Ten years of a Systemic Sclerosis Clinic in a Tertiary Referral Centre – insights and future directions

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ABSTRACT

Systemic sclerosis (SSc) is an uncommon condition, with a wide range of manifestations, characterized by specific antibody production, vasculopathy and fibrosis of the skin and other internal organs. It is a complex disease, which is estimated to be rare in Portugal, although specific incidence data are missing. The aetiology of SSc remains unknown, but is likely to be multifactorial, involving genetic and environmental aspects. Its management is challenging and often requires a multidisciplinary approach. In 2011, we established a dedicated outpatient clinic for patients with SSc. Clinical data of every patient with a confirmed diagnosis of SSc is prospectively registered in Reuma.pt/SSc. In this manuscript, we aim to describe the general functioning of our SSc outpatient clinic, and to characterise the population of patients with SSc who are followed herein.

Keywords: Systemic Sclerosis; Scleroderma; Reuma.pt; Patient Care; Tertiary Care.

INTRODUCTION

Systemic sclerosis (SSc) is an uncommon immune-mediated rheumatic disorder representing a major challenge for both patients and physicians. Despite the evidence of improved survival in recent years[1,2], SSc still has higher mortality than other rheumatic diseases and several unmet needs remain[3]. Besides, SSc patients face uncertain outcomes, both in terms of quality of life and life expectancy[4,5]. Recently EUSTAR (European League Against Rheumatism Scleroderma Trial and Research Group) has proposed new criteria, for a very early diagnosis of SSc (VEDOSS) that are represented by the presence of the three red flags (Raynaud's phenomenon, puffy fingers and antinuclear antibodies (ANAs) positivity) plus disease-specific autoantibodies [anticentromere Ab (ACA) or anti-topo I Ab (Scl70)] or microvascular alterations detected by nailfold videocapillaroscopy. The aim of the VEDOSS criteria is to facilitate SSc diagnosis ate the earliest possible stage and threfore act as a "window of opportunity" to detect and start the appropriate treatment aimed at blocking disease evolution or progression.

The incidence of SSc in the Portuguese population is unknown. EpiReumaPt – the first large epidemiologic study of rheumatic and musculoskeletal diseases (RMDs) in the adult Portuguese population – was not powered enough to detect low prevalence diseases, such as SSc[6].

The Rheumatic Diseases Portuguese Register (Reuma.pt) was created in June 2008 and has been an essential tool in the clinical practice of Portuguese rheumatologists, allowing the structured follow-up of patients with different systemic rheumatic diseases[7,8]. In September 2015, a new protocol dedicated to scleroderma patients (Reuma.pt/SSc) was launched and has been widely used by Portuguese rheumatologists. As of December 2020, 1161 patients are registered in Reuma.pt/SSc protocol, making for a broad overview of this rare patient population at a nationwide level[9].

SSc is still undoubtedly a challenge for clinicians, because of the variety of symptoms and the lack of effective treatments for a number of disease manifestations. SSc course and prognosis depend on clinical picture and character of organ involvement (kidney, heart and lungs in particular). Treatment of patients with a disease as rare and complex as SSc should be carried out by rheumatologists, with the support and in liaison with other specialists. The follow-up of these patients in specialized centres is therefore of great importance

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in order to define the best therapeutic strategies and provide the best patient care.

The Rheumatology Department of Centro Hospitalar Universitário Lisboa Norte has a dedicated outpatient clinic for patients with SSc since 2011. Clinical data of every patient with a confirmed diagnosis of SSc is prospectively registered in Reuma.pt/SSc. In this manuscript, we aim to describe the general functioning of our SSc outpatient clinic, and to characterise the population of patients with SSc who are followed herein.

