Supplementary file

Leiden CCISS (Comprehensive Care in SSc) cohort

The CCISS cohort started in 2009 with a 2-day program (standard) including consultations with a rheumatologist, pulmonologist, cardiologist, physical therapist, specialized nurse and if indicated a social worker or occupational therapist. Afterwards, the results are discussed in a multidisciplinary team hearing to evaluate organ involvement and, if needed, treatment options. Details up to 2012 are published elsewhere (1).

In 2014, two 1-day programs (light and light plus) were added for the mild and stable SSc patients. In both programs, patients have a consultation with a rheumatologist, physical therapist and specialized nurse and perform a laboratory analysis, pulmonary function test and electrocardiogram. In the light plus program, a cardiac ultrasound and a consultation with the cardiologist is scheduled in addition. Based on the results of the investigations, additional investigations are planned if indicated. During the multidisciplinary team meeting, it is decided which program a patient will receive next year. At cohort entry, however, all patients undergo the standard 2-day program.

Additionally, a screening program has been installed for patients referred because of RP. This is a one-day program, consisting of consultations with a rheumatologist, physical therapist and specialized nurse, laboratory analysis, a nailfold capillaroscopy, a pulmonary function test, X-thorax and electrocardiogram. If the diagnosis of SSc is established, then this program will be elaborated to a standard program. In all programs, functional assessments are measured, including the six minute walk test, grip strength, finger-to-palm distance and mouth opening.

Since the start of the CCISS cohort, the Scleroderma Health Assessment Questionnaire for physical disabilities (2), the SF-36 (3) and the EQ5DNL (4) have been collected annually. In 2013, the UCLA Gastrointestinal Questionnaire 2.0 (5, 6) was added. Since 2018, patients are able to complete questionnaires online through Castor Electronic Data Capture system, which is sent two to three weeks before their scheduled visit. With the transition to online questionnaires, multiple new questionnaires were added such as one on environmental exposures, one on sicca complaints, Cochin Hand Function (7), Mouth Handicap in Systemic Sclerosis (8), and Function Assessment of Chronic Illness Therapy (FACIT).

References

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Table S1. Organ involvement at cohort entry stratified for autoantibody status

	2010 – 2013		2014 – 2017		2018 – 2021	
	ACA+ N=88	**ATA+ N=53**	**ACA+ N=87**	**ATA+ N=49**	**ACA+ N=100**	**ATA+ N=36**
RP duration, months	176 (63 ; 306)	95 (37 ; 184)	126 (43 ; 256)	35 (11 ; 161)	90 (35 ; 250)	36 (9 ; 107)
Non RP duration, months	50 (20 ; 126)	35 (15 ; 143)	24 (8 ; 98)	10 (4 ; 60)	25 (8 ; 76)	9 (5 ; 45)
Diagnosis duration, months	15 (5 ; 60)	24 (4 ; 132)	11 (1 ; 68)	5 (2 ; 24)	5 (0 ; 18)	1 (0 ; 20)
Disease subset:						
• Non cutaneous	26 (30)	3 (5)	35 (40)	6 (12)	28 (28)	4 (11)
• Limited cutaneous	60 (68)	30 (57)	49 (56)	23 (47)	71 (71)	22 (61)
• Diffuse cutaneous	2 (2)	20 (38)	3 (3)	20 (41)	1 (1)	10 (28)
Pulmonary arterial hypertension	3 (3)	1 (2)	1 (1)	-	4 (4)	-
Cardiac involvement	2 (2)	4 (8)	1 (1)	4 (8)	11 (11)	5 (14)
Interstitial lung disease on HRCT	11 (13)	35 (66)	6 (7)	32 (65)	15 (15)	18 (50)
Interstitial lung disease on HRCT and FVC<80%	1 (1)	13 (25)	-	13 (27)	-	7 (19)
Gastrointestinal involvement	14 (21)	11 (16)	20 (35)	17 (23)	15 (25)	9 (15)
Renal crisis	-	1 (2)	-	2 (4)	-	-
Musculoskeletal involvement	15 (17)	12 (23)	6 (7)	16 (33)	6 (6)	8 (22)
Digital ulcers	24 (28)	8 (15)	14 (16)	7 (14)	10 (10)	6 (17)

RP: Raynaud's Phenomenon; ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody

Continuous variables are represented with medians and interquartile ranges, and categorical variables with numbers and percentages.

