Systemic sclerosis, myositis and related syndromes – etiology, pathogenesis and animal models

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**MOLAR CHARACTERSATION AND STRATIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES: ON THE BASIS OF SKELETAL MUSCLE TRANSCRIPTOME STUDY**

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**Objectives:** To dissect the global muscle transcriptomic features in IIM based on myositis-specific antibodies (MSA) profiles and investigate the potential molecular pathway of IIM.

**Methods:** Muscle specimen were taken from 60 patients with IIM, 6 patients with non-IIM myopathies and 9 healthy controls. The serum and PBMC samples were also obtained from the IIM patients at the time of muscle biopsy. For RNA-seq, IIM was dissected into eight groups based on their MSA profiles: MSA and ANA negative (n = 10), -Mi-2 positive (n = 7), MSA negative but anti-Ro-52 positive (n = 7). RNA-seq was sequenced using Illumina HiSeq2500. Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) was performed on sequencing cohorts and expanding cohorts to validate the results of RNA-seq. Immunohistochemistry was also performed on muscle biopsy tissue to determine the MxA expression in different MSA subgroups.

**Results:** The global muscle signature of IIM in all IIM samples were compared to NC and total of 1637 transcripts were differentially expressed (log2 Fold Change > 1, Padj < 0.05). Unsupervised hierarchical clustering of these differentially expressed transcripts (DETs) revealed a prevalent interferon (IFN) signature and showed that 68 interferon-stimulated genes (ISGs) were significantly up-regulated in IIM. These 68 ISGs were used to cluster different MSA subgroups and distinct ISG expression was found. The mRNA expression levels of several ISGs (MX1, IFIH1, LAMPI, CMPK2, HERC6) in sequencing cohorts and expanding cohorts also confirmed the diverse ISG expression between different MSA subgroups. An IFN signature scoring system was established to quantify the IFN activity and subsequently IIM could be classified into IFN-Dominant, IFN-Moderate and IFN-Weak respectively based on the IFN intensity and different MSA subgroups. Moreover, the IFN-Dominant group showed much higher MxA expression and showed that 68 interferon-stimulated genes (ISGs) were significantly up-regulated in IIM. The mRNA expression levels of several ISGs (MX1, IFIH1, LAMPI, CMPK2, HERC6) in sequencing cohorts and expanding cohorts also confirmed the diverse ISG expression between different MSA subgroups. An IFN signature scoring system was established to quantify the IFN activity and subsequently IIM could be classified into IFN-Dominant, IFN-Moderate and IFN-Weak respectively based on the IFN intensity and different MSA subgroups. Moreover, the IFN-Dominant group showed much higher MxA expression on muscle biopsy tissue than the IFN-Moderate and IFN-Weak group by immunohistochemistry.

**Conclusion:** We revealed a prominent IFN signature and MSA-based ISG expression heterogeneity in IIM through muscle transcriptomics. Preliminary results showed that the IFN muscle signature may play a predominant role in some subgroups but not all IIM groups in the pathogenesis of IIM.

**REFERENCES:**


**Disclosure of Interests:** None declared

Efficacy and Safety of Riociguat in Patients with Early Diffuse Cutaneous Systemic Sclerosis and Interstitial Lung Disease (SSC-ILD): Results from the Phase II BIBI-SSC Study

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Methods: Patients had SSC of duration <18 months, modified Rodnan skin score (mRSS) 10–22 units, forced vital capacity (FVC) >45% predicted (%pred) and lung diffusion capacity for carbon monoxide (DLCO) ≥40%pred at screening. Patients were randomised to riociguat (n=60) or placebo (n=61) in individually adjusted doses of 0.5 mg up to 2.5 mg tid. The primary endpoint was the change in mRSS from baseline to Week 52. Secondary endpoints included change in FVC%pred from baseline to Week 52. Effects on lung function (FVC%pred) were assessed in the overall population and in post-hoc analyses in patients with FVC%pred 50–75% or medical history of ILD at baseline. Between groups, differences were in least-squares [LS] means.

Results: Although the study did not meet its primary endpoint, there was a reduction in mRSS with riociguat vs placebo (−2.7 vs +0.5; 95% CI: −4.99 to 0.30; p=0.08). There were no significant differences between treatment groups in the changes in FVC%pred (−0.20 vs +0.03; p=0.90) or DLCO%pred (2.01 vs 95% CI: −4.99 to 6.25; p=0.35) which included all patients irrespective of the presence of SSC-ILD. However, differences between riociguat and placebo were observed when patients with SSC-ILD were analysed: At baseline, 11/60 (18%) patients in the riociguat group and 12/61 (20%) in the placebo group had medical history suggesting ILD (SSc-ILD); 11/60 (18%) and 7/61 (11%), respectively, had restrictive lung disease (FVC%pred 50–75%). Results in subgroups were expressed as within-group mean change (SD). In patients with SSC-ILD, the decline in FVC%pred between baseline and Week 52 was smaller in the riociguat group (−2.7) than the placebo group (−8.9). The changes in DLCO%pred were −0.11 (0.22) and −0.87 (0.71), respectively. In patients with restrictive lung disease, FVC%pred decreased by −8.7 (4.0) at Week 52 with placebo but was almost unchanged (+0.75) with riociguat. The changes in DLCO%pred were +0.42 (0.85) and −0.27 (0.39), respectively. Patients with SSC-ILD receiving riociguat had lower incidences of adverse events and serious adverse events (82% [n=9] and 9% [n=1] respectively) compared with placebo (92% [n=11] and 25% [n=3] respectively) with no differences between treatment groups in the incidence of respiratory adverse events. No deaths occurred in the SSC-ILD subgroup, and no new safety signals were observed.

Conclusion: These results suggest that in an exploratory analysis, riociguat may be associated with preservation of lung function and good tolerability in patients with SSC-ILD. A phase III trial in SSC-ILD is planned.