1. TITLE

Predictors of skin score change in systemic sclerosis: a Reuma.pt analysis

2. BACKGROUND

Skin fibrosis is a hallmark feature of systemic sclerosis (SSc) (1). The modified Rodnan skin score (mRSS) is the gold standard for skin thickness assessment not only in clinical practice, but also in clinical trials (2). Identification of predictors of change in mRSS over time is of interest for risk-tailored clinical management, as well as for clinical trial design, in order to enrich for patients with worsening skin fibrosis.

Identification of patients at risk for further progression of skin fibrosis remains challenging (3,4). Two recent, large-scale, observational studies on the European Scleroderma Trials And Research (EUSTAR) database identified the following independent predictors of skin progression:

Worsening in patients with diffuse cutaneous SSc (dcSSc)- short disease duration (<15 months), joint synovitis and low baseline mRSS (4);

Improvement in dcSSc - advanced skin fibrosis at baseline and absence of tendon friction rubs (3).

However, these findings haven´t been validated in other cohorts.

The Portuguese Register of Rheumatic Diseases (Reuma.pt) launched, in September 2015, a new protocol dedicated to scleroderma patients (Reuma.pt/Scl) and by December 2017 the database included almost 500 patients.

Given the rarity of SSc, 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.

The objective of this study is to provide evidence-based predictors of skin improvement/aggravation in SSc patients registered in the Reuma.pt/Scl database.

3. OBJECTIVES

Primary objective

- To identify and describe demographic, clinical and laboratory characteristics of SSc patients associated with significant change in skin score over time (mRSS) (progressors *versus* non-progressors)

4. METHODS

4.1 Type of study: Prospective multicenter open cohort study.

4.2 Inclusion criteria:

(i) Patients registered in Reuma.pt/Scl that fulfil the ACR/EULAR 2013 (4) or American College of Rheumatology 1980 classification criteria for SSc (5) or LeRoy et al (6) criteria for early SSc.

(ii) Only patients with two mRSS evaluations separated by at least 12 months will be included when evaluating skin progression.*

*The follow-up time of 12 months has been chosen since it is considered a relevant period to detect significant changes in mRSS, adopted in many clinical studies of skin fibrosis (Khanna D 2009, Pope JE, 2001).

4.3 VARIABLES TO BE COLLECTED:

Demographic features: age, gender, ethnicity
Smoking habits
Disease features: type of SSc cutaneous involvement, disease duration, organ involvement
Nailfold capillaroscopy: late, early, active, undetermined
Rodnan score: baseline and follow-up (Follow-up time between visits, months)
Digital ulcers (ever and active)
Antibody status: 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)

Lab: ESR, CRP (from the same visit as the Rodnan score)

Medication: Immunosuppressive treatment (Yes/No). If yes, sDMARDs (name, dose, duration, Yes/No), biologics (name, dose, duration, Yes/No), corticotherapy (name, dose, duration, Yes/No)

4.4 ANALYSIS:

Definition of progressive patients ("Progressors"): Skin fibrosis defined as increase in a 5-unit and 25% increase in their mRSS between baseline and 2nd visit, which is considered clinically meaningful (7).

- Descriptive analysis of SSc cohort (progressors, improvers and non-progressors): categorical variables will be presented using absolute and relative frequencies; for continuous data mean, standard deviation, median, minimum and maximum will be calculated.
- Univariate analysis (for potential prediction markers): comparison between progressors *versus* non-progressors of patient and disease characteristics using the Kruskal-Wallis (for continuous variables) or Fisher's test (for categorical variables) or Mann–Whitney U test (for ordinal variables).

Logistic regression analysis will be performed in order to identify independent associations with skin involvement

5. EXPECTED RESULTS AND POSSIBLE LIMITATIONS

We expect to evaluate the change of skin fibrosis in SSc patients and characterize this population regarding demographic, clinical, immunological, imaging and functional features. We expect to find some robust predictors of changes skin fibrosis changes (progressors *versus* improvers *versus* non-progressors).

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.

As soon as we have authorization from Reuma.pt Ethical Committee we will demand the data extraction (≈March 2018). This will serve to assess the current potential of the available dataset and to invite the collaborating centers to insert/complete data, and thus minimize missing data.

6. CALENDAR OF TASKS

- Data extraction: March 2018 (intercalary) and June 2018 (final)
- Data analysis: June 2018- July 2019
- Final report and abstract submission for presentation at ACR 2018, EULAR 2019, CPR 2018.
- Manuscript preparation: July-September 2018

7. PROPONENT

Tânia Santiago - Rheumatology Department of Centro Hospitalar e Universitário de Coimbra

8. RESEARCH TEAM

Tânia Santiago (TS), Mariana Luís (ML), Flávio Costa (FC) Maria João Salvador (MJS) and José A. Pereira da Silva – Rheumatology Department of Centro Hospitalar e Universitário de Coimbra.

TS, ML, MJS – Project design and manuscript writing.

TS, ML, FC, MJS - Data insertion.

All: manuscript revision and approval.

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 are 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 Centro Hospitalar e Universitário de Coimbra.

13. REFERENCES

1- Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum. 2000;43(11):2445-54.

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3- Maurer B1, Graf N2, Michel BA1, Müller-Ladner U3, Czirják L4, Denton CP5, Tyndall A6, Metzig C7, Lanius V7, Khanna D8, Distler O1; EUSTAR co-authors. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis. 2015;74:1124-31.

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5- Subcommittee for SSc criteria of the American Rheumatism Association diagnostic and therapeutic criteria committee (1980) Preliminary criteria for the classification of systemic sclerosis (SSc). Arthritis Rheum 23:581–590.

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