For ACA positive patients: the following characteristics were significantly different between the cohort-entry groups: Non-RP duration (p=0.040), diagnosis duration (p=0.002), cardiac involvement (p=0.003), musculoskeletal involvement (p=0.022), and digital ulcers (p=0.024).

For ATA positive patients: the following characteristics were significantly different between the cohort-entry groups: age (p=0.002), Non-RP duration (p=0.002) and diagnosis duration (p=0.002)

First non-Raynaud's phenomenon symptom

Table S2. First non-RP symptoms in SSc patients, categorized based on cohort-entry.

	Total: n=643	**2010 – 2013 N=229**	**2014 – 2017 N=207**	**2018 – 2021 N=207**	**P-value**
First non-RP symptoms, n (%)					
Skin tightening	241 (38%)	86 (38%)	93 (45%)	63 (30%)	0.008
Sclerodactyly or puffy fingers	118 (18%)	36 (16%)	29 (14%)	53 (26%)	0.006
Fingertip lesions	83 (13%)	32 (14%)	28 (14%)	23 (11%)	0.544
Telangiectasia	25 (4%)	10 (4%)	7 (3%)	8 (4%)	0.823
Interstitial lung disease	49 (8%)	17 (7%)	17 (8%)	15 (7%)	0.929
Pulmonary arterial hypertension/cardiac involvement	3 (0,5%)	1 (0,4%)	2 (1%)	-	0.356
Myositis/synovitis	16 (3%)	8 (2%)	3 (2%)	5 (2%)	0.351
Abnormal nailfold capillaries	17 (3%)	3 (1%)	8 (4%)	6 (3%)	0.270
Gastrointestinal involvement	29 (5%)	15 (7%)	4 (2%)	10 (5%)	0.052
Calcinosis	20 (3%)	6 (3%)	5 (2%)	9 (4%)	0.486

Non-RP: first sign/symptom of SSc other than Raynaud's Phenomenon

The use of immunosuppressive medication in patients with a non-Raynaud's phenomenon duration of less than 1 year at cohort entry.

Introduction

This study raises the question if earlier recognition means earlier treatment. Unfortunately, as our study has a descriptive nature evaluating disease duration and organ involvement at baseline between the different cohort entry years, it is not designed to answer this question. To address this question as close as possible, we evaluated use and start of immunosuppressive medication for patients who had a non-RP duration of less than 1 year at cohort entry. This analysis shows the proportion of patients using and changing/starting immunosuppressive medication in relation to fixed disease duration, thus giving an idea whether patients are treated earlier in their disease course.

Methods

For this sub analysis, we only used patients with a non-RP duration of less than 1 year at cohort entry.

Results

Of the 643 included patients, 209 (33%) had a non-RP duration of less than 1 year at cohort entry. Forty-six (20%) of the 227 patients in the 2010 – 2013 group, 83 (41%) in the 2014 – 2017 group and 80 (42%) in the 2018 – 2021 group had a non-RP duration of less than 1 year at cohort entry. The proportions of patients using immunosuppressive medication were similar between the cohort entry groups (Table S3). In addition, the proportions of patients who started with, or changed, immunosuppressive medication after first evaluation in the care pathway, were comparable between the cohort entry groups.

It is important to note that this analysis does not evaluate the causal effect of disease duration on start of immunosuppressive medication. Table S3 only shows the prevalence of immunosuppressive medication between the cohort entry groups for patients with a non-RP duration of less than one year.

Table S3. Use and change of immunosuppressive medication in SSc patients with a non-RP duration of less than 1 year at cohort entry.

