FRIDAY, 16 JUNE 2017

Scleroderma, myositis and related syndromes

FRI0363 KL6 AND NOT CCL-18 IS A PREDICTOR OF EARLY PROGRESSION IN SYSTEMIC SCLEROSIS RELATED INTERSTITIAL LUNG DISEASE

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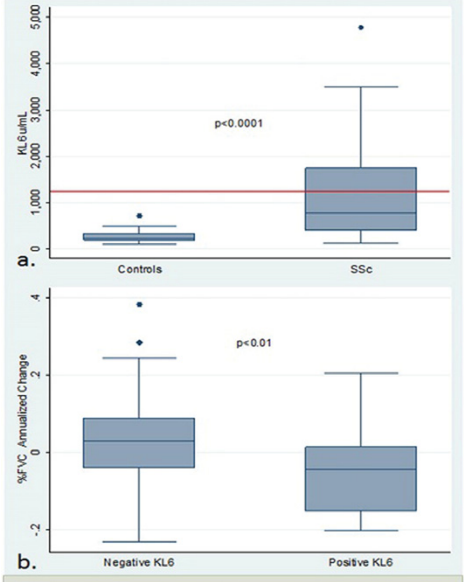
Background: Pneumoproteins are attractive biomarker candidates in systemic sclerosis (SSc) related interstitial lung disease (ILD) because they are easily obtainable and lung-specific. KL-6 and CCL-18 (PARC) have been previously reported as promising predictive biomarkers of lung parenchymal damage in multiple disorders including SSc-ILD.
Objectives: Our goal was to determine the predictive significance of these two pneumoproteins for forced vital capacity % (FVC) decline within the first year of follow-up in patients with early SSc-ILD, in order to inform individualized care in routine clinical practice and facilitate enrichment strategies in clinical trials.
Methods: GENISOS (Genetics versus ENvironment In Scleroderma Outcome Study) cohort patients who had ILD verified by imaging and available pulmonary function tests at enrollment plus 12–18 months thereafter, were included in this study. All patients had disease duration ≤5 years at enrollment. FVC, expressed as percentage of predicted value was used as surrogate for severity of ILD. Annualized percent change in FVC at one year follow up was calculated. Baseline demographic, clinical variables and two pneumo-proteins, KL-6 and CCL-18 were investigated. KL-6 and CCL-18 were measured in the plasma by commercially available, validated ELISA kits. Linear regression with baseline clinical and demographic variables as independent variables was performed in univariable and multivariable models. Only variables that reached p<0.1 were included in the multivariable analyses.
Results: A total of 82 patients with early SSc-ILD were included, 18 were male and 45 had diffuse cutaneous involvement. Mean disease duration was 2.3 years. Rate of FVC% predicted change over time ranged from -0.23 to 0.38, indicating a highly variable course. Baseline KL-6 levels were higher in patients than healthy controls (p<0.0001). Baseline higher KL-6 levels were predictive of faster FVC% decline at the one year follow-up (b=-0.03, *p*=0.04). Upon categorizing KL-6 using a previously determined optimal cut-off of 1273 u/mL (1), its predictive significance remained in the univariate (p=0.01) and multivariable analyses adjusted for Scl-70, disease type and gender (b=-0.03, *p*=0.04). Twenty nine (34.5%) patients had KL6 levels equal or above 1273 u/mL. Although CCL-18 was higher in patients than controls (<0.0001), its levels did not predict rate of FVC decline (provide p-value)

Figure 1. KL-6 levels between patients and controls and %FVC change



a) KL-6 levels (u/mL) in SSc patients versus controls (red line= 1273 cut-off). b) %FVC annualized change in KL-6 positive versus negative patients based on a cut-off of 1273 u/mL. Note: Lower values in %FVC change correspond to a faster FVC decline.

Conclusions: KL-6 but not CCl-18 is predictive of early SSc-ILD progression. In this study, we also validated the previously proposed cut-off of 1273 for KL-6 in an independent cohort. KL-6 is a promising pneumoprotein that can inform individualized clinical care and contribute to enrichment strategies in clinical trials of SSc-ILD.

