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Review

Registries in systemic sclerosis: a worldwide experience

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Abstract

SSc is a multisystem disease characterized by an unpredictable course, high mortality and resistance to therapy. The complexity and severity of SSc is a growing burden on the health-care systems. As a result, researchers are seeking new therapeutic strategies for effectively managing these patients. Disease registries are used to support care management efforts for groups of patients with chronic diseases and are meaningful to capture and track key patient information to assist the physicians in managing patients. For these reasons, SSc surveys, research associations and consortiums are pivotal to conduct ongoing research and data collection to enhance disease knowledge and support research projects. Currently, there are several national SSc registries in the UK, Germany, USA, Canada, Brazil and Australia. There is also an international registry established by the European League Against Rheumatism scleroderma trial and research (EUSTAR) called minimal essential data set (MEDS) Online, which collects data from over 8000 patients from 92 centres worldwide, including 21 European centres and 9 centres outside Europe. By collecting, analysing and disseminating data on disease progression and patient responses to long-term disease management strategies, registries help to improve understanding of the disease and keep medical professionals up to date on the latest advances.

Key words: Systemic sclerosis, Disease registries, Database.

REVIEW

Introduction

SSc is a multisystem disease characterized by an unpredictable course, high mortality and resistance to therapy. The complexity and severity of SSc is a growing burden for all health-care systems. As a result, researchers are seeking new therapeutic strategies for effectively managing these patients.

A registry is just one component of a comprehensive disease management strategy. A systematic and comprehensive approach to disease management includes a range of interventions, such as case management, physician feedback, clinical information systems to track patient care, adoption of clinical practice guidelines, outreach to patients who need to come in for care and a focus on patient self-management skills.

Disease registries are used to support care management efforts for groups of patients with chronic diseases and are meaningful to capture and track key patient information to assist the physicians in managing patients. For these reasons, SSc surveys, research associations and consortiums are pivotal to conduct ongoing research and data collection to enhance disease knowledge and support research projects. The present report provides an overview of the national and international SSc registries that have been created all over the world.

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European national registries

UK registry

A national UK register, started in 1995, comprises details on >3000 UK cases of SSc. It identifies patients that may be included in clinical trials and is essentially a cross-sectional database with information on living individuals. Specifically, basic clinical and demographic data were collected. The register was set up as a paper-based system, underpinned by grant support from Arthritis Research UK to fund data entry into an electronic database and collation of the paper hard copy datasheets. Although it has been valuable in practice, this initiative has also identified a number of problems inherent with initiation of a long-term registry. First, the amount of clinical information has proved not completely sufficient and the absence of longitudinal data has been a major limitation. In addition, the ability to utilize data has been restricted over recent years by the lack of study-specific approval, which was not required initially at the time of setting up the database. Thus, although the concept remains valid, it has not achieved the utility and productivity of similar web-based systems, such as the more recent European League against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) group database.

These aforementioned limitations have also been addressed by an initiative termed Scleroderma Cohort (SMART)—data and sample collection and analysis. It will involve establishment of a simple database, storing coded basic demographic and clinical information about the majority of SSc patients in the UK. This will include a prospective record of clinical data to elicit disease course and predictors of outcome in SSc. Collection of blood samples for autoantibody, biomarker and DNA analysis will be done as part of the project, which also facilitates integration with other international projects. The complementary approach that we have followed is the establishment of an in-house database of cases seen in the Royal Free Hospital (RFH) SSc centre. The RFH SSc cohort represents one of the largest and best characterized single-centre cohorts of SSc patients. Good-quality clinical information on >2200 cases has been recorded on the database. The information data set collected for this cohort is centred upon the information required to determine the SSc International Severity Score. In addition, SSc functional data are routinely recorded and instruments such as the GI questionnaire can be incorporated. Essentially, this database reflects clinical practice in our centre. All patients consent to enrol through provision for biological sample collection and this is linked to ongoing clinical research protocols within the department. Reasons why this cohort has been so productive include the consistent nature of patient evaluation with well-trained observers assessing skin score and other disease-specific parameters as well as the availability of robust autoantibody data. Having a manageable data set and the ability to perform quality control through reference to primary source documents, such as clinical notes, ensures that data collection is not burdensome and the quality is good. The database is maintained on an Microsoft Access® platform and additional domains can be added relatively easily. It is stored on a firewalled and networked university server with all data being anonymized. This can in turn link with laboratory databases for DNA, serum, plasma and skin biopsies. It thus essentially represents and provides a single-centre biobank that can be used as the starting point for many clinical projects. It also links with systematic databases maintained in pulmonary hypertension and interstitial lung disease and these links have permitted serial exploration of outcome.

