1. Title

INTERSTITIAL LUNG DISEASE IN SCLERODERMA PATIENTS

2. Background

Systemic sclerosis (SSc) is a rheumatic disorder characterized by inflammation and fibrosis, involving the skin and internal organs. Lung involvement is a major cause of morbidity and a leading cause of SSc-related mortality (1–3).

The reported prevalence of interstitial lung disease (ILD) in patients with SSc ranges from 25% to 90%, depending on the subtype of SSc and the criteria used to define ILD (3). Higher risk to develop severe progressive ILD has been reported in diffuse cutaneous SSc and in patients positive for antitopoisomerase I (Scl-70)(2,4), anti-fibrillarin or anti-Th/To antibodies (2,4). On the other hand, anti-centromere (ACA) is associated with the absence of ILD (1,2,4).

Male sex has been identified not only as a predictor for ILD development, but also for disease progression and mortality (2,3). Moreover, the extent of disease on high-resolution computed tomography (HRCT) scan, forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO) at baseline have been pointed as predictors of ILD progression (3).

Small studies have been conducted in our country with the aim to characterize SSc patients with ILD and determine predictor features for the development and progression of ILD (5,6). These have shown prevalent ILD in about 20-35% of SSc patients, and suggested an association with anti-Scl70 positivity. One study also concluded that extent of fibrosis and reduction of DLCO at baseline were associated with ILD progression (6). The absence of ACA antibodies was reported as an independent association with ILD in another study (5).

The Rheumatic Diseases Portuguese Register (Reuma.pt), was created in June 2008 and has been an essential tool in our clinical practice, allowing the follow-up of patients with different systemic rheumatic diseases. In September 2015, a new protocol dedicated to scleroderma patients (Reuma.pt/ Scl) was launched and by July 2017 the database included almost 300 patients.

Given the rarity of systemic sclerosis, information obtained from large cohorts is relevant to a better understanding of the disease and to identify clinical and laboratory characteristics that may modify the course of the disease. This would be the first multicenter study, including SSc patients from all over the country, and would allow more complete analysis with more robust, and hopefully new results.

3. Objectives

<u>Primary objectives</u>

- Describe clinical features of SSc national cohort
- Determine ILD prevalence and fully characterize patients with ILD

Secondary objectives

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

4. Methods

Type of study: Prospective multicenter open cohort study

Inclusion criteria:

Patients registered in Reuma.pt/Scl that fulfill the ACR/EULAR 2013 classification criteria for SSc.

ILD will be defined by alterations in chest x-ray and/or HRCT scan suggestive of ILD and/or compromised functional pulmonary function tests (PFTs), including DLCO measurement.

Only patients with HRCT scan and PFTs performed at baseline and at least 6 to 12 months later will be included when evaluating disease progression. Disease progression will be defined by an increase in area of the involved lung parenchyma and/or, development of honeycombing in patients with previous ground glass imaging and/or, reduction of more than 15% in DLCO or 10% in FVC.

Variables to be collected:

- Demographic features: age, gender, race
- Smoking habits
- Disease features: type of SSc cutaneous involvement, disease duration, organ involvement
- Nailfold capillaroscopy
- Rodnan score at baseline
- Digital ulcers (ever and current)
- Auto-antibodies: ANA, ACA, anti-Scl 70, anti- RNA polymerase III, anti-Th/To, anti-U3 RNP, anti-Pm/Scl, anti-Ku, anti-U1 RNP, anti-U11/U12 RNP
- Pulmonary function tests (FVC and DLCO) at baseline and follow-up (every 6-12 months)
- x-ray and HRCT scan results at baseline and follow-up (every 6-12 months)
- Medication: immunosuppressive treatments used (including corticosteroids, sDMARDs and biologics)

Type of analysis:

- Descriptive analysis of 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 ILD
- Cox regression analysis will be used to determine predictors of ILD progression

5. Expected results and possible limitations

We expect to evaluate the incidence of ILD in SSc patients and fully characterize this population regarding demographic, clinical, immunological, imaging and functional features. We expect to found some robust predictors of ILD 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.

6. Calendar of tasks

- Data extraction: November 2017
- Data analysis: December 2017- January 2018
- Final report and abstract submission for presentation at a national / and European congress: 31 January 2018
- Manuscript preparation: February-May 2018

7. Proponent

Ana Catarina Duarte - Rheumatology department Hospital Garcia de Orta

8. Research team

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9. Institutions

The project is open to all national centers willing to participate

10. 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

11. Conflicts of interest

There is no conflicts of interest in this study.

12. 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 Garcia de Orta.

References

1. Kane GC, Varga J, Conant EF, Spirn PW, Jimenez S, Fish JE. Lung involvement in systemic sclerosis (scleroderma): relation to classification based on extent of skin involvement or autoantibody status. Respir Med. 1996 Apr;90(4):223–30.

2. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: Inception cohort study. Mod Rheumatol. 2016 Jul;26(4):588–93.

3. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, et al. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. Chest. 2014 Aug;146(2):422–36.

4. Kranenburg P, Hombergh VD, T WM, Knaapen-Hans HKA, Hoogen VD, J FH, et al. Survival and organ involvement in patients with limited cutaneous systemic sclerosis and anti-topoisomerase-I antibodies: determined by skin subtype or auto-antibody subtype? A long-term follow-up study. Rheumatology. 2016 Nov 1;55(11):2001–8.

5. Sousa S, Duarte A, Cordeiro I, Teixeira L, Canas da Silva J, Cordeiro A, Santos MJ. Interstitial lung disease in Scleroderma portuguese patients. J scleroderma relat disord 2016 Jan; 1(1): 1-2.

6. Morais Castro A, Resende C, Ferreira L, Moniz D, Ponte C, Pereira da Silva JA. Systemic sclerosis (SSc) and interstitial lung disease (ILD): predictors of progression of ILD in patients with SSc. J scleroderma relat disord 2016 Jan; 1(1): 2-3.