Nationwide and international registries on scleroderma. Past, present, and future

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Abstract

Systemic sclerosis (SSc) is a low-incidence autoimmune disease that requires collaborative work through national or international registries to advance scientifically. The present systematic review aims to be an update of all national and international registries to date. In total, 7 first-world countries have SSc registries. In addition, there are also 3 international SSc registries plus 2 other registries focused on SSc-related pulmonary arterial hypertension. These registries not only carry out clinical research but also allow the collection of serum, DNA and tissue samples, as well as collaborative work to carry out randomized clinical trials and collaboration with other registries not directly focused on SSc.

Key words: Scleroderma. Systemic sclerosis. Registry.

Introduction

Scleroderma or systemic sclerosis (SSc) is an autoimmune disease that can be considered a rare disease because of its incidence. As such, it makes it difficult to study in an isolated research center. Many years of follow-up and dedication are needed to be able to gather a sufficient number of patients to be able to undertake research work that will allow valid knowledge to be obtained and extrapolated to other populations. World leadership during the second half of the 20th century was held by large cohorts of a few centers such as the University of Pittsburgh¹, the Johns Hopkins Hospital in Baltimore², the University of Texas and Michigan³, and the Royal Free Hospital in London⁴ or provincial/state registries such as the South Australian Scleroderma Register⁵. All of them, but especially the first one in the 1980s, were the seeds of what later

became known as national or international registries. Today it is mandatory in a disease of low incidence, and the autoimmune ones would enter there too, to work based on a registry of these characteristics. In 2011, an attempt was made to update the existing registries⁶, but it is clear that a decade later, we need to update them and see where we are heading in SSc research through the registries.

This study aimed to conduct an updated review of the different national or international registries on SSc, focusing on their similarities and differences.

Methods

For the present study, a systematic review of national and international registries in SSc has been carried out. The search was performed by reviewing the Medline

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Figure 1. PRISMA 2009 flow diagram.

database following the terms ("Scleroderma, Systemic" [Mesh]) AND "Registries" [Mesh]). Besides, the medical bibliography of the medical coordinator of each of the registries was reviewed as well as a search following the name of the registry on PubMed and the webpage (when available) of the registry (Fig. 1). Not all registries present their data in the same way and at the same time. Thus, the data included in the supplementary tables are indicative and correspond in some cases to the paper of presentation of the registry and, in others, to one of the following papers (Suppl. Tables 1 and 2 and Figs. 2 and 3).

Results

Scleroderma registries

UK, 1995

The **UK Scleroderma Study Group (UKSSG)** is a working group of key centers that have a clinical and research interest in SSc and have worked collaboratively to promote research and clinical practice in SSc patients over the past 25 years. The group was established by Professor Dame Carol Black on the principle of inclusive participation. A national registry in the United Kingdom, initiated in 1995, includes details of 37 centers of SSc and contains data on > 2500 patients. It allows the collection of blood samples for DNA, serum, plasma, and skin biopsies. It also links to systematic

databases maintained on pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD).

The UKSSG, mostly centered in the Royal Free Hospital in London, has enabled the study and development of management guidelines in renal⁷ and gastrointestinal involvement⁸ and in the management of digital ulcers (DU)⁹. It has also deepened the study and management of PAH and ILD¹⁰⁻¹². It has also made advances in the treatment of diffuse forms of the disease^{13,14} and the study of RNA pol III patients¹⁵.

The head office is at the Royal Free Hospital in London and is headed by Dr. C. Denton.

GERMANY, 2003

The **German Network for Systemic Scleroderma (DNSS)** was founded in 2003 with a grant from the German Federal Ministry of Education and Research. There is an intense collaboration of different subspecialties, including dermatologists, rheumatologists, pulmonologists, and nephrologists. Like the other registries, it includes socio-demographic, clinical, laboratory, and follow-up data. DNSS maintains a centralized online patient registry that includes all SSc patient data on a standardized four-page DNSS questionnaire. The network also provides the infrastructure for collecting blood and tissue samples. It now gathers data from more than 3000 patients from over 40 centers.

Figure 2. Map chart of the national systemic sclerosis registries.

Figure 3. Timeline of the national systemic sclerosis registries over time.