SYSTEMIC SCLEROSIS OUTPATIENT CLINIC

PATIENT PATHWAY AND CLINIC CHARACTERIZATION

Patients with SSc are referred to our department from primary health care, other specialties within our institution, or the emergency department. These patients are flagged as high-priority and seen within four weeks in a first rheumatology visit. If the diagnosis of SSc is confirmed or suspected, patients are transferred to the SSc clinic within a short window (2-3 weeks), for further assessment and follow-up.

Our SSc clinic is managed by two dedicated Rheumatologists and by one or two Rheumatology residents. It is a multidisciplinary clinic, in which various medical specialities collaborate closely. There is a regular discussion of selected cases, formalized in monthly meetings with both the Pulmonology (to discuss the approach to patients with lung involvement) and Cardiology departments (to discuss cardiovascular involvement, focusing on pulmonary hypertension). There are also two subspecialty multidisciplinary clinics to which SSc patients are regularly referred to: the Pulmonary Hypertension Clinic, led by cardiologists, and the Interstitial Lung Disease (ILD) Clinic, led by pulmonologists. For digital ulcers (DU), we have a coordinated therapeutic approach with the Department of Vascular Surgery to optimize existing DU management and prevention of new lesions. Patients with moderate-to-severe gastrointestinal involvement are referred to gastroenterologists with expertise in this disease. Cases with suspicion of renal involvement are discussed with nephrologists, on an urgent or scheduled monthly basis, depending on the clinical indication. For patients with rapidly progressive SSc, despite an initial trial of immunosuppression, we have a referral protocol to an autologous hematopoietic stem cell transplantation (HSCT) centre in Porto[10].

In addition, within our department, patients may also be referred to other subspecialty clinics, particularly in the context of overlap syndromes. Assessment in the Sjögren's Syndrome or Myositis Multidisciplinary Clinics may be warranted to optimise the approach to sicca syndrome (Stomatology, Ophthalmology), and muscular involvement (Rehabilitation Medicine), respectively. There is also integration of other health care professionals that are explained in Table I.

Patients who require biological therapies have their cases discussed in our Department's weekly meeting and are afterwards systematically monitored in our day care unit. The latter also applies to patients treated with prostacyclin in an outpatient setting.

These procedures for optimized standard-of-care and quality assessment have been defined in an official document produced by our Department, are regularly applied in our clinic and have been externally audited.

COHORT CHARACTERIZATION

A total of 327 patients were observed in our consultation and have been registered in our Reuma.pt/SSc database between July 2011 and November 2020 (Table II). Fifty patients were diagnosed with VEDOSS, 26 had localized scleroderma, and the remaining 251 had a confirmed diagnosis of SSc, fulfilling the 2013 ACR/EULAR classification criteria for SSc[11] (Table II). Two hundred eighty-five (87.2%) were female, with a mean age of 59.6 ± 16.9 years and a mean disease duration of 15.5 ± 11 years. A total of 2692 outpatient visits were registered, with a mean time of follow-up of 12.5 ± 9.2 years.

Table III represents the clinical and laboratory characteristics of patients with VEDOSS, which is characterized by the presence of red flags (Raynaud's phenomenon (RP), puffy fingers and ANA positivity), in the presence of disease-specific autoantibodies and/or microvascular alterations detected by nail fold capillaroscopy (NC)[12,13].

An additional 36 patients with suspected SSc were assessed in the clinic, but the diagnosis could not be confirmed. Most of these patients were considered to have primary Raynaud's phenomenon (n=29). In the remaining seven patients, five had undifferentiated connective tissue disease and two the Eosinophilic fasciitis diagnosis.