References:
[1] Kuwana M, Shirai Y, Takeuchi T. Elevated Serum Krebs von den Lungen-6 in Early Disease Predicts Subsequent Deterioration of Pulmonary Function in Patients with Systemic Sclerosis and Interstitial Lung Disease. J Rheumatol 2016.

Acknowledgements: This study was funded by the National Institute of Health NIH/NIAMS K23 AR061436 (Assassi); NIH/NIAMS P50-AR05414 and the Department of Defense Congressionally Directed Medical Research Programs (W81XWH-07–01–0111- Mayes).
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.5145

FRI0364 USEFULNESS OF SERUM HAPTOGLOBIN LEVELS AS A NOVEL MARKER FOR PULMONARY ARTERIAL HYPERTENSION COMPLICATED WITH CONNECTIVE TISSUE DISEASE

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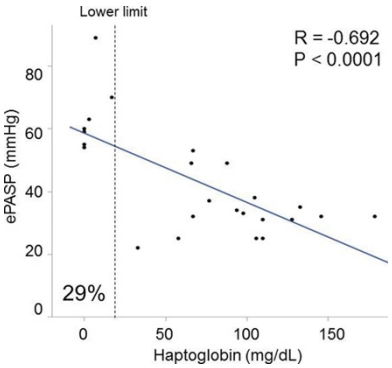
Background: Pulmonary arterial hypertension (PAH) is of great clinical significance as a life-threatening complication of connective tissue diseases (CTD). Pulmonary artery thrombotic microangiopathy (PATM) is an important pathophysiology of PAH. The concept of PATM refers to localized thrombotic microangiopathy to be defined histologically and should be discriminated from systemic thrombotic microangiopathy characterized by microangiopathic haemolysis and thrombocytopenia. The degree of PATM has been suggested to be associated with vasodilator response, severity, and prognosis of PAH, and anticoagulation therapy might be effective in PAH patients with features of PATM [1]. Haptoglobin (Hp) is a plasma protein mainly produced by hepatocytes, which binds free haemoglobin released from erythrocytes and protects the kidneys from damage induced by haemoglobin. The Hp is measured in clinical setting as a sensitive marker to detect intravascular haemolysis including thrombotic microangiopathy [2].
Objectives: We hypothesized that serum Hp levels decreased in patients with PAH due to pulmonary microangiopathic haemolysis. The aim of this study was to investigate the association between serum Hp levels and pulmonary artery systolic pressure estimated by echocardiography (ePASP) in patients with CTD.
Methods: This study included CTD patients with suspicion of PAH who were attending Rheumatology Department in Hokkaido University Hospital between August 2015 and August 2016 and underwent echocardiography. PAH was diagnosed based on right heart catheter findings. Serum Hp levels were measured by standardised turbidimetric immunoassay in all patients. Demographic data, laboratory results, and echocardiographic findings were extracted from the medical records. Decreased serum Hp levels were defined as below 19 mg/dL based on the 95th-percentile of healthy controls.
Results: Twenty-four CTD patients with confirmed PAH (CTD-PAH) and 32 CTD patients without PAH (non-PAH) were enrolled. Decreased serum Hp levels were significantly frequent in patients with CTD-PAH compared with non-PAH patients (29% vs 6%, p=0.03). In patients with CTD-PAH, serum Hp levels had a significant negative correlation (r = -0.692, p<0.0001, Figure 1) with ePASP, and serum lactate dehydrogenase (LDH) levels were significantly elevated in patients with decreased Hp levels (233±47 U/L vs 187±42 U/L, p=0.01). Follow up study showed lowering ePASP led to normalizing serum Hp levels.



Conclusions: Serum Hp levels correlated negatively with ePASP in patients with CTD-PAH, and serum LDH levels were higher in CTD-PAH patients with decreased Hp levels. These findings suggest that decreased Hp levels in CTD-PAH patients may reflect PATM and subsequent subclinical haemolysis. Serum Hp levels are a candidate of additional non-invasive marker of CTD-PAH to assess the degree of PATM.