The large number of publications underpinned by the RFH SSc cohort is a measure of its success. Recent analyses of outcome in both major subsets over a decade are very informative [1], following on from the first studies that looked at predictors of survival [2], which have subsequently been validated in other cohorts. The utility of skin score change in predicting burden of disease and outcome has also been demonstrated [3]. Links to biological samples have proved very valuable and underpin projects to systemically examine candidate biomarkers in SSc. Renal crisis is a rare complication and so single-centre cohorts can be used to assess outcome and current treatment protocols [4]. This has been a complementary approach to the national study in France.

To allow the UK initiative to develop and realize its potential, we have recently obtained long-term ethical approval covering data and sample collection and transfer, which also permits the development of collaboration with EUSTAR, which has followed the UK lead and developed a web-based database.

German registry

The German Network for Systemic Scleroderma (DNSS) was founded in 2003 with a grant by the German Federal Ministry of Education and Research (BMBF). There is an intensive collaboration of different subspecialties including dermatologists, rheumatologists, pulmonologists and nephrologists. Starting with initial 21 centres, the network enhanced and expanded in the course of 6 years with altogether >40 clinical centres at present. The network also includes five centres concentrating on certain organ-specific involvements.

A disease- and organ-specific questionnaire was designed in 2003 and then adapted in the years since depending on gain in experience. It includes basic information on gender, date of birth, height, weight, family history of inflammatory rheumatic diseases and symptoms of visceral organ involvement (heart, lung, gastrointestinal tract, kidney, musculoskeletal system and nervous system), as well as characteristic laboratory data such as ANAs, ESR and CK serum levels. Skin involvement was evaluated using the modified Rodnan skin score (mRSS): to ensure standardized and correct performance of skin scoring. Participants of the involved clinical centres were trained several times by attending the EUSTAR skin score courses. Furthermore, information on physical as well as on systemic therapies was registered, including

vasoactive substances, CSs, immunosuppressive drugs and others. Patients are examined and registered yearly to measure the course of disease between initial patient registration and yearly follow-up visits, and to determine special indicators for disease progression. To provide consistency of registered data, a set of definitions for each item on the registration form, and recommendations for organ-specific diagnostic procedures were prepared. The network also provided the infrastructure to collect blood and tissue samples.

To ensure the detection of disease heterogeneity, the registry defined five different SSc subsets, i.e. lcSSc, dcSSc (according to the ACR criteria), overlap syndrome, undifferentiated SSc with features of scleroderma and SSc sine scleroderma.

Up to date, the DNSS contains data of more than 2500 patients. Of these, the most frequent subset is the limited cutaneous form (48.2%), followed by the diffuse cutaneous form (31.6%), the overlap syndrome (10.5%) and the undifferentiated form (7.4%). SSc sine scleroderma was found only in 0.8% of all registered patients. Our nationwide female : male ratio ranged from 3.1 : 1 in dcSSc to 6.5 : 1 in lcSSc. The data revealed that female patients were on average older than male patients and that a family history of rheumatic diseases was reported by nearly 17% of all patients, being significantly associated with a lower mean age and earlier disease onset of RP, skin involvement and internal organ involvement [5]. Regarding visceral organ involvement, our data analyses showed that patients suffering from the diffuse form of SSc show the highest frequencies of pulmonary fibrosis (62.9%), pulmonary hypertension (20.2%), kidney (15.9%) and heart involvement (20%). In contrast, gastrointestinal involvement did not show significant differences between the subsets of dcSSc (65.2%) and lcSSc (60.7%).