DISEASE FEATURES

As expected, the occurrence of RP was the most prevalent manifestation in all patient groups (Table II). Cha-

TABLE I. SUMMARY OF THE ACTIVITIES CARRIED OUT BY THE ELEMENTS INVOLVED IN THE CARE PROCESS FOR PATIENTS WITH SSC

Clinical staff	Activities	
Nurse	Follow-up assessment	a) distribution to patients of brochure about SSc and introduction to it; b) evaluation of the educational needs of the target population, including the survey of the problems caused by SSc, the skills needed to deal with them and the current level of knowledge and skills; c) orientation of the patient in the realization of immunomodulatory and vasodilator therapies, teaching of cold avoidance/protection measures, airway protection, maintenance care of vasodilator perfusion in elastomeric pump, maintenance care of local dressings and long-term oxygen therapy. d) transmitting recommendations in order to promote an active and participatory life style; e) to teach and motivate the patient to carry out a regular and lifelong exercise plan f) evaluation of weight, stature and BMI, blood pressure, heart rate and peripheral oxygen saturation
Physiotherapist	Follow-up assessment	a) correction of postural defects and static alterations; b) manual medicine (muscular massage, joint mobilization and joint amplification work), occasionally classical physical agents; c) Performance of postures and exercises of muscular-tendinous strengthening and stretching in a regime adapted to the disease, of gradually increasing intensity; d) kinesitherapy or hydrokinesitherapy, preferably in a heated tank/pool; e) aerobic training and cardio-respiratory rehabilitation.
Nutritionist	Nutrition consultation	The Nutrition consultation ensures an appropriate intervention regarding the evaluation of eating habits, counselling and dietary and nutritional prescription, ensuring the continuity of care initiated by the Doctor and Nurse, with registration in the clinical record used (computer system/paper).
Psychologist	Psychological consultation	This consultation should include a cognitive-behavioural component, aiming at coping strategies with the disease, self-efficacy training, learning adaptation, problem-solving and energy conservation techniques, and a cognitive approach to joint limitation, modification of body self-image, pain, fatigue and stress.
Doctor	SSc consultation	Carry out the diagnostic study of patients with clinical suspicion of SSc and ensure the monitoring and follow-up of patients diagnosed with SSc: > Patients with pulmonary hypertension should be identified early and referred to the Pulmonary Hypertension Multidisciplinary Consultation (evaluated periodically according to the severity of the disease). > Patients with interstitial lung disease should be identified early and referred to the Pulmonary Fibrosis Multidisciplinary Consultation (evaluated periodically according to the severity of the disease).

BMI – body mass index; SSc – Systemic Sclerosis

racteristic SSc manifestations, in particular skin involvement, such as skin thickening (quantified by the modified Rodnan skin score, mRSS) and digital tip pitting/scar were significantly more common in the dcSSc group when comparing with lcSSc. Joint involvement was most significantly prevalent in dcSSc patients, namely tendon friction rubs and joint contractures. Arthritis prevalence was similar in both groups

TABLE II. DEMOGRAPHICS, CLINICAL MANIFESTATIONS, COMPLEMENTARY TESTS FINDINGS, ASSESSMENTS AND TREATMENT OF THE PATIENTS WITH A DIAGNOSIS OF SYSTEMIC SCLEROSIS CATEGORIZED ACCORDING TO THE SUBTYPE

