and SSc pts with interstitial lung disease (ILD) and high systolic pulmonary artery pressure (PAP). A linear negative correlation between the high hybrid M1/M2 cell percentage and diffusing capacity of the lungs for carbon monoxide (DLCO)% and the forced vital capacity (FVC)/DLCO ratio higher than 1.5 was observed. No significant correlations were reported with SSc duration, other treatments, NVC patterns, renal artery resistive index, heart and kidney involvements, digital ulcers, telangiectasias, calcinosis.

Conclusion: The study identified a circulating cell population expressing both M1 and M2 surface markers, which is increased together with circulating M2 cells in SSc pts, in particular affected by ILD and high PAP, suggesting their possible involvement in the pathogenesis of those disease complications. Further evaluations are in progress.

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THU0349 AUTOLOGOUS FAT GRAFTING IN THE TREATMENT OF PATIENTS WITH SYSTEMIC SCLEROSIS: CURRENT EXPERIENCE AND FUTURE PROSPECTS

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Background: Systemic Sclerosis (SSc) is a connective tissue disease, characterized by endothelial dysfunction and fibrosis, potentially affecting internal organs and reducing life expectancy. Digital ulcers (DUs), as well as hand and face skin thickening, are the hallmarks of the disease. These alterations lead to pain, functional impairment, aesthetic damages, and psychological distress. Autologous fat grafting (AFG) is a surgical technique used also to promote tissue regeneration. In the last decade, AFG has been successfully developed to treat clinical conditions characterized by skin atrophy or fibrosis. AFG composition of multipotent cells, carrying angiogenic, and immunogenic properties, may be able to restore the damaged tissues.

Objectives: Evaluate our experience with AFG to treat and prevent damage and disability due to DUs and SSc skin complications.

Methods: We analyzed 25 SSc patients, extrapolated from a larger series of 45 subjects, complaining about mouth and/or hand impairment, due to skin involvement, and, in some cases, long-lasting DUs (M/F 6/19, mean age 55.69±9.25-SD-years, mean disease duration 184.68±121.09-SD-months, L/D cutaneous subsets 21/4). Surgical procedures consisted in the injection of centrifuged and purified autologous fat, harvested from hips or abdomen. 2ml of fat were grafted in each of the 8 sites around the mouth, while 0.5 or 1 ml around the neurovascular bundle at the base of each finger. The study included: preoperative data collection; 2 or 3 surgical sessions at a distance of 6 months one from the other; data collection at 3 months after each surgical session; data collection at 3 and 6 months of follow up-FU after the last surgical procedure. Data collection consisted of clinic-serological SSc features and clinimetric measures about hand and mouth, if present DUs were assessed as well. Furthermore, patients were asked to fill in questionnaires in order to express their level of satisfaction with hand and mouth functionality.

Results: Overall 63 surgical procedures were performed. After 1 to 3 procedures, patients reported an improvement of perioral skin tension ($p=0.0238$) and a reduced dry mouth feeling ($p=0.0269$). Similarly, patients stated an improvement of hands tension ($p=0.0037$). Furthermore, we observed a complete healing of DUs in 8/9 patients ($p=0.0297$). These positive clinical changes were mirrored by a subjective amelioration. In particular, pain decreased, evaluated by short-form McGill Pain Questionnaire (SF-MPQ), scrutinizing sensory ($p=0.3340$) and affective ($p=0.2234$) descriptors. The perception of disability improved too, showing an amelioration trend in Health Assessment Questionnaire-HAQ ($p=0.4301$) and Mouth Handicap in Systemic Sclerosis scale-MHISS ($p=0.9775$).

Conclusion: Our results confirm the potential efficacy of AFG to treat SSc skin complications and DUs. We reported an almost complete

healing of DUs and a promising improvement of skin thickness and hardness both at hands and mouth, with good safety profiles. These clinical results were reflected by the subjective improvement of patients' well-being. Population enlargement and extended FU is ongoing to identify more responsive SSc subsets. Long term results with soft tissue biopsies will give us further data to finally evaluate the efficacy of this approach that aims to improve the care and quality of life of our SSc patients.

Disclosure of Interests: None declared

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THU0350 ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS OF INTRAVENOUS ADIPOSE-DERIVED STEM CELL TRANSPLANTATION IN A MOUSE MODEL OF BLEOMYCIN-INDUCED SCLERODERMA

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Background: Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by microvascular damages and fibrosis. The main lesions of SSc are peripheral circulation insufficiency, scleroderma, and interstitial pneumonia. Skin lesions are related to patient's ADL and QOL, however there is no effective treatment for normalizing the disease state. Adipose-derived stem cells (AdSCs) have recently been considered a useful treatment tool for autoimmune disease because of their anti-inflammatory and immunosuppressive effects (ref).