Meanwhile, follow-up data for 1 year are available from 1208, for at least 2 years from 642, 3 years from 336 and at least 4 years from 159 patients. After 1 year, a significant increase in the frequency of nearly all visceral organ manifestations (pulmonary hypertension, lung fibrosis and oesophagus) was detectable, while after 2 years an increased occurrence of pulmonary arterial hypertension (PAH), lung fibrosis, oesophagus, kidney involvement and heart involvement was found.

Further statistical analyses facilitated an overview of the prescription of different immunosuppressive agents and the development of recommendations for diagnostic as well as therapeutic procedures [6, 7]. Besides the particular importance of the networks for clinical trials and epidemiological/descriptive analyses, the DNSS provides close interdisciplinary cooperation and intensified care for patients with SSc.

American registries

University of Pittsburgh Scleroderma Databank

The University of Pittsburgh Scleroderma Databank was the first SSc registry initiated in 1980. It is the prototype of all registers in SSc as it includes a comprehensive initial evaluation, standard SSc examination, laboratory studies, an SSc HAQ, yearly serum samples and in more recent years DNA samples. Most importantly, it includes a comprehensive annual to biannual follow-up of patients, which resulted in a very high (93%) accountability of the patients. Since 2002, when additional institutional board review requirements and costs made this intensive follow-up impossible to maintain, the survival outcome is maintained through the Social Security and National Death Index. This databank now has >4000 patients with >30 years of follow-up data. It has resulted in >150 publications relating to the epidemiology, natural history, risk factors, outcomes and survival in all aspects of SSc. Many of these studies are sentinel papers, whose initial findings are now being confirmed by the newer registries from around the world.

Pulmonary hypertension registry

Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS), is a multicentre registry looking at patients with pre-PAH and definite pulmonary hypertension. There are 20 sites throughout the USA that enter patients and follow them every 6 months with patient and physician data and objective studies. The entry criteria for the pre-PAH patient group includes those who are at high risk for developing PAH including a DL_{CO} <55% of predicted, a FVC%/DL_{CO}% ratio >1.6 or an echocardiographic estimated pulmonary artery pressure of >40 mmHg. These patients complete questionnaires about dyspnoea (University of California San Diego Dyspnoea Index), function (SHAQ) and quality of life (SF-36) every 6 months. They have a yearly physician evaluation for symptoms, examination and medication, and hospitalization history. They also have yearly PFTs, echo, 6-min walk tests and laboratory tests as part of their standard of care. Any patient who has a change in symptoms or findings is catheterized to determine whether they have developed pulmonary hypertension.

Patients who have a positive right heart catheterization showing a mean pulmonary artery pressure >25 mmHg are defined as definite pulmonary hypertension. They are then divided into WHO groups according to the Dana point meeting. Group 1 with PAH; Group 2 with pulmonary venous hypertension or diastolic dysfunction (systolic failure or non-scleroderma heart disease patients are excluded); or Group 3 with pulmonary hypertension secondary to interstitial lung disease. Patients are followed at least every 6 months with symptoms, questionnaires, 6-min walk and BNP. Other tests are yearly.

After 2.5 years of patient entry, 250 patients with pre-PAH have been registered. Of the 206 patients who have had at least 1 year of follow-up, 14 have proceeded to definite PAH and 5 developed Group 2 pulmonary venous hypertension. Thus, the time to evolution to PAH for these patients was 22% at 2 years. Of the 133 PH patients entered, only 69% of them had PAH; 24 (or 18%) had pulmonary venous hypertension and 17 (13%) had PH from interstitial lung disease. During the follow-up, a 91% 2-year survival could be achieved.

This prospective study's objective is to identify the patients at highest risk for developing PH and to determine the best risk factors to identify them and to determine the outcome of aggressive treatment of these early diagnosed patients. It is critically important for us to make this diagnosis as early as possible in order to treat these patients aggressively and prevent severe heart failure. Taken together, this procedure will facilitate early diagnosis and the treatment will greatly improve the survival of the most common cause of SSc-related deaths.