	Overall (n=251)	lcSSc n=129	dcSSc n=65	Sine Scleroderma n=16	SSc overlap syndrome n=41	p-value (all groups)
Demographics						
Age (years), mean (SD)	59 (17)	60 (17)	59 (17)	60 (18)	46.9 (13)	NS
Female, n (%)	220 (88)	119 (92)	53 (81)	14 (87)	34 (82)	NS
Follow-up (years), mean (SD)	12 (11)	15 (13)	13 (11)	9 (17)	9.4 (7)	NS
Clinical manifestations						
Raynaud phenomenon, n (%)	233 (93)	120 (93)	61 (94)	14 (87)	38 (93)	NS
Skin involvement						p-value (dcSSc vs lcSSc)
mRSS, mean (SD)		4.1 (3)	13 (11)	0 (0)	3.2 (5)	<0.01
Puffy fingers, n (%)	122 (49)	69 (53)	44 (68)	0 (0)	9 (22)	0.81
Digital tip pitting/scar, n (%)	53 (21)	21 (16)	27 (41)	0 (0)	5 (12)	<0.001
Sclerodactyly (proximal to MCP), n (%)	140 (56)	89 (69)	47 (72)	0 (0)	4 (10)	0.06
Digital ulcer, n (%)	92 (37)	53 (41)	25 (38)	2 (12)	12 (30)	0.87
Telangiectasias (any), n (% positive)	134 (53)	77 (57)	44 (68)	0 (0)	13 (32)	0.72
Organ involvement						
Musculoskeletal	164 (65)	69 (53)	62 (95)	4 (25)	22 (54)	<0,001
Tendon friction rubs, n (%)	35 (14)	11 (8)	19 (29)	0 (0)	1 (2)	<0.01
Joint contractures, n (%)	43 (17)	16 (12)	23 (35)	0 (0)	1 (2)	<0.01
Arthritis, n (%)	86 (34)	42 (33)	20 (31)	4 (25)	20 (49)	0.62
Gastrointestinal involvement	180 (72)	92 (71)	63 (97)	10 (62)	15 (37)	0.186
Oesophageal, n (%)	124 (45)	60 (46)	49 (75)	8 (50)	7 (17)	0.029
Stomach, n (%)	42 (16)	25 (19)	10 (15)	2 (12)	5 (12)	0.142
Intestinal, n (%)	14 (6)	7 (5)	4 (6)	0 (0)	3 (7)	0.21
Pulmonary involvement	111 (44)	51 (39)	44 (68)	7 (44)	12 (30)	0.05
ILD, n (%)	85 (34)	32 (25)	39 (60)	5 (31)	9 (22)	<0.01
Pulmonary arterial hypertension, n (%)	26 (10)	17 (13)	5 (78)	2 (12)	2 (5)	0.06
Cardiovascular system	192 (76)	98 (76)	46 (71)	8 (50)	26 (63)	0.67
Arterial hypertension, n (%)	114 (45)	52 (40)	27 (41)	5 (31)	16 (39)	0.89
Systolic dysfunction, n (%)	25 (10)	11 (8)	9 (14)	2 (12)	3 (7)	0.12
Diastolic dysfunction, n (%)	32 (13)	21 (16)	5 (8)	0	6 (15)	0.23
Conduction abnormalities, n (%)	13 (5)	11 (8)	1 (1)	0	1 (2)	<0.01
Pulmonary hypertension (group 2), n (%)	8 (3)	3 (2)	4 (6)	1 (6)	0	0.08
Renal involvement	5 (2)	0	5 (8)	0	0	
Scleroderma renal crisis, n (%)	5 (2)	0	5 (8)	0 (0)	0 (0)	NA
Laboratory parameters						
ANA positive, n (%)	237 (94)	120 (93)	61 (94)	16 (100)	40 (98)	0.67
ACA positive, n (%)	112 (45)	81 (63)	13 (11)	8 (50)	10 (24)	<0.01
Anti-Scl70 positive, n (%)	59 (23)	15 (12)	36 (53)	4 (25)	4 (10)	<0.01

