Assessment of sensitivity to change of the European Scleroderma Study Group activity index

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ABSTRACT

Objective. *The European Scleroderma Study Group (EScSG) activity index meets nearly all the OMERACT-standards of truth, discrimination and feasibility. The sensitivity to change remains to be attested. This study assesses sensitivity to change of the EScSG activity index in patients with early and severe diffuse cutaneous Systemic Sclerosis (dcSSc) treated with rituximab.*

Methods. *12-months follow-up (open-label study) of 14 consecutive patients with early dcSSc. Patients received an infusion of two times 1000mg rituximab at month 0 and 6, together with 100mg methylprednisolone. Clinical read outs (modified Rodnan skin score [mRSS], lung function and echocardiography) and EScSG activity index were performed at month 0, 3, 6 and 12. Mixed models analyses (MMA) were used to evaluate changes in parameters over time.*

Results. *There was a clinically significant change in skin score with a mean (SD) mRSS of 24.8 (4.44) at baseline and 10.4 (3.12) at month 12 (MMA $p<0.001$). Also the EScSG activity index decreased significantly, with a mean (SD) of 4.3 (1.79) at baseline and 0.7 (0.83) at month 12 (MMA $p<0.001$). The estimated mean change of the EScSG activity index was -3.6 (95%CI -4.9;-2.4) over 12 months. Indices of internal organ involvement remained stable throughout the study.*

Conclusion. *A significant improvement of the EScSG activity index was observed, in line with the significant improvement of the mRSS and the stabilisation of internal organ involvement. To our knowledge, this is the first study to attest sensitivity to change of the EScSG activity index in the subset of 'early' dcSSc.*

Trial registration. *ClinicalTrials.gov Registration, http://clinicaltrials.gov, number NCT00379431.*

Introduction

Systemic sclerosis (SSc) is a multisystemic disease, which affects various organs (1). The assessment of overall disease activity in SSc is upon these days not yet standardised (2). As it stands, the proposed European Scleroderma Study Group (EScSG) activity index has a good evidence of validity, containing face, content and construct validity, it is reliable and feasible, but the sensitivity to change remains to be investigated (2). Sensitivity to change is defined as the methodological characteristic of a measurement to detect change over time within groups (3).

In order to assess the sensitivity to change of an outcome measure, there must exist a trial of a therapy with known effectiveness (4). Several trials using rituximab as treatment have shown promising results in patients with early dcSSc (5-8). In this study, the sensitivity to change of the EScSG activity index is assessed in a clinical trial of patients with early dcSSc treated with rituximab.

Patients and methods

Study design

This study was an open-label therapeutic trial, as described previously (5, 9). Patients received a first course of rituximab (1000 mg) with methylprednisolone (100 mg) at Week 0 and Week 2 and a second course at Week 26 and Week 28. The EScSG activity index together with the skin score and indices of internal organ functioning were evaluated at months 0, 3, 6 and 12.

The protocol and patient informed consent form were approved by the Ethics Committee of the Ghent University Hospital and are in accordance with the Declaration of Helsinki (Trial Registration Number: NCT00379431). Written consent was obtained from all patients.

Table I. Description of patients at baseline (n=14).

Characteristic		Statistic
Age, yrs, median (range)		52 (37-69)
Sex, female		4 (29%)
SSc-specific antibodies*	Anti-RNA-polymerase III	4 (29%)
	Anti-topoisomerase I	7 (50%)
	Anti-topoisomerase I and anti-centromeric protein B	1 (7%)
Disease duration¥ (months), median (range)		10 (5-34)
mRSS, mean (SD)		24.8 (4.44)

*SSc: systemic sclerosis; ¥Disease duration from onset of first non-Raynaud's disease manifestation; mRSS: modified Rodnan Skin Score.

Study patients

Patients with dcSSc, fulfilling the ACR-EULAR classification criteria for SSc (10), were screened at the Ghent University Hospital.