	Patients with a non-RP duration of less than 1 year at cohort entry				
	Total: n=209/643	**2010 – 2013 n=46/227**	**2014 – 2017 n=83/209**	**2018 – 2021 n=80/209**	**P-value***
COHORT ENTRY					
Use of immunosuppressive medication, n (%)	65 (31%)	14 (30%)	29 (35%)	22 (28%)	0.587
Change in immunosuppressive medication, n (%)	94 (45%)	20 (44%)	39 (47%)	35 (44%)	0.893
Start of immunosuppressive medication, n (%)	73 (35%)	17 (37%)	30 (36%)	26 (33%)	0.527

Follow-up year 1	n=168	n=39	n=73	n=56	
Use of immunosuppressive medication, n (%)	75 (45%)	17 (44%)	31 (43%)	27 (48%)	0.800
Change in immunosuppressive medication, n (%)	46 (27%)	6 (15%)	20 (27%)	20 (36%)	0.092
Start of immunosuppressive medication, n (%)	10 (6%)	3 (8%)	4 (5%)	3 (5%)	0.469

*P-value between cohort-entry groups.

Disease progression

For the definitions of disease progression, we kindly refer to the study by van Leeuwen et al. 2021. Rheumatology (Oxford). We compared the proportions of disease progression after one year between the cohort-entry year groups. The results are shown in Table S4. In the more recent cohort-entry groups the proportion of progression to diffuse cutaneous SSc is higher. The proportion of patients with new digital ulcers is decreasing between the cohort-entry groups. The same trend is observed for pulmonary progression and musculoskeletal progression, while cardiac progression seems to increase over time. It is difficult to draw firm conclusions from this analysis, as possible bias could have occurred. For example, for cardiac progression greater awareness and more elaborate investigations might have resulted in increased detection rates. On the other hand, for pulmonary progression, this complication might continue to worsen over time, and as such it is not observed yet in the more recent cohorts.

Table S4 . One-year progression for the cohort-entry groups

	2010 – 2013 N=229	**2014 – 2017 N=207**	**2018 – 2021 N=207**	**P-value**
Total disease progression after one year, n (%)	119 (52%)	107 (52%)	69 (33%)	<0.001
mRSS progression, n (%)	20 (10%)	15 (8%)	9 (7%)	0.570
Progression to limited cutaneous SSc, n (%)	5 (2%)	17 (8%)	6 (2%)	0.004
Progression to diffuse cutaneous SSc, n (%)	1 (0,4%)	10 (5%)	7 (3%)	0.017
Cardiac progression, n (%)	3 (1%)	10 (5%)	8 (4%)	0.100
Pulmonary arterial hypertension progression, n (%)	-	2 (1%)	-	0.167
Pulmonary progression, n (%)	41 (21%)	46 (25%)	18 (15%)	0.118
Gastrointestinal progression, n (%)	41 (18%)	34 (16%)	35 (17%)	0.858
Digital ulcers progression, n (%)	22 (11%)	9 (5%)	5 (4%)	0.013
Renal progression, n (%)	2 (1%)	2 (1%)	-	0.580
Musculoskeletal progression, n (%)	41 (18%)	21 (15%)	18 (9%)	0.019

Total disease progression was yes if a patient had progression of one of the following domains: skin, cardiac, pulmonary arterial hypertension, pulmonary, digital ulcers, gastrointestinal, renal, and musculoskeletal.

Sensitivity analysis with two groups based on cohort-entry: 2010 – 2015 and 2016 – 2021

The 2010 – 2015 group included 317 SSc patients, of whom 266 (84%) female and 51 (16%) male.

The 2016 – 2021 group comprised 326 SSc patients, of whom 243 (75%) female and 83 (25%) male.

Disease duration

In Table S5, the characteristics of these groups are shown, also stratified for sex.

Disease duration at cohort-entry for the total group is lower in the 2016 – 2021 group, compared to the 2010 – 2015 group. Stratified for sex, the 2010 – 2015 group had a longer disease duration at cohort-entry in both females and males. Females had a longer disease duration at cohort-entry than males. These results are in line with the results using three cohort-entry groups (2010 – 2013, 2014 – 2017, 2018 – 2021).

Organ involvement

The proportion of females decreased between the cohort-entry groups from 84% in the 2010 – 2015 group to 2016 – 2021 group, whereas the proportion of ACA positivity increased from 38% to 47%. In addition, the proportion of patients presenting with ILD or digital ulcers at cohort-entry was lower in the 2016 – 2021 group, compared to the 2010 – 2015 group.

Stratification for sex showed that the increase in ACA positivity between the two cohort-entry groups mainly occurred in female SSc patients. Females presented more often with digital ulcers, whereas males more often had ILD and gastrointestinal involvement.