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TABLE II. CONTINUATION

	Overall (n=251)	lcSSc n=129	dcSSc n=65	Sine Scleroderma n=16	SSc overlap syndrome n=41	p-value (all groups)
Anti-Pm/Scl positive, n (%)	12 (5)	3 (2)	2 (3)	2 (12)	5 (12)	0.87
Anti-Th/To positive, n (%)	4 (2)	2 (3)	0	2 (12)	0	NA
Anti-U1RNP positive, n (%)	13 (5)	0	3 (5)	0	10 (24)	NA
Anti-NOR90 positive, n (%)	1 (0)	0	1 (1)	0	0	NA
Anti-U3RNP positive, n (%)	1 (0)	0	1 (1)	0	0	NA
Anti-RNA polymerase III positive, n (%)	11 (4)	5 (4)	3 (5)	0	3 (7)	0.78
Nailfold capillaroscopy						
Scleroderma pattern present, n (%)	230 (92)	124 (96)	62 (95)	13 (81)	31 (76)	0.85
Scleroderma pattern						
Early pattern, n (%)	88 (35)	60 (46)	7 (11)	8 (50)	13 (32)	<0.01
Active pattern, %	84 (33)	35 (27)	35 (54)	3 (17)	11 (27)	<0.01
Late pattern, %	58 (23)	29 (22)	20 (31)	2 (12)	7 (17)	0.52
Treatment, n (%)						
Calcium channel blocker, n (%)	113 (45)	47 (36)	35 (54)	8 (50)	23 (56)	0.61
Proton pump inhibitor, n (%)	70 (28)	32 (25)	20 (31)	5 (31)	13 (32)	0.57
Iloprost (intravenous), n (%)	60 (24)	38 (30)	9 (14)	1 (6)	12 (29)	<0.01
Pentoxifylline, n (%)	57 (23)	33 (26)	18 (28)	2 (12)	4 (10)	0.78
Methotrexate, n (%)	56 (22)	32 (25)	15 (23)	2 (12)	7 (17)	0.84
Aminaphtone, n (%)	26 (10)	17 (13)	8 (12)	0	1 (2)	0.89
Mycophenolate mofetil, n (%)	25 (10)	7 (5)	8 (12)	6 (37)	4 (10)	<0.01
Cyclophosphamide, n (%) **	24 (97)	4 (3)	15 (23)	3 (19)	2 (5)	<0.001
Bosentan, n (%)	20 (8)	15 (12)	4 (6)	0	1 (2)	0.07
Sildenafil, n (%)	13 (5)	9 (7)	3 (5)	1 (6)	0	0.09
Azathioprine, n (%)	11 (4)	2 (2)	6 (9)	1 (6)	2 (5)	0.04
Nintedanib, %	5 (2)	0	4 (6)	1 (6)	0	NA
Riociguat, n (%)	2 (1)	0	2 (3)	0	0	NA
Rituximab, %	2 (1)	0	0	1 (6)	1 (2)	NA
Selexipag, n (%)	2 (1)	2 (2)	0	0	0	NA
Tadalafil, n (%)	2 (1)	2 (2)	0	0	0	NA
Ambrisentan, n (%)	1 (1)	1 (1)	0	0	0	NA
Macitentan, n (%)	1 (1)	1 (1)	0	0	0	NA

ACA, anticentromere antibodies; ANA, antinuclear antibodies; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; MD, missing data; mRSS, modified Rodnan skin score; NA - non applicable; NS – not significant; RP, Raynaud's phenomenon; Scl70, anti<topoisomerase I antibodies; SD - standard deviation; SSc: Systemic Sclerosis; U1RNP, uridine-rich ribonucleic protein. * Pulmonary hypertension non group 1; ** induction therapy for lung or skin involvement

(Table II).

Antinuclear antibodies were observed in more than 90% of the patients across all patient groups (Table II). The positivity for ACA autoantibodies was more frequent in lcSSc than the other subtypes, whereas positivity for anti-Scl70 autoantibodies was more prevalent in dcSSc. Notably, 11 and 12% of patients with dcSSc and lcSSc were positive for ACA and anti-Scl70, respectively. ACA was the most prevalent autoantibody in SSc sine scleroderma, whereas the overlap group mostly associated with ACA and anti-U1RNP (Table II).