Objectives: We investigated the therapeutic effect of intravenous mouse AdSCs (mAdSCs) transplantation in a SSc mouse model.

Methods: SSc was induced by bleomycin (BLM) in Balb/c mice, and the mice were assigned in the following groups: 1. Control (BLM-SSc), 2. mAdSCs (1.0×10^4 cells), 3. mAdSCs (1.0×10^5 cells). After the administration of BLM, mAdSCs were injected via a tail vein on day 7. The mice were sacrificed at 14 days after mAdSCs injection, and the skins were harvested for histological analysis.

Results: In mAdSCs (1.0×10^5 cells) group, thickening of skin, hydroxyproline content, infiltration of inflammatory cells, gene expression of inflammatory cytokines, and fibrotic factors were significantly reduced compared with control group (Figure). But in mAdSCs (1.0×10^4 cells) group, there were no reduction of them. mAdSCs did not accumulate in skin. The levels of MMP-2, MMP-9, and COL1A1 mRNA expression at 21 days after BLM administration were significantly lower in mAdSCs (1.0×10^5 cells) group compared with those in control group.

Abstract THU0350 – Figure 1

Conclusion: Intravenous mAdSCs inhibited both skin inflammation and fibrosis of BLM-SSc mice in a dose-dependent manner.

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THU0351 LOW ERA EXPRESSION MIGHT BE IMPLICATED IN THE DEVELOPMENT OF PULMONARY HYPERTENSION IN FEMALE MICE LACKING PSGL-1

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Background: Pulmonary arterial hypertension (PAH) is a rare disease with unknown etiopathogenesis and no curative treatment [1]. PAH is one of the major complications of connective tissue diseases, and 7-15% of patients with systemic sclerosis (SSc) develop PAH [2]. Mice deficient for the leukocytic receptor P-selectin glycoprotein ligand-1 (PSGL-1^{-/-}) spontaneously develop a SSc-like autoimmune syndrome with ageing [3].

Objectives: To check whether PSGL-1^{-/-} mice may develop PAH and the molecular mechanisms that might be implicated in the initiation and establishment of the disease.

Methods: Doppler pulse echocardiography was used to evaluate pulmonary artery flow acceleration time/ejection time (PAAT/ET) ratio in WT and PSGL-1^{-/-} C57BL/6 mice. Isolated pulmonary artery rings were incubated with acetylcholine and responses were registered with a wire myograph coupled to an isometric force transducer. Expression levels of the NO-sensing probe DAR-4M AM by fluorescence microscopy and flow cytometry. Angiotensin II lung concentration was quantified by ELISA. eNOS, p-ENOS, AT1R and AT2R expression was evaluated by western blot. In all cases, data are expressed as the mean±SD.

Results: Aged PSGL-1^{-/-} females showed reduced flow PAAT/ET ratio indicating PAH. Moreover, pulmonary arterial rings from aged PSGL-1^{-/-} females presented ROS-independent reduced vasodilation response to acetylcholine. Importantly, eNOS phosphorylation was impaired and NO production by lung EC was reduced in aged PSGL-1^{-/-} females. Vascular remodeling and reduced expression of AT2R were observed in lungs of PSGL-1^{-/-} females from a younger age. With ageing, the levels of angiotensin II and the percentages of IFN γ -producing interstitial macrophages, T and B lymphocytes were increased in PSGL-1^{-/-} females. The differences in the gender-biased genotype could be explained by the reduced expression of ER α in the lungs of aged PSGL-1^{-/-} females while WT and PSGL-1^{-/-} males showed similar expression.

Conclusion: PSGL-1 deficiency leads to pulmonary hypertension in >18-months-old female mice, involving various mechanisms:

1. Lung vessel wall remodeling and reduced AT2R expression.
2. Reduced eNOS phosphorylation and reduced NO production with the subsequent specific lung endothelial dysfunction in PSGL-1^{-/-} females. Importantly, ROS production is not increased nor help to NO reduction.
3. Increased pulmonary AngII levels with ageing in PSGL-1^{-/-} females.
4. Increased Th1 polarization, reduced Treg population and increased IFN- γ production by interstitial macrophages.