Inclusion criteria were as described previously: age older than 18 years; disease duration less than or equal to four years (time since first non-Raynaud's disease manifestation); a modified Rodnan Skin Score (mRSS) ≥14, or a EScSG activity score ≥3. Low-dose prednisolone (≤10 mg/day) was allowed, provided that the patients were on a stable dose at least 12 weeks before inclusion (5, 9). All disease-modifying anti-rheumatic drugs (except methotrexate) were stopped 12 weeks before screening and were replaced by methotrexate 15 mg per week (unless contraindicated). Exclusion criteria were: forced vital capacity (FVC) ≤50%, a diffusing capacity of the lung for carbon monoxide (DLCO) ≤40%, echocardiographically assessed left ventricular ejection fraction (LVEF) ≤40%, serious and uncontrolled coexisting diseases, infection, immunodeficiency, or a history of cancer (5, 9).

Measurements

The EScSG activity score was calculated (11, 12). The 10 items of the index were recorded by anamnesis (patient-reported items), clinical examination (mRSS, scleredema, digital necrosis, arthritis), laboratory measures (erythrocyte sedimentation rate [ESR] and complement factors C3 and C4) and pulmonary function test (DLCO). The skin score (17-site mRSS, scale 0-3) was obtained by the same investigator throughout the study (VS), according to the standard method (13). Lung involvement was assessed by pulmonary function tests. Cardiac involvement was assessed by echocardiography.

Screening for antinuclear antibodies was performed as described previously (9).

Statistical analysis

Descriptive statistics were calculated for age, disease duration, EScSG ac-

Table II. Changes in clinical parameters in the study upon treatment with rituximab.

Variable	Statistic	0M, n=14		3M, n=14		6M, n=13·		12M, n=13		P-value (MMA)
mRSS (0-51 points)	Mean, SD	24.8	4.44	18.9¥	6.29	14.1¥	4.17	10.4¥	3.12	<0.001
	Median	24.5		18.0		16.0		10.0		
	Min, max	17.0	33.0	11.0	33.0	8.0	20.0	6.0	19.0	
DLCO (% of normal)	Mean, SD	71.9	18.57	65.6*	18.65	70.0	16.81	71.2	17.06	0.044
	Median	63.0		61.0		66.0		69.0		
	Min, max	53.0	111.0	44.0	106.0	41.0	98.0	38.0	96.0	
FVC (% of normal)	Mean, SD	95.7	11.21	90.8	12.11	93.9	14.65	95.2	14.55	0.478
	Median	94.5		94.0		93.0		97.5		
	Min, max	76.0	117.0	68.0	105.0	71.0	125.0	64.0	113.0	
TLC (% of normal)	Mean, SD	84.9	9.93	82.8	11.20	85.7	14.17	89.5	12.72	0.206
	Median	84.5		81.0		86.0		91.0		
	Min, max	64.0	103.0	61.0	100.0	62.0	112.0	67.0	118.0	
FEV (% of normal)	Mean, SD	87.6	9.71	84.9	16.0	83.9	13.04	88.0	14.69	0.283
	Median	87.0		83.0		81.0		87.0		
	Min, max	71.0	105.0	49.0	105.0	66.0	107.0	62.0	113.0	
LVEF (% of normal)	Mean, SD	65.5	7.24	67.2	5.04	63.8	5.76	64.1	4.72	0.291
	Median	69.0		68.0		64.0		67.0		
	Min, max	50.0	72.0	55.0	75.0	55.0	72.0	55.0	69.0	
sPAP (mmHg)	Mean, SD	31.3	3.32	29.2	5.59	30.2	7.66	29.3	4.47	0.790
	Median	31.0		28.0		29.5		29.0		
	Min, max	26.0	36.0	23.0	39.0	17.0	44.0	23.0	36.0	

Significance of all values *versus* baseline: *p<0.01; ¥p<0.001 (P-values are not Bonferroni corrected, but should be compared to $\alpha = 0.05/3=0.017$). One patient died, thus from this visit data are given for n=13; MMA: Mixed Model Analysis; mRSS: modified Rodnan skin score; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure.