Canadian registry

In 2003, 17 rheumatologists from across Canada created the Canadian Scleroderma Research Group (CSRG) with the aim of increasing the capacity to perform high-level SSc research in Canada. The Group includes scientists from both inside and outside the field of SSc (rheumatologists, cardiologists, respirologists, gastroenterologists, dermatologists, dentists, psychologists, basic scientists, epidemiologists and statisticians) and new trainees interested in pursuing SSc research (including 22 summer students and 15 graduate trainees who have worked with CSRG mentors on various projects in the past 4 years alone). As of 1 March 2010, the CSRG had enrolled a total of 1095 patients, of which 86% were females, mean age was 55 years, mean disease duration since the onset of their first non-Raynaud's symptoms was 11 years and 59% had limited disease. Funding has come from multiple sources including grants from the Canadian Institutes of Health Research (CIHR), the Scleroderma Society of Canada, Cure Scleroderma Foundation, Scleroderma Society of Ontario, Sclérodermie Québec, as well as unrestricted grants from several Canadian pharmaceuticals companies. Detailed patient data collected yearly are entered and stored via the web in a central database. Indeed, the easy availability of high-quality and detailed patient-level data has stimulated numerous ideas for projects over and above our initial objectives. The network was interested in measurement and started with a demonstration of the value of office capillaroscopy and then reported on the reliability of widefield microscopy in SSc (Hudson *et al*. 2010, data not published). Other measurement projects have included the validation of health-related quality of life instruments in SSc [8, 9], including the SF-36 [9] and the World Health Organization Disability Assessment Schedule II [10]. The participating centres also looked at correlates of health-related quality of life [11–13], were interested in measurement of disease activity, severity and damage in SSc [14] and have a number of studies ongoing in these areas [15–16]. In addition, disease classification is a major focus [10] in combination with work in various areas including depression [17–20], work disability [21], pain [22] and pruritus [23]. Moreover, the data were used to produce robust estimates of the economic costs of SSc [24, 25], helped to develop an interest in nutritional aspects of the disease, showed that malnutrition is common in SSc [26] and that serum albumin is not a good marker for malnutrition [27]. There were very few laboratories doing SSc work in Canada before the establishment of the CSRG. At present, projects are ongoing in six different laboratories, only one of which had prior experience with SSc. It must, however, be noted that the CSRG relies on the goodwill of the participating rheumatologists to collect and record all the data that we require yearly.

Brazilian registry

As there were no large studies analysing disease patterns of SSc in the heterogeneous Brazilian population, the Brazilian Society of Rheumatology organized the GEPRO, the Pronuclear Project SSc Study Group. A common protocol of investigation (including demographic, clinical and immunological aspects) was designed and applied to SSc patients in 28 university centres from different geographical areas all over Brazil in the period between 2003 and 2006. A series of 1139 patients, 508 with lcSSc (44.6%), 504 with dcSSc (44.2%), 73 with overlap syndromes (6.4%) and 54 with SSc sine scleroderma (4.8%) was included. Most patients were females [996 (87.4%)]. There were 740 Caucasian (65%), 390 African-Brazilian (34.2%, originating from white and black miscegenation) and 9 Japanese-Brazilian (0.8%) patients. Calcinosis was present in 19.2% of the patients, while leucomelanodermia was observed in 45.8% and telangiectasia in 47.2% of the patients. Fingertip pitting scars were referred by 62.9%, and 37.5% presented previous ischaemic ulcers. Inflammatory polyarthralgia was referred by 35.6% of the patients, while arthritis was observed in 39.7% and tendon friction rubs in 11.2%. Dysphagia was referred by 62.2% of the patients; barium-contrasted oesophagram showed reduced motility in 68.2% and gastro-oesophageal reflux in 41.7%; 3.2% of the patients had to be submitted to GER surgery. Intestinal malabsorption was present in 4.8% and anal incontinence in 3.6%. Dyspnoea was referred by 55% of the patients, with bibasilar crackles in 27.5% and an altered chest X-ray in 32.7%; pulmonary function test was abnormal in 52%, with an altered chest high-resolution CT in 45.2%. Clinical arrhythmia was present in 9% of the patients, pericardial effusion in 5.8%, angina in 7.4%, myocardial infarction in 6.7% and congestive heart failure in 9.4%. Echocardiographic signs of pulmonary hypertension were observed in 13.3% of the patients. Scleroderma renal crisis was diagnosed in 3.4% of the patients.

