differences disappeared. Adverse events were mostly mild and comparable between groups. Activity and sub-six-week treatment with low-dose oral prednisolone led to a substantial improvement of symptoms in patients with painful hand OA and signs of inflammation. This trial provides evidence that local inflammation is a suitable target for drug-treatment in hand OA.

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THURSDAY, 13 JUNE 2019

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

OP0181 MOLECULAR CHARACTERIZATION AND STRATIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES: ON THE BASIS OF SKELLETAL MUSCLE TRANSCRIPTOME STUDY

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Background: Idiopathic inflammatory myopathies (IMI) are a group of complicated heterogeneous autoimmune diseases, to date, little is known about its skeletal muscle transcriptomic features.

Objectives: Here, we performed skeletal muscle RNA-sequencing (RNA-seq) to discover the global muscle transcriptional signature of IMI based on myositis-specific antibodies (MSA) profiles and investigate the potential molecular pathway of IMI.

Methods: Muscle specimen were taken from 60 patients with IMI, 6 patients with non-IMI myopathies and 9 healthy controls. The serum and PBMC samples were also obtained from the IMI patients at the time of muscle biopsy. For RNA-seq, IMI was dissected into eight groups based on their MSA profiles: MSA and ANA negative (n = 4), ANA positive (n = 13), -MDAs positive (n = 6), -NXP2 positive (n = 13), -Ro52/SSA positive (n = 10), -SRR or anti-HMGCR positive (n = 6), -Mi-2 positive (n = 7), MSA negative but anti-Ro52 positive (n = 7). RNA from muscle specimen were extracted according to manufacture guide and 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 to determine the MxA expression in different MSA subgroups.

Results: To define the global muscle signature of IMI, all IMI 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 (DET's) revealed a prevalent interferon (IFN) signature and showed that 68 interferon-stimulated genes (ISGs) were significantly up-regulated in IMI. Then 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, LAMP3, 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 IMI could be classified into IFN-Dominant, IFN-Moderate and IFN-Weak respectively based on the IFN intensity and different MSA subgroup. Moreover, the IFN-Dominant group showed much higher MxA expression on muscle biopsy than the IFN-Moderate and IFN-Weak group by immunohistochemistry.

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

REFERENCES:

Op0182 SYNTHETIC PEPTIDES TARGETING CD206 INHIBIT PATHOGENIC MACROPHAGES IN SYSTEMIC SCLEROSIS

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Background: In systemic sclerosis, activated macrophages having M2-like properties are believed to contribute to the fibroblastic pathology by secreting profibrotic factors such as TGFβ. Certain synthetic peptides (10-12mers) studied here could co-opt the mechanism used by macrophages to detect bacteria by binding to certain regions of CD206, a receptor highly expressed in the M2 macrophages, and repolarise them to an M1 phenotype.

Objectives: We aimed to determine the macrophage activation signature in SSc, assess CD206 as a biomarker of ongoing fibrotic activity, and measure the effect of the peptides on macrophage activation and macrophage-fibroblast cross-talk.

Methods: scCD206 was assayed in plasma (n=50 healthy, 50 limited SSc, 50 diffuse SSc), and suction blister fluid (BF) obtained over active lesions by ELISA, sIGLEC (monocyte interferon signature) and IL-31 (Th2 signature) were assayed for comparison. Cell surface CD206 and DAMP receptor P2X7, were assayed by flow cytometry. The macrophage activation signature was investigated further by qPCR for inflammatory M1, as well as M2-like gene expression (IFNy, Arg1, CD206). Macrophage-fibroblast cross talk was assessed using media transfer following heat activation to SSc dermal fibroblasts assayed by qPCR for collagen I. The macrophage secretome was determined by Luminex.

