POS0881

DETECTION OF THE GENE EXPRESSIONS IN PERIPHERAL BLOOD INVOLVED IN THE PROGRESSION OF PULMONARY VESSEL DISEASE AT THE SUBCLINICAL STAGE OF PULMONARY HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS

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Background: Pulmonary hypertension (PH) is prominent as a vascular involvement of systemic sclerosis (SSc), which remains a leading cause of death in spite of current best treatments. Recently, hemodynamic definition of PH was updated from mPAP $\geq$ 25mmHg to mPAP $>$ 20mmHg and PVR $\geq$ 3WU. Although new definition may improve the prognosis of PH associated with SSc by giving a chance to start management early, it may be insufficient as more than 2/3 of the pulmonary circulation is already impaired by the time of meeting the definition. Therefore, the ideal therapeutic intervention should be started at the subclinical stage of PH in SSc patients, but little is known about underlying pathological mechanisms at the stage. In this study, we investigate progression to exercise-induced PH (exPH)¹, which is considered subclinical PH, in the prospective registry of high-risk population for developing PH associated with SSc.

Objectives: To detect the gene expressions in peripheral blood involved in the progression of pulmonary vessel disease (PVD) at the subclinical stage of PH associated with SSc.

Methods: Total of 180 patients who had not met PH criteria with Raynaud phenomenon, skin sclerosis or SSc-related autoantibody was registered. To detect the early PVD, exercise Doppler echocardiography (exDE) was carried out every 6 or 12 months for up to 6 years. The definition of exPH was maximum sPAP $>$ 40mmHg or increase in sPAP $>$ 20mmHg estimated by exDE during exercise. For gene expression analysis, total RNAs from whole peripheral blood cells were extracted by PAXgene system, and then multiplex sequencing was done. To identify candidate genes involved in the progression to exPH, random forest machine learning method was employed. Volcano plots, a scatter plots to visualize fold-changes and p-values of differentially expressed genes (DEGs) between exPH and others (exN), were also used for seeking the important genes for disease progression.

Results: At the time of registration, 34.4% of patients met exPH criteria, and 15.6% of patients developed exPH during follow-up period (35.0 $\pm$ 18.1 months). Expression of TNF gene was selected as the most useful genes to predict progression to exPH by random forest, and the accuracy of the model was about 87%. Volcano plots indicated that expressions of TMEM176A and TMEM176B were prominent (fold-change $>$ 2.4 and -log₁₀ p-value $>$ 3.5) in exPH patients. The accuracy was improved to 90% if the expression of TNF and TMEM A/B were used for the prediction of progression to exPH. We found that statistically significant increase in the expression of TNF was eliminated at the time of fulfilling the exPH criteria, while increase in expressions of TMEM A/B were still kept.

Conclusion: It was reported that TNF α drives pulmonary arterial hypertension by suppressing the BMP type-II receptor and altering NOTCH signalling². Our findings suggest that TNF α plays important role only in the period of pre-exPH. On the other hand, increase in expressions of TMEM A/B were observed through the period of pre-exPH to post-exPH. It suggests that there are multiple phases before developing PH associated with SSc. It is very important to understand the phases for the precise treatment to arrest the progression of PVD.

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POS0882

AMINAPHTONE LONG-TERM TREATMENT IN SYSTEMIC SCLEROSIS

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Background: Aminaphtone has been used since many years to treat microvascular disorders. Aminaphtone seems to improve clinical symptoms of Raynaud's phenomenon (RP), either primary or secondary to systemic sclerosis (SSc) by

increasing peripheral blood perfusion as assessed by Laser speckle contrast analysis (1).

Objectives: To evaluate long-term survival and tolerability of Aminaphtone in SSc patients with secondary RP.