Table S5. Characteristics of SSc patients categorized in two groups based on cohort-entry year

	2010 – 2015			**2016 – 2021**		
	Total N=317	**Female N=266**	**Male N=51**	**Total N=326**	**Female N=243**	**Male N=83**
Age, mean (SD)	54 (15)	55 (15)	53 (13)	56 (14)	56 (14)	55 (12)
RP duration	121 (39 ; 235)	124 (40 ; 237)	99 (32; 215)	70 (19 ; 201)	95 (27 ; 241)	30 (7 ; 124)
Non RP duration	40 (13 ; 136)	41 (14 ; 135)	32 (6 ; 167)	17 (6 ; 73)	18 (6 ; 82)	13 (5 ; 44)
Diagnosis duration	17 (4 ; 81)	18 (5 ; 81)	14 (2 ; 108)	5 (0 ; 28)	8 (0 ; 30)	3 (0 ; 13)
Anti-centromere antibodies	122 (38%)	111 (42%)	11 (22%)	153 (47%)	136 (56%)	17 (20%)
Anti-topoisomerase antibodies	75 (24%)	58 (22%)	17 (33%)	63 (19%)	32 (13%)	31 (37%)
Disease subset:						
- Non cutaneous	61 (19%)	55 (21%)	6 (12%)	75 (23%)	68 (28%)	7 (8%)

- Limited cutaneous	193 (61%)	166 (62%)	27 (53%)	190 (58%)	144 (59%)	46 (55%)
- Diffuse cutaneous	63 (20%)	45 (17%)	18 (35%)	61 (19%)	31 (13%)	30 (36%)
Pulmonary arterial hypertension	11 (4%)	10 (4%)	1 (2%)	8 (3%)	6 (3%)	2 (2%)
Cardiac involvement	17 (5%)	11 (4%)	6 (12%)	31 (10%)	19 (8%)	12 (15%)
Interstitial lung disease on HRCT	134 (42%)	108 (41%)	26 (51%)	94 (29%)	63 (26%)	31 (37%)
Interstitial lung disease on HRCT and FVC<80%	35 (11%)	25 (9%)	10 (20%)	24 (7%)	13 (5%)	11 (13%)
Gastrointestinal involvement	75 (24%)	55 (21%)	20 (40%)	82 (25%)	49 (20%)	33 (40%)
Renal crisis	6 (2%)	5 (2%)	1 (2%)	7 (3%)	6 (3%)	1 (1%)
Musculoskeletal involvement	59 (19%)	45 (17%)	14 (28%)	51 (16%)	33 (14%)	18 (22%)
Digital ulcers	58 (18%)	52 (20%)	6 (12%)	36 (11%)	26 (11%)	10 (12%)

RP: Raynaud's Phenomenon

Stratification for autoantibody showed that presence of DU at cohort entry decreased between the cohort-entry groups in ACA+ patients, whereas for ATA+ patients this remained stable (Table S6). Almost no ACA+ patient presented with clinically meaningful ILD, while in ATA+ patients this proportion was 24% in both groups (Table S6). Additionally, the proportion of ATA+ patients with the non-cutaneous subset increased in the cohort-entry groups from 5% in the 2010 – 2015 group to 14% in the 2016 - 2021 group.

Table S6. Characteristics of SSc patients categorized in two groups based on cohort-entry year, stratified for autoantibody status.

	2010 – 2015		**2016 – 2021**	
	ACA+ N=122	**ATA+ N=75**	**ACA+ N=153**	**ATA+ N=63**
RP duration, months	176 (63 ; 306)	80 (24 ; 182)	95 (35 ; 249)	36 (9 ; 157)
Non RP duration, months	46 (15 ; 127)	28 (6 ; 121)	25 (8 ; 83)	10 (4 ; 53)
Diagnosis duration, months	14 (3 ; 58)	16 (3 ; 100)	8 (1 ; 26)	5 (0 ; 32)
Disease subset:				
• Non cutaneous	39 (32)	4 (5)	50 (33)	9 (14)
• Limited cutaneous	80 (66)	42 (56)	100 (65)	33 (52)
• Diffuse cutaneous	3 (2)	29 (39)	3 (2)	21 (22)
Pulmonary arterial hypertension	4 (3)	1 (1)	4 (2)	-
Cardiac involvement	2 (2)	5 (7)	12 (8)	8 (13)
Interstitial lung disease on HRCT	15 (12)	50 (67)	17 (12)	35 (59)
Interstitial lung disease on HRCT and FVC<80%	1 (1)	18 (24)	-	15 (24)
Gastrointestinal involvement	21 (17)	16 (21)	28 (18)	21 (33)