Nailfold capillaroscopy, carried out in the first eval-

TABLE III. DEMOGRAPHIC AND CLINICAL 50 PATIENTS CLASSIFIED AS VEDOSS

Clinical and laboratory characteristics	VEDOSS n=50
Demographics	
Female, n (%)	45 (90)
Age (years), mean (SD)	54.1 (15)
Physical examination	
Raynaud's phenomenon, n (%)	47 (94)
Previous or current digital ulcers, n (%)	5 (10)
Previous or current digital pitting scars, n (%)	1 (2)
Previous or current puffy fingers, n (%)	10 (20)
Skin involvement (sclerodactyly), n (%)	2 (4)
Telangiectasia, n (%)	10 (20)
Oesophageal symptoms, n (%)	4 (8)
Tendon friction rubs, n (%)	0
Calcinosis, n (%)	2 (4)
Autoantibodies	
ANA positive, n (%)	47 (94)
ACA positive, n (%)	28 (56)
Scl70 positive, n (%)	10 (20)
Pm/Scl positive, n (%)	2 (4)
Th/To positive, n (%)	2 (4)
U1RNP positive, n (%)	0
Anti-NOR90 positive, n (%)	0
RNA polymerase III positive, n (%)	0
Nailfold capillaroscopy (NC)	
Early NC pattern, n (%)	22 (47)
Active NC pattern, n (%)	5 (11)
Late NC pattern, n (%)	0
No specific alteration, n (%)	20 (43)

uation, revealed a scleroderma pattern[14] in more than 90% of the patients with lcSSc and dcSSc (Table I). The early pattern, as defined by Cutolo et al., occurred more often in lcSSc and the active pattern was more common in dcSSc.

In patients with VEDOSS, RP was the most frequent clinical manifestation, followed by puffy fingers and telangiectasia (Table III). Ninety-four percent of patients were ANA positive. The most frequently detected disease-specific autoantibodies were, as expected, ACA and Scl-70. Alterations in NC were present in 91.6% of cases, being the early pattern the most prevalent (38.3%). Three ANA-negative patients were classified as VEDOSS due to compatible changes in capillaroscopy (all with early pattern).

ORGAN INVOLVEMENT

Lung

The prevalence of ILD was higher in dcSSc (60%) and *sine scleroderma* (31.3%) patients than in other forms of the disease (Table II). Nonetheless, a quarter of patients with lcSSc had lung involvement. The prevalence of ILDs in our cohort is similar to that described in many European countries such as Spain and Italy with 27.7% and 33.9% respectively[15]. Patients with ILD were more commonly positive for anti-Scl70. Of note, ACA was present in 11.8% of patients with ILD, of whom 90% had a limited skin disease phenotype.

The prevalence of pulmonary arterial hypertension (PAH) was around 10.4%, with 66% of patients with limited form, which is in line with other international series.[16] ACA was the antibody most frequent in patients with PAH. On the other hand, Scl-70 was positive in 15% of patients.

Gastrointestinal tract

Disease of the gastrointestinal tract (GIT) occurs in approximately 90% of patients with SSc and has a major impact on their quality of life[17]. Every part of the GIT can be involved in SSc. We analyze in our cohort the involvement in oesophagus (dysmotility, acid reflux), stomach (vascular ectasia, gastroparesis) and intestines (vascular lesions, hypomotility, bacterial overgrowth, intestinal pseudoobstruction). The overall prevalence of GIT involvement was approximately 70% with dominance in dcSSc, followed by the limited form (Table II). As for esophageal involvement, oesophageal reflux disease (GERD) is the most common. Gastroparesis is the most frequent complaint of gastric involvement, while diarrhea and chronic constipation are the most commonly associated with intestinal symptoms. Scl-70 was the antibody more frequent (present in 81 patients – 45%), followed by ACA in 21.7% of patients with GIT disease.

Cardiovascular system

Cardiac involvement is common in SSc and is often unrecognized until late in the disease course. All aspects of the heart can be affected, including the myocardium, pericardium, and conduction system, although typically one manifestation predominates in a particular patient[18]. We analysed the occurrence oh hypertension (HTA), conduction defects, systolic and diastolic dysfuntion and pulmonary hypertension group 2 (due to left heart disease).

Almost half of the patients are found to have HTA and their frequency distribution is similar in all groups.

Diastolic dysfunction was slightly more frequent than systolic (12.7% vs 10%), with systolic dysfunction being a widespread feature in all SSc groups.