Methods: Eighty SSc patients (mean age 64 $\pm$ 12 years; mean disease duration 9 $\pm$ 8 years) treated with Aminaphtone due to active RP were enrolled (ACR/EULAR 2013 criteria). Patients were taking also various concomitant treatments, including aspirin, cyclic intravenous iloprost, immunomodulators, endothelin receptor antagonists. SSc patients performed periodic clinical and laboratory assessments on average every four months per our clinical practice. Duration of Aminaphtone administration, side effects, and self-assessment of Raynaud Condition Score (RCS) with a scale from 0 (absence of pain) to 10 (maximal pain) were retrospectively assessed.

Results: The observation period was between twelve and seventy months (mean 36 $\pm$ 19 months). Aminaphtone was administered at 75 mg twice daily, as standard initial posology per our clinical practice. During the follow-up, five patients (6.2%) referred headache as side effect: three of them had to reduce Aminaphtone posology to 75 mg per day, while maintaining clinical benefits; two patients had to stop the treatment. No other side effects related to the drug appeared during the treatment period, and repeated blood tests did not reveal any significant alteration ascribable to Aminaphtone. After 3 months of treatment sixty-six patients (83%) referred a subjective improvement of RP (RCS 3.6 $\pm$ 0.8, vs baseline RCS 7.4 $\pm$ 0.8, p=0.032), whereas fourteen patients (17%) were clinically unsatisfied (RCS 6.1 $\pm$ 0.4, p=0.12). In this last group of patients, Aminaphtone posology was increased to 75 mg three times a day with a satisfactory amelioration in further nine patients (94% of total) (RCS 4.0 $\pm$ 0.6, p=0.04), while five patients (6.2%) definitively discontinued therapy for subjective ineffectiveness within six months. Patients referred a sustained improvement of RCS along the observational period (36 $\pm$ 19 months) (last RCS 3.6 $\pm$ 0.7 vs baseline, p=0.031).

Conclusion: During an average observation period of three years, Aminaphtone showed a good tolerability profile along with sustained efficacy in 94% of patients with SSc-related RP, without disabling side effects. The absence of a placebo-control group, the retrospective design limit the results, and a randomized controlled trial for Aminaphtone use in the management of SSc-related RP is needed.

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POS0883

DETECTION OF AUTOANTIBODIES AGAINST MUSCLE-SPECIFIC FOUR-AND-A-HALF-LIM DOMAIN 1 (FHL1) IN INFLAMMATORY MYOPATHIES: RESULTS FROM A SINGLE-CENTER COHORT

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Background: Autoantibodies targeting a muscle-specific autoantigen, four-and-a-half-LIM-domain 1 (FHL1), have been previously identified in patients with idiopathic inflammatory myopathies (IIM) (1).

Objectives: The aim of this project was to determine the prevalence and associations of anti-FHL1 antibody in South Australian patients with histologically-confirmed IIM and in an autoimmune disease control (systemic sclerosis (SSc)).

Methods: Sera from patients with IIM (n=267) from the South Australian Myositis Database (SAMD), and SSc (n=174) from the Australian Scleroderma Cohort Study (ASCS) followed at the Royal Adelaide Hospital, and healthy controls (HC, n=100) were analyzed for anti-FHL1 autoantibodies by Enzyme-Linked ImmunoSorbent Assay (ELISA). Clinical, serological and histological details were retrieved from the SAMD and the ASCS.

Results: Autoantibodies to FHL1 were more frequent in patients with IIM (55/267, 20.5%) compared with SSc (18/174, 10%) (p<0.001) and HC (4/100, 4%) (p<0.001). Muscular vessel inflammation and atrophy were seen more frequently in IIM anti-FHL1⁺ patients compared with anti-FHL1⁻ (p<0.01 and p<0.05). Dysphagia, marked muscle atrophy, and high CK levels were frequent in anti-FHL1⁺ patients with inclusion body myositis (IBM) and immune-mediated necrotizing myopathy (IMNM). In 35/54 anti-FHL1⁺ patients, there were no other myositis-specific autoantibodies present. Anti-FHL1 autoantibodies in patients with SSc were associated with gastric antral vascular ectasia.