Reuma.pt project protocol

Title

Pulmonary Hypertension in systemic sclerosis: data from Reuma.pt

Keywords

Pulmonary hypertension; systemic sclerosis; Reuma.pt

Background

Systemic sclerosis (SSc) is a rare connective tissue disease with a heterogeneous clinical course. Pulmonary hypertension (PH) is a serious and potentially life-threatening condition that can develop in patients with SSc.

Pulmonary arterial hypertension (PAH) occurs when the blood vessels supplying the lungs constrict and then become stiffer and thicker because of irreversible fibrosis. The increased resistance in pulmonary circulation makes it difficult for blood to flow through to the lung vessels, and thus the heart has to produce higher systolic pressures. This eventually leads to myocardial hypertrophy and right-sided heart failure.[1]

Of interest, SSc patients may have other causes of pulmonary hypertension (PH) such as Group 3 PH (chronic lung disease) (20%) and Group 2 PH (left-sided heart involvement) (16%). However, most SSc patients with PH actually have Group 1 PH (PAH) (64%). PH is defined as a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg on right heart catheterization (RHC). While PAH is further distinguished by a pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) >3 wood units, without chronic hypoxemia from interstitial lung disease (ILD). Approximately 30% of patients with SSc have an elevated right ventricular systolic pressure (≥40 mmHg) on screening echocardiogram. However, in prospective studies, the prevalence of PAH in patients undergoing RHC is only 7%–12%.[2,3]

The treatment algorithm of SSc-PAH has dramatically changed due to the introduction of new therapeutic agents used as monotherapy or in combination. Despite these promising advances, the 3-year survival in the modern era is only 56%–75%.[4,5]

Some studies have been developed in order to identify predictors of PH development in SSc patients. Kolstad et al. identified IL-1β and IL-15 as potential biomarkers associated with progression to PAH in SSc.[6] Some reports identified age, forced vital capacity, and diffusing capacity for carbon monoxide/ alveolar volume as factors independently associated with the presence of PH.[7,8]

This study has the propose of describing the clinical characteristics, haemodynamics, and mortality of Portuguese patients with SSc-PAH registered in Reuma.pt and to identify clinical parameters associated with the development of PAH.

Given the rarity of SSc-PAH, information obtained from large cohorts is relevant for identifying predictor of the course of the disease. The Rheumatic Diseases Portuguese Register (Reuma.pt) was created in June 2008 and has been an essential tool in Rheumatology clinical practice, allowing a uniformized follow-up of patients with different systemic rheumatic diseases. In September 2015, a new protocol dedicated to scleroderma patients (Reuma.pt/ Scl) was launched.

Objectives

<u>Primary objectives</u>

- Describe the clinical features of the patients with PAH in the SSc national cohort
- Determine PAH prevalence in SSc patients registered in Reuma.pt and fully characterize this subset of patients

Secondary end-points:

- Determine clinical and immunological features associated with the presence of PAH
- Determine predictors of PAH progression

Methods

Type of study: cross-sectional study

Inclusion criteria:

- Patients registered in Reuma.pt/Scl that fulfill the ACR/EULAR 2013 classification criteria for SSc.
- Follow-up period of ≥12 months
- Availability of at least one screening echocardiogram
- Diagnosis of PAH based on RHC.

Exclusion criteria

- Overlap syndromes

Variables to be collected:

- Age (continuous variable)
- Gender (categorical variable)
- Age at disease onset (continuous variable)
- ANA (categorical variable: positive; negative)
- Disease-specific auto-antibodies (categorical variables: anti-centromere, anti-topoisomerase I, anti-RNA polymerase III, anti-Th/To, anti-U3 RNP, anti-Pm/Scl, anti-Ku, anti-U1 RNP, anti-U11/U12 RNP, none)
- Phenotype of cutaneous involvement (categorical variables: systemic sclerosis sin scleroderma; very early diagnosis of systemic sclerosis; limited cutaneous systemic sclerosis; diffuse cutaneous systemic sclerosis)
- Clinical manifestations (continuous variable: Rodnan skin score; categorical variables: skin thickening, calcinosis, Raynaud's phenomenon, telangiectasia, digital ulcers, oesophageal involvement, gastric involvement, intestinal involvement, cardiac involvement, musculoskeletal involvement (joint contractures, tendon friction rubs, arthralgia, myositis/CK elevation), renal involvement/proteinuria
- Nail fold capillaroscopy pattern (categorical variable)
- Pulmonary involvement:
    - Pulmonary function tests (FVC and DLCO) at baseline and follow-up (every 6-12 months)
    - Pulmonary fibrosis, lung restrictive defect (categorical variable)
- Cardiac involvement
    - Cardiovascular comorbidities: Ischemic cardiac disease, Hypertension (categorical variable)
    - NYHA FC I-II/III-IV (categorical variable)
    - NTPro-BNP (continuous variable)
    - ECG (arrhythmia, heart block conduction, normal) - (categorical variable)
    - Echocardiogram (FEVE%, diastolic disfunction, RA dimensions (cm^2), RV dimensions (mm), TRV, PSAP (mmHg))
    - RHC (Mean PAP, mmHg; Cardiac index, L/min/$m^{2;}$ mPAWP, mmHg; RV/AV gradient; Right atrial pressure, mmHg)
- Pulmonary Hypertension type: group 1 (PAH), group 2 (left-sided heart involvement), group 3 (chronic lung disease); group 4 (chronic thromboembolism); group 5 (miscellania) - (categorical variable)
- Treatment (PDE, ERA, Prostacyclin, IBP, Domperidone, amlodipine, nefidipine…) - (categorical variable)

- Class
- Single, double, Triple therapy

Type of analysis:

- Descriptive analysis of PAH-SSc cohort: categorical variables will be presented using absolute and relative frequencies; for continuous data mean, standard deviation, median, minimum and maximum will be calculated.
- Logistic analysis regression will be performed in order to identify independent association with PAH
- Cox regression analysis will be used to determine predictors of PAH

Blood samples

The collection of blood samples from patients with Systemic Sclerosis and Pulmonary Hypertension is proposed to be stored in the IMM Biobank and subsequently analyzed, with the possibility of researching new innovative biomarkers.

Expected results and possible limitations

We expect to evaluate the prevalence of PAH in SSc patients in Portuguese patients registered in Reuma.pt and fully characterize this population regarding demographic, clinical, immunological, imaging and functional features. We expect to find predictors of PAH development and progression.

Limitations such as underreporting and missing data are expected. In order to minimize missing data, all participating centers will be asked to complete the dataset with information from the medical charts, when available.

Calendar of tasks

- Submission of research protocol to Reuma.pt and Ethics Commission: October 2019
- Invite all national centres to participate in the project: November 2019
- Data completion by all participating centres: November - December 2019
- Data extraction: May 2020
- Data analysis: May-September 2020
- Final report and abstract submission for presentation in national/international congresses: 2020/2021
- Submission for publication: 2021

Proponent

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Institutions

The project is open to all national centers willing to participate

Co-authors
Clinicians who actively collaborate in the project will be co-authors, according to the rules of Vancouver, with a maximum of 2 co-authors per Participating Center

Conflicts of interest
The authors declare no conflicts of interest.

Ethical considerations
The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and will be submitted for evaluation and approval to the Ethics Committee of Hospital Santa Maria.

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