The German registry has firstly served to characterize German patients with SS¹⁶. It has provided advances in the correlation of cutaneous and visceral involvement as well as in the management of cutaneous vascular complications¹⁷⁻²⁰. It has also served to immunologically characterize German patients on a national level²¹. It has also deepened the knowledge and prognostic evaluation of patients with overlap syndrome²² and late-onset SS²³ and the excessive use of corticosteroids and immunosuppressants in patients with SS²⁴.

The Central Coordination Office was established at the Department of Dermatology and Venereology at the University of Cologne and acts as a data manager. It is directed by Dr. N. Hunzelmann.

EUSTAR, 2004

The **EULAR Scleroderma Trials and Research Group (EUSTAR)** was founded in 2004 at the University Hospital of Florence (Italy) with the support of a EULAR research grant under the chairmanship of

Marco Matucci. To promote awareness, understanding, and research into SSc and its care and treatment throughout Europe, the EUSTAR group was launched under the auspices of the EULAR standing committee on international clinical trials involving therapeutic trials (ESCISIT) and a prospective multicenter cohort of SSc was established. EUSTAR was initiated in 2003 and the SSc database was launched in 2004. It represents a multinational, prospective, and open SSc cohort. Participating centers enter the minimum essential data set (MEDS) with all consecutive consent patients who meet the ACR classification criteria for SSc. The MEDS was designed by consensus by EUSTAR members and covers demographics, disease duration, organ involvement, and laboratory data. Annual follow-up examinations are conducted. To improve long-term data analysis and follow-up of patients suitable for clinical and basic research trials, an online database (MEDS Online) was launched in June 2006²⁵. Simultaneously, the MEDS was expanded with features such as right heart catheter measurements, medication, and a center-based biobank, which collects sera, tissue samples, and DNA material. To date, more than 11,000 patients from 234 centers are included in the study.

EUSTAR has been a constant source of recommendations in management, research, and biobanking strategies in SSc²⁶⁻³⁰. It has also contributed to the improvement of the clinical assessment of organic manifestations and the implementation of the modified Rodnan skin score and organic damage^{31,32}. It has allowed the characterization of different geographical regions³³ and the study of differences between races³⁴. It has made advances in the study of disability³⁵, cutaneous involvement^{36,37}, articular^{38,39}, vascular⁴⁰⁻⁴², cardiac⁴³, pulmonary⁴⁴⁻⁴⁷ and digestive involvement^{48,49}, also the identification of phenotypic clusters in SSc⁵⁰. It has also made advances in the study of different subpopulations such as patients with young and late-onset SSc^{51,52}, early and very early SSc⁵³⁻⁵⁵, also in those patients with anti-topoisomerase I anti-bodies (ATA), anticentromere antibodies (ACA), anti-Ku, PM-Scl, RNA pol III antibodies, and in those antinuclear antibody (ANA) negative⁵⁶⁻⁶⁰. It has also contributed to the study of risk factors, including 2 prognostic scores⁶¹⁻⁶⁶. It has finally conducted studies to assess the efficacy of tocilizumab, abatacept, rituximab, cyclophosphamide, and hydroxychloroquine in different subpopulations⁶⁷⁻⁷¹.

The current data center is located at the University Hospital of Zurich and is directed by Dr. O. Distler.

CANADA, 2004

In 2003, a group of 17 rheumatologists from across Canada met and recognized the need to unite to better treat patients with SSc. The **Scleroderma Research Group of Canada (CSRG)** is a multicenter research cohort established in 2004. The CSRG has been made possible by grants from the Canadian Institutes for Health Research, private donations, Scleroderma Canada, all provincial scleroderma patient groups, the Scleroderma Healing Foundation, as well as several Canadian pharmaceutical companies. At present, the patient registry contains detailed longitudinal clinical data on over 1750 patients from 15 different sites, plus a biobank of samples.