Total skin score was significantly higher in males when compared with females ($P < 0.0001$). Male gender was statistically associated with higher total skin score ($P < 0.0001$). Leucomelanodermia ($P = 0.025$), flexion contractures ($P < 0.0001$), pulmonary rales at auscultation ($P = 0.017$), smoking habit ($P < 0.0001$) and scleroderma renal crisis ($P = 0.003$) were also more frequent in males, while arthritis ($P = 0.001$) and ACAs ($P = 0.008$) were more frequent in females. Caucasian patients presented statistically significant association with pruritus ($P < 0.0001$), leucomelanodermia ($P < 0.0001$), calcinosis ($P = 0.009$), dysphagia ($P = 0.045$), higher pulmonary artery systolic

pressure at echo-doppler ($P = 0.004$) and ACAs ($P < 0.0001$). African-Brazilian patients presented association with skin ulcers ($P = 0.007$), tendon friction rubs ($P = 0.034$), flexion contractures ($P = 0.045$), smoking habit ($P = 0.044$) and anti-Scl-70 ($P < 0.0001$). ANA, determined in commercial HEp-2 cells, was positive in 82.9% of the tested patients. ACAs were detected in 14.4% and anti-Scl-70 in 19.1% of the patients. The most frequently observed ANA patterns were speckled (41.8%), nucleolar (14.5%), centromeric (14.4%) and homogeneous (10.4%). ACA showed a significant statistical association with limited SSc ($P < 0.001$), calcinosis ($P = 0.001$), anal incontinence ($P = 0.033$), nervous system involvement ($P < 0.001$) and lower mRSS ($P < 0.001$). The presence of anti-Scl-70 antibodies was associated with diffuse SSc ($P < 0.001$), pruritus ($P = 0.004$), pigmentary disturbances ($P < 0.001$), digital microulcerations ($P = 0.016$), arthritis ($P = 0.013$), tendon friction rubs ($P = 0.009$), flexion contractures ($P < 0.001$), dyspnoea ($P < 0.001$), interstitial lung involvement ($P < 0.001$) and higher mRSS ($P < 0.001$). Other autoantibodies were positive in 17.5% of the tested patients; the most frequently observed ones were anti-SSA/Ro (5.7%), anti-U1-RNP (5.1%) and aCL (3.4%). There were no specific manifestations associated with these antibodies.

The analysis of this large Brazilian cohort showed that male gender, African-Brazilian ethnicity, diffuse SSc and positive anti-Scl-70 antibodies are associated with a more severe disease. Oesophageal and lung involvement were the dominant clinical manifestations and renal crisis was quite uncommon in the series. After the implementation of this national database, most rheumatology units in the main university centres in Brazil have an SSc outpatient clinic, and basic and clinical research focusing on specific SSc aspects in the heterogeneous Brazilian population can now be performed.