Other problem usually seen is the conduction system disease, with a prevalence in SSc that ranges from 4 to 51 percent depending on whether resting electrocardiogram (ECG) or 24-hour ambulatory ECG monitoring is used[19]. Conduction abnormalities were significantly more common in lcSSc patients (Table II). The most common alteration was left bundle branch block (53.8%), followed by first-degree atrioventricular block (23.1%) and right bundle branch block (15.4%) while second-degree atrioventricular block were less frequent (7.7%). Eight patients were diagnosed with pulmonary hypertension due to left heart disease.

Kidney

Scleroderma renal crisis (SRC), a feared complication of SSc, was documented in five patients, four positive for anti-RNA polymerase III autoantibodies and one for Scl-70.

TREATMENT

Due to the wide spectrum of disease manifestations and organ involvement, the management of the disease is tailored to the individual patient, taking into account the disease subset and type of internal organ involvement.

Overall, the poorer prognosis and general clinical status of dcSSc patients led to more aggressive treatment plans (Table II), that more frequently included the use of immunosuppressant agents, especially cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine (AZA) and methotrexate (MTX).

Across all groups, the most commonly prescribed drugs were calcium channel blockers (whose main indication was Raynaud's phenomenon), proton pump inhibitor and iloprost (Table II). The latter was administered in patients with active DUs or patients with severe RP refractory to oral vasodilators. The most common scheme is monthly treatment with 11-hour perfusions (50mcg/0.5mL). This therapy was more used in patients with lcSSc when compared with dcSSc ($p<0.01$). Despite the lower degree of evidence, pentoxifylline and aminaphtone are also used in the clinic due to the possible benefits in microcirculation[20,21]. The first was used in 57 patients, while the second in 26 patients. For patients with multiple digital ulcers despite use of calcium channel blockers, eight are under sildenafil and nine under bosentan.

For PAH, the oral therapy included phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil and tadalafil), oral prostacyclin receptor agonists (selexipag), guanylate cyclase stimulant (riociguat), endothelin receptor antagonists (ERA) [bosentan, macitentan and ambrisentan]. A total of 14 patients with PAH were treated with ERA (1 ambrisentam, 11 bosentan and 2 macitentan) and 7 with PDE-5 inhibitors (5 sildenafil and 2 tadalafil). There are 2 patients under riociguat and other 2 under selexipag for PAH therapeutic indication.

In SSc-ILD patients, immunosuppressive therapy is started to prevent disease progression. MMF has been used as first-line therapy over CYC due to a better safety profile and comparable efficacy[22,23]. AZT is an alternative that can be considered for patients with contraindications to or intolerance to CYC and MMF.

A total of 19 patients did CYC as induction therapy due to lung involvement followed by switch to MMF or AZT. MMF was prescribed in 25 patients while AZT was the treatment of choice in 11 patients. The high percentage of patients under MMF in the sine scleroderma group is due to the high prevalence of severe ILD patients in this subgroup (Table III).

In patients who experience progressive lung function loss despite the above therapies, nintedanib and rituximab (RTX) can be considered. Currently, five patients are under nintedanib and two under RTX, with effective stabilization of lung function.

Treatment for GI involvement in SSc is presently limited to symptom relief and does not adequately address the underlying problem. Improved therapies in SSc are therefore highly needed[24,25]. In our patient population approximately one third are under proton pump inhibitors, with similar use in both disease subgroups (Table III)