The Canadian registry (CSRG) has been very prolific since its inception. It has focused on the study of quality of life⁷², fatigue⁷³, frailty⁷⁴, pain⁷⁵, sleep disturbances⁷⁶, depression⁷⁷, malnutrition⁷⁸, work disability⁷⁹, self-reported physical health⁸⁰, oral health⁸¹, SSc-associated cancer⁸², sexual activity⁸³, the impact of socioeconomic status⁸⁴, and the cost of SSc⁸⁵. It has also made advances in the immunological characterization of patients with SSc and its clinical implications, especially in those patients with antifibrillarin anti-bodies, ACA, Ro52, PM/Scl, TRIM 21, Th/To, Ku, and HMGCR⁸⁶⁻⁹³, also those patients with negative ANA⁹⁴. Knowledge of visceral gastrointestinal⁹⁵⁻⁹⁷, pulmonary⁹⁸⁻¹⁰⁰, renal¹⁰¹, muscular¹⁰², cutaneous¹⁰³, and vascular involvement¹⁰⁴ has also improved. It has also provided knowledge in aspects of the diagnosis of the disease¹⁰⁵ and in the assessment of organ damage¹⁰⁶. It has also served to characterize a Native North American population with SSc¹⁰⁷. Finally, it has furthered the study of a large subpopulation of patients with scleroderma sine scleroderma¹⁰⁸.

The head office is located at the Jewish General Hospital in Montreal and is headed by Dr. M. Baron and K. McKenna.

SPAIN, 2006

The **Spanish Registry of Scleroderma (RESCLE)** was created by the Autoimmune Systemic Disease Group (GEAS) of the Spanish Society of Internal Medicine in 2006 to compile a wide range of Spanish patients with SSc. At that time, there were 14 participating centers; today, there are 40 centers throughout the country. Thus, until 2006 the data were collected retrospectively and since 2006 (or the date of inclusion of a new center), it has been done prospectively. Epidemiological, clinical, laboratory, capillary, and immunological data covering

267 variables are included in the database. Annual follow-up examinations are conducted.

The Spanish scleroderma registry has not only characterized the Spanish population with SSc¹⁰⁹ but has also made advances in the characterization of liver involvement¹¹⁰, vascular¹¹¹, ILD¹¹², and PAH¹¹³, as well as the role of phosphodiesterase inhibitors and endothelin receptor antagonists as bi-therapies in the prognosis of PAH versus monotherapy¹¹⁴. The preventive role of these drugs in the development of PAH and the renal crisis has also been evaluated¹¹⁵. The registry has furthered the study of the immunological profile and, in particular, the study of serodiscordant patients with the cutaneous subtype^{116,117}. It has also studied the subpopulation with early and very early SSc¹¹⁸, as well as deepened into the causes of death and their change over time^{119,120}. It has identified new risk factors and created a new long-term prognostic tool^{121,122}.

There is no registry-associated biobank to store evidence. To date, collects data from 2,238 patients. The central database coordinator and administrator is S&H Medical Science Service and medical coordination is directed by Dr. C.P. Simeón and V. Fonollosa from Vall d'Hebron University Hospital in Barcelona.

AUSTRALIA, 2007

The **Steering Committee of the Scleroderma Interest Group of Australia** (Australian Scleroderma Interest Group [ASIG]) met for the 1st time in November 2005 and in 2007 became a special interest group under the auspices of the Australian Rheumatology Association, a non-profit organization incorporated as a corporation in Australia. The ASIG is a multidisciplinary collaboration of rheumatologists, immunologists, cardiologists, and respiratory physicians from across Australia with a special interest in improving outcomes for patients with SSc and mixed connective tissue disease. In 2007, ASIG established the Australian Scleroderma Cohort Study (ASCS), using a web-based platform to detect the cardiac and pulmonary complications of these diseases as a service to patients with SSc and their rheumatologists. The main goal of the ASCS is to improve clinical care by increasing the rate of detection of SSc-related PAH and ILD to enable earlier identification of high-risk patients and the institution of timely treatment. Blood samples are collected and processed at most centers and transferred to Adelaide for storage in the ASIG blood biobank. All members of the ASIG are clinical rheumatologists. To date, over 1600 patients from 13 centers are included in the registry.

The ASIG registry has contributed to the field of PAH screening^{123,124}, GI involvement¹²⁵, overlap syndrome¹²⁶, quality of life¹²⁷, and activity impairment¹²⁸. Furthermore, in the immunological characterization of patients, especially patients with anti-Ku, anti-RNA pol III, and anti-PM75-100^{86,129-130}, also the relation with occupational silica exposure¹³¹.

The project coordinator and database administrator for ASIG were appointed in 2006 and is based in the Department of Rheumatology at St. Vincent's Hospital in Melbourne. It is directed by Dr. S. Proudman and M. Nikpour.