Oceania national registries

Australian Scleroderma Special Interest Group Scleroderma Screening Programme

The Australian Scleroderma Special Interest Group (ASIG) was established in 2007 and is a nationwide collaboration currently underway in more than a dozen centres. The programme aims to increase screening for PAH in patients with SSc and mixed CTD. It aims to provide a screening algorithm, to establish a web-based database, to support compliance with guidelines as well as to stimulate scleroderma research in Australia. The programme provides yearly reviews including echocardiography and lung function testing and provides a comprehensive report to the treating doctor. To date, >900 patients have entered the programme on an ongoing basis, with age range 18–88 years, 88% females, 66% with limited and 26% diffuse disease. The prevalence of PAH has been shown to be 11% using right heart catheterization as the gold standard for diagnosis with disease duration of 5.4–18 years and 64% in WHO Class 3 and 10% in WHO Class 4 at diagnosis, hence it will be important over time to see if the screening programme allows earlier diagnosis at an earlier WHO class with potentially better prognosis. Tracking patients on PAH therapy over time is facilitated. Twenty-four per cent of the cohorts have had significant interstitial lung disease. It has been estimated using Australian prevalence and incidence figures that ~25% of the Australian scleroderma population has been enrolled. Research projects including utility of BNP, genome-wide scanning and mycophenolate in scleroderma-ILD are underway.

International registries

EUSTAR online database

In order to foster awareness, understanding and research of scleroderma and its care and management throughout Europe, the EUSTAR group (www.eustar.org) was inaugurated under the auspices of the EULAR standing committee on international clinical studies including therapeutic trials (ESCISIT) and has established a prospective multicentre SSc cohort.

EUSTAR was started in 2003 and the SSc database launched in 2004 [28]. It represents a multinational, prospective and open SSc cohort. Participating centres enter the minimal essential data set (MEDS) with all consecutive consenting patients who fulfil the ACR classification criteria for SSc [29]. Scleroderma subsets are classified as diffuse SSc if skin thickening extends proximal to the elbows and knees or includes the trunk, and as limited SSc if confined to distal extremities and face [30]. The MEDS was designed in consensus by the EUSTAR members and covers demographic aspects, disease duration, organ involvement and laboratory data [31]. Disease activity is calculated as a composite score from MEDS parameters according to the preliminary index for SSc as a whole, proposed by the ESSG and detailed elsewhere [32]. Annual follow-up examinations are implemented. To improve long-term data analysis and tracking of patients suitable for clinical and basic research trials, an online database was launched in June 2006 (MEDS Online). Simultaneously, the MEDS was extended by items such as right heart catheter measurements, medication and a centre-based biobank, which collects sera, tissue samples and DNA material. As of March 2010, MEDS Online follows a total number of 8147 patients with SSc. A total of 92 centres from 21 European and 9 non-European countries have initiated online status. Each EUSTAR member is strongly invited to submit research proposals that are subject to peer review by the EUSTAR scientific committee.

The MEDS Online database uses a very intuitive and easy to use web interface. A series of web forms are accessible through a side menu. The forms contain patient-specific data that are sorted according to dates of patient visits where applicable in order to allow the documentation of static and follow-up data. Users can also download printable documentation of their patients' visit data for their files. This printable visit-based

Table 1 Strengths and limitations of registry-based studies

Strengths	Limitations
Longitudinal data of large sample size	Assessment or treatment criteria may be not uniform—potential for selection bias
Track the natural history of the disease over time	Patients seen in diverse centres/countries
Track the long-term effectiveness and safety of treatments	Lack of data verification
Enable time-to-event analysis	May not have complete data/follow-up
Allow subset analyses	Patients are not monitored as rigorously as in randomized controlled studies—the rate of some events may be underestimated
Essential information source for rare diseases	Data are collected anonymously—avoid duplicate records on same patient
Provide generalizable evidence	No control population
Provide evidence of the effectiveness of treatments in the real world	Potential for industry influence on analytical methods
Generate new hypotheses for further investigation	

documentation also contains an overview of the evolution of the patient's clinical outcome parameters over past visits. The MEDS Online database provides unrestricted online data search and export capabilities that allow each centre to use and export its own data.

In addition, the system provides for each centre a full overview of its biosamples stored locally. These features also render the MEDS Online database a useful tool for centre-initiated research purposes. Access to the MEDS Online database is only granted following local ethics committee approval. Data monitoring includes automated online algorithms to identify double entries, missing data and plausibility checks. Most data entry fields feature a pop-up window providing assistance, definitions and coaching material. The centres were and will be coached on a regular basis and during EUSTAR courses on how to fill out the forms. Coaching sessions included the ACR classification of SSc, definitions of the subgroups and the activity score. Standardized teaching sessions included the documentation of the mRSS at the bedside, following two teach the teachers sessions held in 2004 and 2005 [33]. The definitions of the MEDS parameters and video coaching material are also available on the EUSTAR web site.

