Systemic sclerosis, myositis and related syndromes - aetiology, pathogenesis and animal models

POS0467 DERSIMELAGON, A NOVEL ORAL MELANOCORTIN 1 RECEPTOR AGONIST, DEMONSTRATES DISEASE-MODIFYING EFFECTS IN PRECLINICAL MODELS OF SYSTEMIC SCLEROSIS

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Background: Activation of melanocortin 1 receptor (MC1R) is known to have broad anti-inflammatory and anti-fibrotic effects. The bleomycin (BLM)-induced skin fibrosis murine model is well-established for systemic sclerosis (SSc). α-melanocyte-stimulating hormone, an endogenous ligand of MC1R, inhibits skin fibrosis and MC1R knock-out enhances skin fibrosis in this model. These pieces of evidence suggest that MC1R agonism has potential in the treatment of SSc.
Objectives: Dersimelagon phosphate (MT-7117) is an investigational small molecule that is an orally administered, selective agonist for MC1R. The purpose of this study is to investigate the potential of MT-7117 as a therapeutic agent for SSc by evaluating its efficacy and mechanism of action in complementary preclinical models. The expression and distribution of MC1R in the skin of SSc patients was investigated.
Methods: The effects of MT-7117 on skin fibrosis and lung inflammation were evaluated in BLM-induced SSc murine models that were optimized for prophylactic and therapeutic evaluation. Microarray-based gene expression analysis and serum protein profiling were performed to investigate the mechanism of action of MT-7117 in the BLM-induced SSc models. The effect of MT-7117 on TGF-β-induced activation of human dermal fibroblasts was evaluated *in vitro*. Immunohistochemical analyses of MC1R expression in skin samples from SSc patients were performed.
Results: Prophylactic treatment with MT-7117 (≥0.3 mg/kg/day p.o.) significantly inhibited the increase in collagen content of the skin, the serum level of surfactant protein D, and the weight of the lungs from BLM-induced skin fibrosis and lung inflammation model. Therapeutic treatment with MT-7117 (≥3 mg/kg/day p.o.) significantly suppressed skin thickening and the numbers of myofibroblasts in pre-established BLM-induced skin fibrosis model. Gene array analysis using the BLM-induced SSc model demonstrated changes in numerous categories related to macrophages, monocytes, and neutrophils, followed by endothelial cell-related categories after treatment with MT-7117. In the analysis that focused on biological functions, categories of inflammatory response, activation of antigen-presenting cells, angiogenesis, atherosclerosis, vasculogenesis, and vaso-occlusion were suppressed by MT-7117. In the analysis that focused on molecular signaling pathways, triggering receptor expressed on myeloid cells-1, IL-6, and oncostatin M involved in inflammation, and peroxisome proliferator-activated receptor that is related to fibrosis were all affected by MT-7117. Serum protein profiling using BLM-induced SSc model revealed that multiple SSc-related biomarkers including P-selectin, osteoprotegerin, cystatin C, growth and differentiation factor-15 and S100A9 were suppressed by MT-7117. MT-7117 inhibited the activation of human dermal fibroblasts by suppressing TGF-β-induced *ACTA2* (encoding α-smooth muscle actin) mRNA elevation in vitro. Immunohistochemical analyses showed that MC1R positivity was observed in 40 of 50 diffuse cutaneous SSc patients. MC1R was expressed by monocytes/macrophages, neutrophils, blood vessels (endothelial cells), fibroblasts, and epidermis (keratinocytes) in the skin of SSc patients.
Conclusion: MT-7117 demonstrates disease-modifying effects in preclinical models of SSc. Investigations of its mechanism of action and target expression analyses indicate that MT-7117 exerts its positive effects by affecting the pathologies of inflammation, vascular dysfunction, and fibrosis through inflammatory cells, endothelial cells, and fibroblasts. In view of its potent beneficial impact on all these three main pathologies of SSc, MT-7117 is a potential therapeutic agent for the treatment of clinically challenging SSc, which has diverse and difficult to treat symptoms. A phase 2 clinical trial investigating the efficacy and tolerability of MT-7117 in patients with early, progressive diffuse cutaneous SSc is currently in progress.
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POS0468 EXTRACELLULAR VESICLES FROM SERUM OF MYOSITIS PATIENTS AS CIRCULATING BIOMARKERS AND DISEASE MEDIATORS

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Background: Inflammatory myopathies (IM) are a heterogeneous group of disorders characterized by autoimmune inflammatory destruction of skeletal muscles. It is many times associated with lung, skin and joint involvement. Identifying biomarkers that can differentiate IM from other muscle disorders may elucidate the pathophysiology of IM, guide novel therapies, monitor disease activity/response to treatments and predict prognosis. Exosomes are membrane-bound nanovesicles with diameters of 30-150 nm that contain multiple proteins, nucleic acid, lipids and other molecules in a tissue- and cell-specific manner. Exosomes are secreted by a large variety of cells, play major roles in cell-cell interactions, and have recently emerged as circulating biomarkers in a variety of pathological conditions, including several autoimmune diseases.
Objectives: To characterize exosomes from serum of IM patients, analyze protein expression and study their potential mediators of disease pathologies.
Methods: Serum was collected from patients suffering from IM(n=5) and from patients suffering from Becker (BMD) and Duchenne (DMD) muscular dystrophies (n=6). Exosomes were isolated by Exoquick precipitation and analyzed for size distribution and by nanoparticle tracking analysis (NTA) and by Western blot for exosome markers. The effects of the isolated EVs on human satellite cell proliferation and differentiation and macrophage activation were examined.
Results: Exosomes from IM patients decreased human satellite cell proliferation (51%, P<0.01) and inhibited their myogenic differentiation as indicated by lower fusion index (24% inhibition, P<0.01) and expression of myosin heavy chain (72% inhibition, P<0.001). Similar results were obtained also with exosomes derived from DMD and BMD patients; however, their inhibitory effect were more pronounced on MyoG expression. Treatment of macrophages with exosomes from IM patients significantly increased the expression of IL-10 (3-fold, P<0.001), compared to exosomes of healthy controls and DMD patients. Another significant difference was in the expression of signaling molecules: Thus, exosomes from BMD patients increased the phosphorylation of Erk and p38, whereas a smaller effect was induced by IM exosomes.
Conclusion: Exosomes from IM patients decrease satellite cell proliferation and myogenic differentiation compared to healthy exosomes. In addition, these exosomes increased the expression of IL-10 in macrophages. These effects are unique to exosomes of IM patients compared to muscular dystrophies. These promising results suggest that serum exosomes should be further investigated as a novel biomarker with potential therapeutic implications.
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POS0469 ENDOTHELIAL TO MESENCHYMAL TRANSITION AND SENESCENCE ARE PART OF THE FIBROTIC PATHOGENESIS IN SYSTEMIC SCLEROSIS

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