SCLERODERMA PATIENT-CENTERED INTERVENTION NETWORK (SPIN), 2012

The **SPIN**, an international collaboration of patient organizations, clinicians, and researchers, was recently organized and funded by the Canadian Institutes of Health Research. The long-term goals of SPIN are to develop, test, and disseminate accessible interventions to complement standard medical care and improve outcomes in SSc. The SPIN uses a novel research design, the Multiple Cohort Randomized clinical trial Design, to collect longitudinal data related to the problems experienced by people living with SSc and as a framework for the development, evaluation, and delivery of psychosocial and rehabilitation interventions. The first step toward the long-term objectives of the SPIN is the establishment of the SPIN Cohort¹³¹. It does not have an associated biobank. By 2020, more than 1700 patients have been recruited from 43 centers in Canada, the USA, UK, France, Spain, Mexico, and Australia.

The SPIN cohort has furthered the study of physical activity¹³², physical and occupational therapy¹³³, hand function¹³⁴, and online self-care intervention in patients with SSc¹³⁵. It has also made advances in the evaluation of mental health in the SSc population, recently also concerning COVID-19^{136,137}.

The SPIN is led by Dr. B. Thoms of the Jewish General Hospital and McGill University in Montreal, Canada.

THE US, THE CONQUER REGISTRY, 2013

In 2011, the Prospective Registry of Early SSc (PRESS) was developed in the US in response to FDA and NIH calls for attention to Therapeutics for Rare and Neglected Diseases and developing tissue banks linked to clinical outcomes. PRESS researchers were contacted by the Scleroderma Research Foundation

(SRF) to build on their efforts. The overall goal of the SRF partnership with participating academic Scleroderma Centers is to accumulate the largest possible cohort of early-stage scleroderma patients. This highly collaborative effort, initially among 12 of the largest SSc centers in the United States, has been named **CONQUER** (an acronym for COllaborative, National QUality and Efficacy Registry for Tracking Disease Progression in SSc [scleroderma] Patients). The CONQUER Registry was developed in 2013. The SRF is a non-profit organization based in San Francisco. It is the nation's leading non-profit investor in medical research and its mission is to fund and facilitate the most promising and highest quality research aimed at improving therapies and ultimately curing scleroderma. The SRF has established strategic partnerships with several other sponsors who are providing financial and other support elements to ensure the success of the CONQUER Registry, in special Boehringer Ingelheim and Actelion laboratories. The Biorepository Center at The University of Texas Health Science Center at Houston will provide processing, storage, and management services for CONQUER Registry members, as it does for a variety of national research networks. The registry includes 12 SSc centers geographically distributed throughout the U.S., including California, Texas, Utah, Illinois, Michigan, Massachusetts, Maryland, New York, South Carolina, and Washington, D.C.

The CONQUER register has only published its initial set-up with baseline data from its longitudinal cohort¹³⁸.

The data center is based at the University of Utah, and the biospecimen repository is located at the University of Texas Health Science Center in Houston.

THE US, THE GRASP REGISTRY, 2013

The **African American Scleroderma Genome Research Project (GRASP)** was established to improve our understanding of the clinical manifestations of SSc in African Americans and to conduct genomic analyses to identify key factors contributing to the occurrence and severity of their disease. To achieve these goals, a large cohort of African-American patients with SSc has been assembled and clinical data and DNA samples have been collected from all enrolled patients. The GRASP clinical database was established in 2013 and includes the sociodemographic and clinical characteristics of a U.S. cohort of exclusively African-American SSc patients enrolled retrospectively and prospectively over 30 years (1987-2016). African-American race was determined by patient self-identification. The GRASP consortium was

supported by research funding from the SRF and the Intramural Research Programs of the National Human Genome Research Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The GRASP cohort currently consists of more than 1,200 extensively evaluated African-American SSc patients enrolled at 23 participating academic centers in the United States. This is the largest multicenter cohort of African American patients with SSc ever studied.

The GRASP cohort has published only its baseline data in which it characterizes the largest Afro-American SSc cohort described to date¹³⁹.

The data center is based at the Johns Hopkins University coordination site and is led by Dr. F. Wigley and F. Boin.