Impaired ageing up-regulation of ER α expression in the lungs of PSGL-1^{-/-} females.

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THU0352 THE ROLE OF PRURITOGENIC MEDIATORS IN DERMATOMYOSITIS RELATED ITCH

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Background: Pruritus is a common symptom in systemic autoimmune diseases like dermatomyositis (DM). Recent researches have indicated that interleukin-31 (IL-31), IL-33, IL-6, or inflammatory cytokines, such as tumor necrosis factor (TNF α), peroxisome proliferator-activated receptor γ (PPAR γ) and ion channels belonging to the transient receptor potential (TRP) family are involved in pruriception.

Objectives: We examined targeted gene expression analysis of lesional versus non-lesional skin samples of patients affected with active DM. We looked for correlations between the examined pruriceptive signaling molecules, disease activity and itching sensation of DM patients.

Methods: Gene expression of TNF α , PPAR γ , IL-33, IL-6 and TRPV channels in lesional DM skin was evaluated by RT-qPCR and was compared with non-lesional DM skin samples. Pruritus and disease activity of DM was evaluated by the 5-d itch scale and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), respectively. Statistical analysis was performed with IBM SPSS 20.0 software.

Results: Skin samples of 17 active DM patients were analyzed. We could show, that itching index in DM was positively correlated with CDASI score with a correlation coefficient of 0.82 ($p < 0.001$). TNF α gene expression was significantly higher (34.87%) in lesional DM skin than non-lesional DM skin ($p = 0.03$). The normalized TNF α mRNA expression was positively correlated with itch scale ($R = 0.605$, $p = 0.022$) and its level was significantly higher in skin samples of patients with severe itch (itching score: 15-20) versus mild itch (itching score: 5-10) (2.02 ± 0.38 vs. 1.12 ± 0.20 ; $p < 0.01$). The level of PPAR γ was decreased in lesional DM skin, but this was statistically not significant. The mRNA expression of normalized PPAR γ was negatively correlated with itch scale ($R = -0.618$, $p = 0.019$), and its level was significantly lower in skin samples of patients with severe itch versus mild itch (0.28 ± 0.36 vs. 1.53 ± 0.98 ; $p = 0.038$). Lesional IL-6 mRNA levels were associated with CDASI activity score ($R = 0.619$, $p = 0.018$). The mRNA levels of TRPV1-4 channels were not associated with 5-D itch score, but normalized TRPV1 and TRPV4 mRNA expressions were positively correlated with CDASI damage score ($R = 0.699$, $p = 0.008$; $R = 0.789$, $p = 0.001$). Interestingly, itching sensation of DM patients was not correlated with IL-33 mRNA levels measured in skin samples.

Conclusion: Our results argue for that higher cutaneous disease activity generate pruritus. TNF α and PPAR γ might play a determining, but opposite role in DM-associated itch. Furthermore IL-6, TRPV1 and TRPV4 channels might participate in pathomechanism of cutaneous manifestation of the disease.

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None declared

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THU0353 AN ORALLY AVAILABLE HIGHLY SELECTIVE 5-HYDROXYTRYPTAMINE 2B (5-HT_{2B}) RECEPTOR ANTAGONIST AMELIORATING PULMONARY AND DERMAL FIBROSIS IN PRECLINICAL MODELS OF SYSTEMIC SCLEROSIS

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Background: Serotonin or 5-hydroxytryptamine (5-HT) is well known as a stimulator of tissue fibrosis and a significant role of peripheral 5-HT_{2B} receptors in fibrosis has been suggested with the receptor being upregulated in fibrotic tissues. In addition, agonism of the 5-HT_{2B} receptor has been implicated in human tissue fibrosis caused by drugs known to activate the receptor. Pharmacologic inhibition of 5-HT_{2B} receptor signalling consequently represents a promising treatment strategy for fibrotic disorders including systemic sclerosis. 5-HT is released from platelets activated upon vascular damage, one of the first pathological events in systemic sclerosis. The local 5-HT concentration is increased and leads to activation of 5-HT_{2B} receptors on e.g. fibroblasts. The pro-fibrotic effects of 5-HT and the 5-HT_{2B} receptor are believed to be mediated through activation of the TGF- β /Smad signaling pathway.

Objectives: The objective of the present study was to evaluate a novel highly selective orally available 5-HT_{2B} receptor antagonist, AM1476, for its ability to reduce pulmonary and dermal fibrosis in the sclerodermatous