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Background: Interstitial lung disease (ILD) is the leading cause of mortality in patients with Systemic Sclerosis (SSc). Forced Vital Capacity (FVC) is a major indicator of severity in SSc ILD. The ELF serum test and its constituent biomarkers (HA, PIINP and TIMP-1) have shown to correlate with FVC in two large, independent multicentre cohorts of 457 patients, but also showed a correlation with age.

Objectives: Here we aimed to investigate the relationship of the ELF biomarkers and age in a large population of healthy controls and to identify a combined clinical and biomarkers model to stratify for risk of ILD progression in a multicentre longitudinal cohort of patients with SSc.

Methods: ELF score was measured in sera from 925 healthy controls in one centre and 869 longitudinal samples from 254 SSc patients from 6 centres across 4 European countries. Clinical data were recorded according to EUSTAR Minimal Essential dataset. FVC% change over time was estimated by Mixed-effects modelling. Patients were then divided in two groups: progressors, with a %FVC drop > 3%/year (according to published MCID) and a group of patients with stable or improving FVC. Lasso penalised regression was carried out with biomarkers and the available clinical and demographic variables at patient's first visit as potential predictors. The resulting linear predictor was used to derive two thresholds, one for optimal sensitivity (rule-out) and one for optimal specificity (rule-in). Patients within thresholds were further selected according to the ratio of TIMP-1: PIINP (Figure 1).

Results: HA was the only ELF biomarker that correlated significantly with age in the healthy control cohort. Therefore, we defined by linear regression a "residual HA" which accounted for age. TIMP1, PIINP and residual HA were then considered as distinct biomarkers in the analysis of the SSc cohort. 189 SSc patients with 785 time-points had complete datasets and were included in the analysis. Median follow up was 33 months (IQR 18-48). One-hundred and forty patients (74%) were classified as non progressors, 94 (50%) with no change or improving FVC and 46 (24%) with FVC drop <3% year. 49 patients (26%) were classed as progressors (drop of 3%/year or more in FVC, median slope -4.7%/year). Variable selection via Lasso penalised logistic regression resulted in a model with a c-index of 0.69 (95% CI: 0.60-0.78) and contained age, disease duration (from first non-Raynaud's symptom), residual HA, anti-centromere antibodies (ACA) status, previous diagnosis of ILD, joint synovitis and history of protein pump inhibitor use. A two-step process was developed using the linear predictor from the model and the ratio of TIMP-1 and PIINP (Figure 1). The stratification tool increased by nearly two-fold the ability to predict progressors in any 12 months interval (46 to 49% predictive value vs 26% probability) identifying an 82 to 91% negative predictive value for progression.

Conclusion: Building on the face and content validity of the biomarkers included in the ELF score, here we identify an easy to assess combined clinical and biomarker model to stratify patients for their risk of ILD progression. Despite its derivation from a large multicentre cohort, independent validation will determine the clinical value of Sclerosiscore as a stratification tool for risk of progression of SSc ILD.

Figure 1: Two-step process to stratify patients for risk of ILD progression
Patients with overall 24% risk of 3% yearly FVC drop are stratified by regression model in patients with 49% (rule in) vs 9% risk (rule out) in (Step 1). Patients in between thresholds of Step 1 are further stratified according to the biomarker ratio (TIMP1/PIINP) in the same risk categories.

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OP0270 LONG-TERM EFFICACY AND SAFETY OF BOSENTAN IN PATIENTS WITH DIGITAL ULCERS RELATED TO SYSTEMIC SCLEROSIS

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Background: Two pivotal studies, RAPIDS-1 and RAPIDS-2 revealed that bosentan reduces the development of new digital ulcers (DUs) in patients with systemic sclerosis (SSc). However data regarding the long-term use of this dual endothelin antagonist receptor in the treatment of DUs is scarce.

Objectives: The aim of the present study was to evaluate long term efficacy and safety profile of bosentan in patients with DUs related to SSc.

Methods: A prospective observational case-control study, conducted between 2014 and 2020 enrolled 65 SSc patients with ≥1 active DUs at baseline, who received bosentan therapy. Demographic and clinical features, including DUs incidence and patients subjective perception of DU pain and/or Raynaud's Phenomenon, were collected. Nailfold videocapillaroscopy was performed in all patients.

Results: The study included 51 females and 14 males, with a mean age of 52.6 years, 30 with diffuse subset, most of them with late scleroderma pattern (46/65). Number of DUs at baseline was 4.55 (±2.8), median duration of treatment was 25.95 (±19.4) months. Microangiopathy evolution score (MES) was 5.1 (2.19), visual analog scale (VAS) for DU was 77.9, VAS for Raynaud was 73.4.

Patients receiving bosentan had clinically significant reduction in the mean number of DU ($p<0.001$). The effect was most powerful for the first 6 months of treatment, but the improvement was sustained until 24 months' follow-up, when the mean DU number reached a plateau that was kept until end of study. 6 month and 24 month evaluations also revealed significant decrease in the VAS for DU ($p<0.05$) and in the VAS for Raynaud ($p<0.01$). Statistically significant difference was noted between bosentan-treated and the control group with respect to the decrease in the mean number of digital ulcers. ($p=0.005$).

There was a clear trend towards an improvement in MES score, between baseline and the next follow-up assessments ($p=0.003$). The difference was statistically significant when compared to control group, but only for the first 18 months of treatment ($p<0.001$).

14 patients (28.75%) discontinued bosentan therapy for administrative reasons. The median time among patients who interrupted the treatment was 6.9 months. An accelerated development of new DU was described 6 months after ($p=0.02$). Following recommencement of bosentan, the mean number of DU has rapidly decreased ($p=0.008$). There was no significant difference between patients who temporarily discontinued bosentan for 6 or 12 months.

Bosentan was stopped due to lack of efficacy in 2 cases and due to side effects in 7 cases: 4 elevated liver enzymes, 1 severe thrombocytopenia, 1 dyspnea aggravation and low blood pressure.

Conclusion: The present data suggest that treatment with endothelin receptor antagonist bosentan was associated with a significant reduction in the mean number of DU in patients with SSc. The beneficial effect of bosentan persisted throughout the study but was most evident in the first 6 months of treatment. Statistical analysis showed a significant improvement of the microangiopathy evolution score from baseline to end of therapy. 14 patients had a high relapse rate due to potential rebound effect, 6 months after bosentan withdrawal. The drug was reintroduced successfully for 10 (70%) patients with a significant decrease in the number of DU.

REFERENCES:

- [1] UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis, *Rheumatology*, Volume 54, Issue 11, November 2015, Pages 2015
- [2] Groseanu L, Berghia F, Bojinca V, et al AB0779 Long term follow-up of a systemic sclerosis group treated with bosentan, *Annals of the Rheumatic Diseases* 2018;77:1523-1524.

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