ITALY, 2015

The **SPRING** is the last national registration to date. It was promoted by the Italian Society of Rheumatology in 2015. Study data were collected and managed using REDCap, electronic data capture tools hosted by SIR REDCap (Research Electronic Data Capture), which is a secure web-based application designed to support data capture for research studies. Patients were screened consecutively and enrolled at each participating center according to standardized study procedures. All patients were hierarchically classified into 4 different cohorts: (1) primary Raynaud's phenomenon (RP); (2) suspected secondary RP; (3) very early diagnosis of SSc (VEDOSS); (4) definitive SSc according to ACR/EULAR 2013 classification criteria for SSc. A biobank associated with the registry is not available to store evidence. To date, it includes more than 1700 patients from 38 centers.

Still, in its early days, the SPRING has served to characterize the Italian population with SSc¹⁴⁰.

The SPRING is led by Dr. C Ferri of the University of Modena and M Matucci of the University of Florence.

INSYNC, 2018

In 2018, the **International SSc Initiation Cohort (INSYNC)** pooled data from the ASCS, the cohort study of the Canadian Scleroderma Research Group (CSRG), the Leiden SSc cohort (Leiden CCIS cohort), Spain (the scleroderma cohort of the University Hospital 12 de Octubre in Madrid), and Sweden (the SSc cohort of the Rheumatology Unit of the Skane University Hospital, Lund). Here, data from national registries and cohorts from a single-center are combined. To date, INSYNC

includes sites in Canada, Australia, the Netherlands, Spain, Germany, Brazil, the United States, and Sweden. It should be noted that INSYNC relies entirely on the infrastructure of the CSRG for administrative and statistical support.

Still, in its early days, the INSYNC cohort has advanced the assessment of the health-related quality of life in patients with SSc¹⁴¹.

It currently has more than 600 patients from 31 centers. It does not have a biobank.

Registries focused on SSc-related PAH

FRANCE, ITINÉRAIR-SCLÉRODERMIE, 2002

The **ItinérAIR-Sclérodermie Investigators Group** was established in 2002 to prospectively collect patients with SSc and group I PAH. The ItinérAIR-Sclérodermie registry includes data on 599 patients diagnosed with SSc. It has made advances in the diagnostic algorithm of PAH and its early detection¹⁴². It has also served to study the prevalence and incidence of PAH in a SSc population^{143,144}, as well as survival and risk factors for poor prognosis¹⁴⁵⁻¹⁴⁷.

The registry is run by ACTELION PHARMACEUTICALS FRANCE, SAS and is headed by Dr. M. Humbert.

US/CANADA, PHAROS, 2006

The **Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS)** Registry is a prospective multicenter study in compliance with the US Health Insurance Portability and Accountability Act (HIPAA) conducted at 19 US and Canadian sites. There were two patient populations enrolled in the registry: patients with SSc at risk for PAH and those with incident PAH. At-risk patient enrollment criteria were: (1) DLCO < 55% predicted with an FVC of > 70% predicted; (2) FVC/DLCO ratio > 1.6; or (3) estimated right ventricular systolic pressure > 40 mm Hg on ECG. At-risk patients underwent PAH screening annually or sooner if clinically indicated. Right heart catheterization (RHC) was performed for at-risk patients based on clinical indication during follow-up. Patients with incident PAH were diagnosed by RHC within 6 months of enrollment¹⁴⁸.

The PHAROS registry has allowed the study of risk factors in a subpopulation at risk of PAH and in a population already diagnosed with PAH¹⁴⁹⁻¹⁵¹. It has also contributed to the hemodynamic study of these patients^{152,153}, the prognostic role of related antibodies,

and biomarkers^{154,155}, the influence of ILD in these patients¹⁵⁶, and the response to oral therapy¹⁵⁷.

This is being coordinated by Dr. V. Steen at Georgetown University (Washington DC).

Discussion

The University of Pittsburgh Scleroderma Databank was the first SSc registry initiated in 1980. Although it has always functioned as a reference center in the US, it is still a single-center and, therefore, far from the objective of the present review. It is the prototype of all registries in SSc as it includes a comprehensive initial evaluation, standard SSc examination, laboratory studies, and yearly serum and DNA samples. Most importantly, it includes a comprehensive annual to biannual follow-up of patients. This databank now has > 4000 patients with > 30 years of follow-up data.