The MEDS Online database also features easy extendibility for additionally small- or large-scale scientific projects either within EUSTAR itself or in collaboration with industrial partners. Among the many ongoing EUSTAR projects, several analyses have been completed. EUSTAR gained insight into factors that are associated with particular organ manifestations and thus potentially also with the disease process [34, 35]. By focussing on age at onset of RP, gender and autoantibodies, this project examined whether the dichotomy into limited and diffuse cutaneous subsets of SSc is the best way to capture the disease and its organ manifestations, or whether other clinical or laboratory parameters may be more appropriate. While the dcSSc subset was found to be associated with more prevalent internal organ complications, an antibody-based classification added independent information in predicting some scleroderma manifestations. In fact, autoantibody status in this EUSTAR analysis appeared more closely associated with some clinical manifestations than were SSc subsets [31].

Heart involvement in SSc may be life threatening. Another EUSTAR analysis focused on left ventricular dysfunction and found a prevalence of 5.4%. Independent risk factors for its presence were age, male gender, digital ulcerations, myositis and lung involvement [36].

Large geographical variations in SSc prevalence and incidence have been described. EUSTAR documentation covers a broad geographical area, allowing the analysis of geographical variation among different SSc presentations, autoantibody associations and gender ratio, which could help in identifying genetic or environmental factors in the aetiology of the disease. The main EUSTAR finding is that there was no clear regional trend with regard to key factors thought to influence organ involvement, such as clinical SSc subsets, gender and mRSS. In addition, there was no geographical association between organ manifestations related to ambient temperature such as RP. There was also no association between geographical longitude or latitude and age at disease onset [37].

A very recent analysis of SSc-related mortality indicates that the disease-specific mortality is still high in the current era despite the possibility to prevent or mitigate some organ complications by new pharmacological interventions. Most patients die from SSc-related complications rather than from other causes. Renal involvement, pulmonary complications, skin induration and age at SSc onset predict the excess mortality [38].

Conclusions

Disease registries are large, often multinational observational databases that collect clinical data on patients with SSc. By collecting, analysing and disseminating data on disease progression and patient responses to long-term disease management strategies, registries help improve disease understanding and keep medical professionals up to date on the latest advances [39–41].