Renal crisis	-	2 (3)	-	1 (2)
Musculoskeletal involvement	19 (16)	19 (25)	8 (5)	17 (27)
Digital ulcers	32 (26)	12 (16)	16 (11)	9 (14)

RP: Raynaud's Phenomenon, ACA: anti-centromere antibody, ATA: anti-topoisomerase I antibody
Continuous variables are presented as medians with interquartile ranges, and categorical variables as number with percentage.

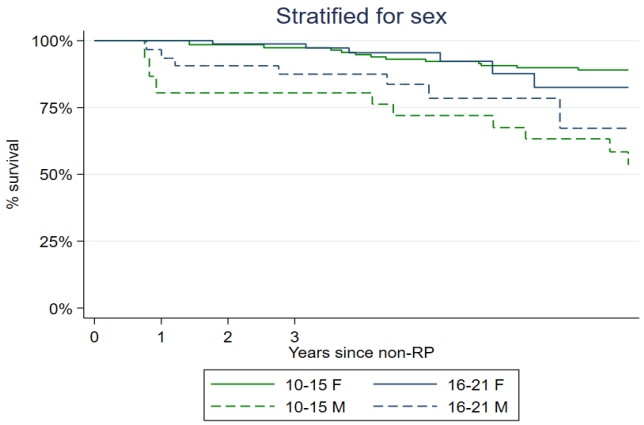
Survival

Overall 8-year survival was 82% (95% CI: 76% to 87%) for the total group, 82% (95% CI: 73% to 88%) for the 2010 – 2015 group and 78% (95% CI: 63% to 88%) for the 2016 – 2021 group. In both groups, females had a better survival than males. Stratification for autoantibodies showed that ACA+ SSc patients have a better survival than ATA+ SSc patients. For male and ATA+ SSc patients, survival showed an upward trend in the 2016 – 2021 group (Figure S1).

Figure S1. Kaplan-Meier curves for survival for SSc patients categorized in two cohort-entry groups: 2010 – 2015 and 2016 – 2021

In each figure, the green lines represent the patients from 2010 – 2015 group, and the blue lines from 2016 –2021. The upper figure shows the Kaplan-Meier curves for 8-year survival for the cohort-entry groups, the middle for cohort-entry groups stratified for sex, and the lower for the cohort-entry groups stratified for autoantibody status.

RP: Raynaud's Phenomenon, F: Female, M: Male, ACA: anti-centromere antibodies and ATA: anti-topoisomerase I antibodies


Stratified for sex
100%
75%
50%
25%
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1
2
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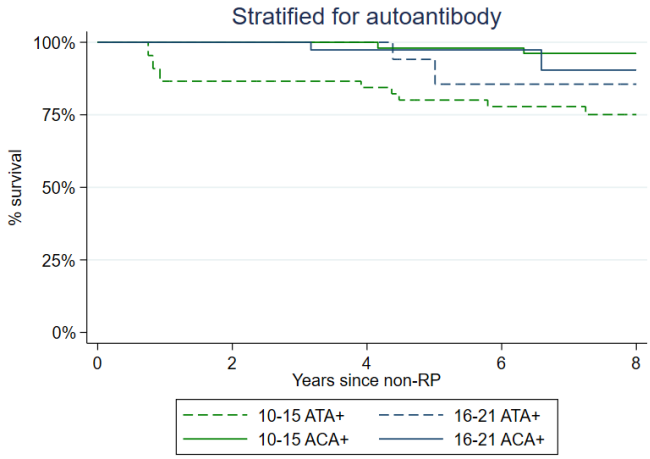
Years since non-RP
10-15 F
16-21 F
10-15 M
16-21 M


Stratified for autoantibody
100%
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