The path of clinical research in SSc has been through national registries. It has opened up possibilities unimaginable in the last century for most centers and has increased clinical knowledge of the disease. It has allowed better characterization of patients and improved knowledge of prognostic factors of the disease. We owe this luck firstly to the world reference center in Pittsburgh and its researchers and secondly to the researchers promoting the different registries in each of these countries mentioned above. In short, we are talking about 7 countries, not many, but they give a good account of what SSc is, at least in the first world (Suppl. Tables 1 and 2 and Figs. 2 and 3). Unfortunately, we do not have national registries in 3rd world countries or in developing or emerging countries. We do not have national data from Asia or Africa either. In general, national registries cover the entire spectrum of the disease, although the ASIG is mainly focused on pulmonary manifestations (PAH and ILD). In recent years, supranational initiatives have appeared, first with EUSTAR and later with SPIN and INSYNC. The case of the SPIN is special because it is specifically designed to perform randomized clinical trials, it opens a door to a different type of systematic collaboration between various working groups.

If the same disease has already benefited from this large amount of data included in the same registry despite its low incidence, it has been even more important to study certain clinical manifestations that only a small group of patients suffer. This is where PAH, ILD, and scleroderma renal crisis (SRC) would come in. The study of these continues to be difficult due to the limitation in the number of patients who suffer from it, but

it is no longer impossible. Furthermore, it allows the isolated study of these clinical manifestations in a homogeneous group of patients with SSc and not included in studies with other types of patients as occurs, for example, in studies of PAH including patients with idiopathic PAH and other subtypes. In this regard, several national registries dedicated to the study of pulmonary hypertension have emerged in recent decades. Two of them have focused on SSc-related PAH, such as the ItinerAIR-Sclérodemie registry and the PHAROS registry ([Suppl. Tables 3 and 4 and Figs. 1 and 2](#)). They are cohorts of patients with incident PAH patients and patients not yet diagnosed with PAH. The inclusion of patients without PAH is broader in the former, so the incidence of PAH in the French cohort is lower. These cohorts allow a more rigorous study of this organic condition but they need years to be able to gather a sufficient number of patients to allow their study given their low incidence. There are no similar registries for SSc-related ILD or SRC.

On the other hand, the limitations inherent in these registries have to be commented on. First, as in all multicenter studies, there is heterogeneity between centers in terms of knowledge of the disease, management. The constant feedback from scientific meetings minimizes these differences, but they are there. Second, they are databases with several predefined variables and not designed for a specific study. This sometimes limits the study in depth of a specific topic that requires data not present in the database. Third, the management of the SSc overlaps between several specialties, mainly Internal Medicine and Rheumatology, Dermatology, Pneumology, among others. The registries are usually endorsed on occasions by a single scientific society so that certain patients may not be represented in the registry and this could lead to a bias toward inclusion. Fourth, it is important that a registry has reference centers in SSc but also 2nd and 3rd level centers without so much experience in its management. This may not occur in all registries and the big picture of the SSc in that country would not faithfully reflect the real seriousness of the patients. Fifth, most of the registries are prospective, but not all. A registry with retrospective data runs the risk of committing an inclusion bias. If a rigorous search has not been carried out to include previously deceased patients, it will only be including patients who have arrived alive at the time of recruitment and therefore those patients with severe SSc and risk factors of bad outcomes will be minimized in oblivion. Besides, the information in retrospect is not

always available and this leads to loss of information in the registry.

In conclusion, the registries have shown their benefits in terms of progress in knowledge, and in a few years and with a greater follow-up of patients will be able to continue providing very interesting data from which we will learn even more. We can see that this type of research can have a limit and we should think about going further. Some of these registries include blood and tissue biobanks. This opens the door to new lines of research not possible until now. International cooperation is increasingly common and some of the latest registries have been born on this basis. Finally, registries are the basis of many observational studies, but the example of the SPIN shows the possibility of conducting clinical trials on a cooperative and systematic international basis. All this is good news for a disease like SSc, orphaned in the last century and of which we know more every day that passes. Our patients will be grateful for it.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Supplementary data

Supplementary data are available at *Spanish Journal of Medicine* online (www.spanishjmed.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole author's responsibility.

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