Table III. Overview of deaths and SAE.

No. of deaths	1
No. of patients experiencing a SAE	3
Total no. of SAEs	4
SAE 1. Coronary arterial bypass grafting*	1
SAE 2. Episode of noninfectious subfebrility*	1
SAE 3. Sepsis leading to death*	1
SAE 4. Renal crisis	1

*Described in previous reports of this trial (5, 9).

tivity index, mRSS and parameters for internal organ involvement (DLCO, FVC, total lung capacity [TLC], forced expiratory volume in one second [FEV1], systolic pulmonary arterial pressure [sPAP], LVEF). Mean (SD)/ median (min;max) of all clinical parameters and EScSG activity score for baseline and all-time points were calculated. The observed mean/median percentage improvement of mRSS and EScSG activity score *versus* baseline was calculated for 12 months. Mixed models analyses (MMA) with random intercept for patient were used to evaluate changes in clinical parameters and EScSG activity score over time. Moreover, the estimated mean change of mRSS and EScSG activity score *versus* baseline was calculated for 12 months, together with the effect size. Models with heterogeneous variances were selected when the AIC (Akaike's information criterion) improved at least with two units, compared to the homogeneous model.

Data analysis was performed using SPSS 22 (SPSS Inc., an IBM company, Chicago, IL, USA). A statistical significance level of 0.05 was used. In case of multiple testing, the Bonferroni correction was applied (14).

Results

Patient characteristics

All 14 consecutive patients were diagnosed with early dcSSc (a disease duration less than three years, as described) (15). Patient characteristics at baseline are given in Table I. The EScSG activity index-items per patient at baseline are given in supplementary file 1.

Clinical efficacy

Evaluation of mRSS and internal organ involvement is presented in Table II.

The clinical skin score (mRSS) improved steadily over 12 months. There was a statistically and clinically significant decrease in mRSS, with a mean mRSS of 24.8 (SD: 4.44) at baseline *versus* 10.4 (SD: 3.12) at month 12 (MMA $p<0.001$), which is a mean percentage improvement of 58%. A median mRSS of 24.5 at baseline *versus* 10.0 at month 12 was seen, which is a median improvement of 59%. The estimated mean change of the mRSS after 12 months of follow-up compared to baseline was -14.4 (95% CI -17.3;-11.6). This statistically significant change of mRSS applies also to each time-point in between, even after Bonferroni correction for multiple testing.

The DLCO showed a statistically, but not clinically significant, overall decrease with a mean DLCO 71.9% of normal at baseline (SD: 18.57) *versus* 71.2% at month 12 (SD: 17.06) (MMA $p=0.044$). After Bonferroni adjustments, no statistically significant change was noted. Also, the other lung parameters remained stable over 1 year of follow-up. There was no significant change in sPAP, with a mean sPAP of 31.3 mmHg (SD: 3.32) at baseline *versus* 29.3 mmHg (SD: 4.47) at month 12 (MMA $p=0.79$). Indices of internal organ involvement remained stable during follow-up.

Deaths and serious adverse events occurring during the study period are given in Table III. They were all considered to be probably unrelated to the study medication.

Disease activity

Evolution of EScSG activity index is shown in Table IV. Interestingly, the mean score of all 14 patients changed significantly at all time-points compared with baseline, even after Bonferroni correction. Over 12 months the mean EScSG activity score improved from 4.3 (SD: 1.79) to 0.7 (SD: 0.83) (MMA $p<0.001$), which is a mean percentage improvement of 84%. The median EScSG activity score improved from 3.5 (range: 1.5–7.5) to 0.5 (range: 0.0–2.5) (MMA $p<0.001$), which is a

Table IV. Changes in the European Scleroderma Study Group (EScSG) activity score upon treatment with rituximab.