Table 2 Patients characteristics and main findings of SSc registries

Patients characteristics	UK registry	DNSS	Pittsburg Scleroderma Databank	PHAROS	CSRG registry	Brazilian registry (GEPRO)	ASIG scleroderma screening programme	EUSTAR MEDS
Year	1995	2003	1980	–	2003	2003	2007	2004
Patients enrolled	>2200	>2500	>4000	250	1095	1139	900	8147
Gender								
Male, %	–	–	–	–	14	12.6	12	–
Female, %	–	–	–	–	86	87.4	88	–
Female to male ratio	–	3.1 : 1 dcSSc 6.5 : 1 lcSSc	–	–	–	–	–	–
Mean age, years	–	–	–	–	55		–	–
Mean disease duration, years	–	–	–	–	11		–	–
Subsets								
dcSSc, %	–	31.6	–	–	–	44.2	26	–
lcSSc, %	–	48.2	–	–	59	44.6	66	–
Overlap, %	–	10.5	–	–	–	6.4	–	–
Undifferentiated, %	–	7.4	–	–	–	–	–	–
Sine scleroderma, %	–	0.8	–	–	–	4.8	–	–
Lung involvement								
Pulmonary fibrosis, %	–	62.7 dcSSc	–	–	–		24	–
Pulmonary hypertension, %	–	20.2 dcSSc	–	–	–	13.3	11	–
Renal involvement, %	–	15.9 dcSSc	–	–	–	3.4	–	–
Heart involvement, %	–	20.9 dcSSc	–	–	–		–	–
Arrhythmias, %	–	–	–	–	–	9	–	–
Pericardial effusion, %	–	–	–	–	–	5.8	–	–
Angina, %	–	–	–	–	–	7.4	–	–
Myocardial infarction, %	–	–	–	–	–	6.7	–	–
Gastrointestinal involvement, %	–	65.2 dcSSc 60.7 lcSSc	–	–	–		–	–
Dysphagia, %	–	–	–	–	–	62.2	–	–
Oesophageal dysmotility, %	–	–	–	–	–	68.2	–	–
GE reflux, %	–	–	–	–	–	41.7	–	–
Intestinal malabsorption, %	–	–	–	–	–	4.8	–	–
Anal incontinence, %	–	–	–	–	–	3.6	–	–
Articular involvement	–	–	–	–	–		–	–
Polyarthralgia, %	–	–	–	–	–	35.6	–	–
Arthritis, %	–	–	–	–	–	39.7	–	–
Tendon friction rubs, %	–	–	–	–	–	11.2	–	–
Calcinosis, %	–	–	–	–	–	19.2	–	–
DU	–	–	–	–	–		–	–
Ongoing DU, %	–	–	–	–	–	62.9	–	–
Previous DU, %	–	–	–	–	–	37.5	–	–
Leucomelanodermia, %	–	–	–	–	–	45.8	–	–
Telangiectasia, %	–	–	–	–	–	47.2	–	–
Autoantibodies							–	–
ANA, %	–	–	–	–	–	82.9	–	–
Speckled, %	–	–	–	–	–	41.8	–	–
Nucleolar, %	–	–	–	–	–	14.5	–	–
Centromeric, %	–	–	–	–	–	14.4	–	–
Homogeneous, %	–	–	–	–	–	10.4	–	–
ACA, %	–	–	–	–	–	14.4	–	–
Scl-70, %	–	–	–	–	–	19.7	–	–
Others	–	–	–	–	–		–	–
Anti-SSA/Ro, %	–	–	–	–	–	5.7	–	–
Anti-U1-RNP, %	–	–	–	–	–	5.1	–	–
aCL, %	–	–	–	–	–	3.4	–	–

Well-characterized cohorts of SSc patients are the cornerstone of clinical research that addresses important topics such as outcome assessment and the potential efficacy of current treatment protocols. Although cohort studies cannot provide the same level of evidence as prospective controlled trials, they are a valuable clinical resource. A cohort of patients derived from a disease registry addresses different research questions from those of a simple practice-based cohort, which is typically comprised of consecutive patients seen in a particular practice setting, or consecutive patients who meet certain predefined case criteria and who are then followed over time according to a set protocol for particular outcomes. This distinction between a registry-based population and a restricted cohort may have many practical implications. The registry population includes samples from many sources and therefore cannot control the type or frequency of laboratory testing of patients, having to rely on community standards of care for these data. Although this may result in incomplete information on some cases, the trade-off is that many more cases can be included and referral bias is diminished. Prevalence, incidence and survival data can then be derived for the study population, followed over time to determine temporal trends, and extrapolated to larger populations of similar demographic characteristics. A summary of strengths and limitations of registry-based studies is shown in Table 1. The limitations of disease registries may be overcome considering possible confounding factors that may distort the results and reducing possible sources of bias (covariate adjustment, case control matching, etc.) with a rigorous database design and data collection, and with training courses on standardized criteria of patient assessment and distributing coaching materials on data entry. Unfortunately, it was impossible to compare registries, due to non-uniformity of the data presented in this report (Table 2).

In conclusion, national registries are very useful to understand the prevalence/incidence of SSc in single countries, but international registries remain of invaluable utility to understand the overall behaviour of SSc and its clinical features as well as being a solid base for large-scale genetic, clinical and basic studies [42].

Rheumatology key messages

- Registries improve disease understanding and keep medical professionals up to date on the latest advances.
- International registries remain of invaluable utility to understand the overall behaviour of SSc and its clinical features.

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