Results: scCD206 was significantly elevated in SSc BF (SSc median scCD206 42, HC 31 pg/ml, p<0.041). Plasma scCD206 was raised in diffuse versus limited SSc (P<0.0103) and was correlated with ESR (R=0.364, p<0.009) and sIGLEC (R=0.244, p<0.05), but not disease duration or IL-31. By flow cytometry both CD206 and P2X7 were highly expressed by SSc macrophages (mean fluorescence SSc, 776.1 SD=409.1, 724.4 SD=455.3 vs HC 632.2 SD=73.7, 472.9 SD=25.4), correlating with modified Rodnan Skin Score (mRSS) (p<0.05, r=0.51). Double positive P2X7 and CD206 cells were seen in a subgroup with higher mRSS. Four RP peptides (RP182, 185, 832 & 837) were assessed for effect on growth of SSc and control macrophages. In general, the RP peptides selectively inhibited SSc macrophage growth, with RP185 and RP832 reaching significance (p<0.05) for 1 and 10µM concentrations at 96 hours. Pro-fibrotic cross-talk leading to elevated fibroblast collagen I, was characteristic of 4 out of 9 SSc macrophage cell lines examined. A mixed activation signature was identified by qPCR of the fibroblast-stimulating macrophages (elevated Arginase1, CD206 and IFNy) but not the non-fibroblast inducing cell lines. Pre-treatment of the pro-fibrotic SSc macrophages with RP832, but not the others, eliminated the pro-fibrotic cross-talk (fibroblasts treated with SSc macrophage media mean collagen I, 1995 (SEM 134), RP832 treated macrophages 1551 (SEM 133) p<0.038 relative expression units, paired t test), and suppressed the macrophage activation signature (reduced mean Arg1 p<0.030, CD206 p<0.058, IFNy p=0.058, paired t test). Secretome analysis confirmed the mixed activation signature of SSc macrophages including elevated total TGFβ, PDGF-ββ, VEGF as well as inflammatory factors IL-6, IL-18, TNFα and type I cytokine IFNy. Treatment with RP 832c reduced TGFβ in 6 out of 9 SSc macrophage cell lines but this did not reach statistical significance.

Conclusion: A macrophage activation signature is identified in SSc patients, in proportion to the severity of disease. A mixed activation signature with inflammatory as well as pro-fibrotic M2-like properties is seen. RP peptides, which target the cells via CD206, reduce the activation signature and inhibit pro-fibrotic cross-talk in these cells.

Disclosure of Interests: H. Henry Lopez Shareholder of: Murigenics, Ripptide Bioscience, Employee of: Pfizer, Kimi Kumar: None declared, George Martin: None declared, Richard Stratford: Shareholder of: Murigenics, Riptide Bioscience, Grant/research support: Pfizer, IMI-APPROACH (Grant Agreement n° 115770), Consultant for: GlaxoSmithKline, Merck-Serono, Abbvie, Levicept, Pfizer


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

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Background: Diffuse cutaneous systemic sclerosis (dcSSc) is an autoimmune connective tissue disease characterised by fibrosis, and in some patients, interstitial lung disease (ILD). Riociguat is a soluble guanylate cyclase (sGC) stimulator with vasoactive, anti-proliferative and anti-fibrotic effects. We hypothesised that riociguat may preserve lung function in patients with dcSSc.

Objectives: To evaluate the effect of riociguat on lung function in patients with early dcSSc from the multicentre, randomised, double-blind, placebo-controlled Phase IIb RISE-SSC Study (NCT02283762).

Methods: Patients had dcSSc 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 matched pairs and outcomes compared using ANCOVA including baseline values and riociguat dose. As a secondary outcome, the incidence of respiratory adverse events was compared between treatment groups in the incidence of respiratory adverse events. No differences were observed.

Results: Of 121 patients enrolled, 117 (56 riociguat, 61 placebo) were evaluable for the primary analysis of lung function with no differences between treatment groups in the incidence of respiratory adverse events. No differences were observed.

Conclusions: Observations suggest that interstitial lung disease in SSc-ILD may be heterogeneous with different mechanisms driving disease progression.

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