Variable	Statistic	0M, n=14		3M, n=14		6M‖, n=13		12M, n=13		*p*-value (MMA¶)
EScSG activity score	Mean, SD	4.3	1.79	2.0	1.35*	1.1	0.67*	0.7	0.83*	<0.001
	Median	3.5		1.8		1.0		0.5		
	Min, max	1.5	7.5	0.0	5.0	0.0	2.0	0.0	2.5	
	Estimated mean change¥							-3.6 ·		
	95% CI (units)							-4.9	-2.4	
	Effect size							-2.07		
	Observed mean change (%)¥							84%		
	Observed median change (%)¥							86%		
EScSG activity score without mRSS$ and DLCO§	Mean, SD	3.00	1.77	1.08	1.17*	0.38	0.65*	0.27	0.67*	<0.001
	Median	2.5		0.5		0.0		0.0		
	min, max	0.5	6.5	0.0	2.0	0.0	2.0	0.0	2.0	

Significance of values *versus* baseline: $p<0.001$ (P-values are not Bonferroni corrected, but should be compared to $\alpha = 0.05/3=0.017$); ¥12M vs 0M; $p<0.001$ and *p*-value is 95% Bonferroni corrected CI (taking 3 multiple comparisons into account, more specific, each visit *vs*. baseline visit); ‖One patient died, thus from this visit on data are given for n=13; ¶MMA: mixed model analysis; $mRSS: modified Rodnan skin score; §DLCO: diffusion capacity for carbon monoxide.

median percentage improvement of 86%. The estimated mean change of the EScSG activity score after 12 months of follow-up compared to baseline was -3.6 units (95%CI -4.9; -2.4, $p<0.001$). The calculated effect size was -2.07, which means a large effect.

Moreover, without considering the mRSS and/or DLCO, the EScSG activity score is still improving significantly at all time-points compared with baseline (MMA $p<0.001$). More details on the evolution of the EScSG activity index-items per patient are given in supplementary file 1.

Discussion

To our knowledge, this manuscript is the first to assess the sensitivity to change of the EScSG activity index in a clinical trial. Results show a statistically significant improvement of EScSG activity score over 1 year in early dcSSc patients on a two-treatment course with rituximab (month 0 and 6). These data may suggest that the EScSG activity index is an effective index to capture change in disease activity in treated patients, proving its sensitivity to change.

In line with the improvement of the EScSG activity index, a significant improvement of the skin score was found. The skin score improvement was clinically meaningful since it largely exceeds the consensus based minimal clinically relevant treatment effect of 3.0–7.5 units and the data driven based minimal important difference of 3.2-5.3 (16). The improvement of skin score is more than can be expected as a spontaneous improvement in patients with similar disease duration, which was in a RCT with D-penicillamine between 2.2 units and 3.9 units after one year (17). Furthermore, as seen in our previous results, there was no significant progression in internal organ involvement under treatment with rituximab (5, 9). This, while normally the largest prevalence of progressive organ involvement is to be expected in the early subset of dcSSc (18). Only the DLCO showed a statistical significant difference, but it was not significant after Bonferroni correction. Moreover, it did not exceed the consensus based 'minimal clinically relevant treatment effect' of 9–10% (16).

We presume the change in EScSG activity index to be clinically meaningful, since the skin score, that also showed a major change, is one of the 10 variables included in the index. But even without considering the skin score (mRSS) in the analysis, the EScSG activity index changed significantly over time. Thus, we conclude that variables other than the mRSS, are also responsible for the improvement of the EScSG activity index.

Notwithstanding these results, the authors are aware of the limitations of this study, which is the rather small number of patients together with the open lable study design. Moreover, a new index of outcome measures has been recently developed and partially validated, namely the Combined Response Index for Systemic Sclerosis (CRISS). The CRISS is of value too for evaluating response in future clinical trials (19).

The EScSG activity index has been recognised to be a valid, reliable and feasible outcome measure (2). This manuscript argues that it may also be a sensitive tool in assessing change over time in patients with early dcSSc. Hence, the EScSG activity index may be considered to be included as a standardised outcome measure in future studies.

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