medications than older SSc patients; our data could not discern (nor was it designed to discern) whether this is because younger patients have symptoms or signs requiring these medications (*e.g.* Raynauds syndrome or pulmonary hypertension) or that older patients cannot tolerate or are not prescribed these medications.

Adjustment for population norms revealed statistically significant differences between reference and SSc patient values between the two age categories for alkaline phosphatase, AST, and diastolic blood pressure, but the differences tended to be very small and unlikely to be of clinical significance. Younger SSc patients have higher CKs than their normal contemporaries (difference 175 U/L) or older SSc patients compared to their normal contemporaries (difference 83 U/L). There were CK differences between older SSc patients and their contemporaries that were statistically significantly different but of unclear clinical significance. CK differences between the younger SSc and their contemporaries were more pronounced. However, these trials excluded subjects on high doses of prednisone such that subjects with significant myositis were unlikely to be included.

After adjusting for literature age norms, demographics and medications in the generalised linear models, only differences in alkaline phosphatase and CK remain. Older SSc patients have higher alkaline phosphatase than younger SSc patients, although all values fall within the limits of normal. The difference may be statistically significant but is probably of little clinical significance as the mean difference is 7.8 U/L.

One possible reason for the lower CK in our older SSc patients is that older SSc patients may have less muscle mass than younger SSc patients beyond what is expected from the aging process. An alternative explanation could be that younger patients are more likely to develop myopathy or develop mild increases in CK secondary to higher degrees of physical activity (25). In general, the CKs in our study were not overly high (mean of 187U/l and 123U/l-younger versus older group) – only 12.8% of subjects had CKs above 200U/L.

In our multivariable analyses, CK was also significantly affected by race, NSAIDs, corticosteroid and calcium channel blocker or pulmonary hypertension medication use. We postulate that increased use of NSAIDS and corticosteroids in patients with higher CK may be due to bias by indication, as SSc patients with higher CK may be given corticosteroids to decrease inflammation and NSAIDS to treat myalgias.

Our study is limited by the inclusion of only patients enrolled in clinical trials. These trials have defined inclusion and exclusion criteria that pre-select the enrolled group of patients. We also limited our findings to early diffuse cutaneous SSc. Thus, the results of this study may not be generalised to SSc populations as a whole, such as patients with limited SSc and will need to be replicated in observational study cohorts. However, even in this select clinical trial population, we were able to detect baseline differences.

Our study is unique because no other studies have adjusted for the effect of age in the normal population for numerous other variables including

BMI, blood pressure, albumin, alkaline phosphatase, AST, creatinine, HAQ-DI, modified Rodnan Skin Score, and pulmonary function. We also assessed the effect of medications on various measures, not done in any other studies comparing younger to older SSc patients (4-6). Complex relationships between medications and outcomes are documented in our study; however, without a prospective study, we cannot examine causation and these results will need to be confirmed in a larger cohort.

Conclusion

This study included adjustment for population norms with aging including BMI, blood pressure, albumin, alkaline phosphatase, liver function tests, creatinine, HAQ-DI, modified Rodnan Skin Score, and pulmonary function. We also assessed the effect of medications on various measures, which were different when comparing young and older patients. We found that older SSc patients have SSc-related (not expected age-related changes) in musculoskeletal function that are reflected by CK compared to younger SSc patients. Most other baseline differences between younger and older SSc patients, such as renal function, blood pressure, HAQ-DI disappeared or were clinically insignificant after controlling for age related norms and covariates, including medication use.

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