Two patients (female, 22 and 45 years-old, mean disease duration 2.55 years) followed in our center underwent successful autologous HSCT. Mean mRSS at the time of HSCT was 19.5 ± 4.7. Both patients were ANA and anti-Scl70-positive, had severe RP, with daily recurrence, digital ulcers, and digital pitting. One of the patients had concomitant lung involvement with interstitial lung disease (nonspecific interstitial pneumonia). A remarkable improvement in RP was observed post-transplanation in both patients. The frequency of RP decreased from 3 to 4 episodes per day to occasional episodes in one patient, and complete resolution after the first year of transplant in another. Further, there was no recurrence of digital ulcers. The mean mRSS reduced to 18.2 ± 4.3 (-1.3) after 1 year. The patient with ILD had a significant improvement in lung function over 24 months (14.5% increase in func-

tion vital capacity, 8% increase in carbon monoxide transfer factor). None of the patient had any significant procedure-related complication or any new organ involvement during the whole period of follow up. These two patients carried out the transplantation in a specialized centre. On the other hand, we have to register the death of a patient, female, 37-year-old with dcSSc, anti-RNA III Pol-positive, with rapidly progressive skin involvement, Raynaud's phenomenon with recurrent DUs, previous episode of SRC in 2016 and documented esophageal dysmotility by manometry. Despite treatment with MTX, Iloprost and CYC, disease progression was noted and therefore the patient was proposed for autologous HSCT at three years of disease duration. Unlike the other two patients, she underwent transplantation at a different centre with less experience in SSc-related HSCT and had several early post-HSCT complications, especially infectious, and died one month following the transplant.

PATIENT OUTCOMES

The mean follow-up time of the 251 patients with confirmed SSc was 12.5 ± 11 years. Seventeen were lost to follow-up (6.8%), 11 were transferred to other centres due to change of residence (4.4%), and 44 died (17.5%).

Twenty-five out of the 44 (56.8%) deceased patients died because of events directly attributable to SSc, mostly associated with pulmonary involvement (Table IV). ILD progression was the most frequent SSc-related causes of death (n=16, 36.4%) followed by pulmonary hypertension [(group 2), n= 4, 9.1%] and by isolated PAH (n=3, 6.8%). SRC was the cause of death in 2 (4.5%) dcSSc patients. Albeit overall rare, SRC was fatal in 2/4 (50%) of cases, underlining the severity of this manifestation.

Thriteen out of the 44 (29.5%) deceased patients died because of non-SSc–related causes, with infection being the most common cause (table 4). One patient died from infectious complications after hematopoietic stem-cell transplantation (see above). In 6 patients the cause of death could not be ascertained.

COLLABORATIVE RESEARCH AND PATIENT CARE

Our centre is part of the EUSTAR group[26]. Moreover, we integrate the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)[27]. These collaborations enable the continued growth of our SSc clinic, facilitating partnerships with other clinical and research centres and the development of new research projects within the Rheumatology Research Unit at Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa. In 2019, we started a collection of blood samples from SSc patients in our institutional biobank, which will be crucial for future collaborative works.

CONCLUSION

We present the clinical description of the patients followed up in our dedicated SSc clinic and registered in Reuma.pt/SSc. Patients in our cohort reflect a typical SSc population, having a wide range of symptoms from multiple organs and systems, with different patient phenotypes, as in other populations already studied (EUSTAR database)[28].

Implementing a standardized approach with regular multidisciplinary work has proven very helpful in evaluating patients with SSc, aiming at providing the best care. Besides, a structured and focused workflow promotes the professional development of team members, facilitates the interaction between medical specialities, and ultimately improves outcomes and patient satisfaction. Additionally, recognizing patients that fulfil the VEDOSS criteria is central to the identification of this at-risk population at the earliest possible stage. Screening of pre-clinical internal organ involvement can then be swiftly implemented.

In the future, it would be interesting to speed up the referral of patients for HSCT, and eventually to start this treatment in our centre routinely. On the other hand, the introduction of patient-reported outcomes measures (PROMs) in a more systematic way in the assessment of patients with gastrointestinal involvement or ILD that are an essential reflection of a patient's experience of disease for clinical practice and clinical trials.

In summary, our SSc clinic, with the support of Reuma.pt/SSc, has allowed a systematic follow-up of patients with this rare disease, thus improving the quality of care and promoting research.

CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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