AB0211

NEUTROPHIL-DERIVED EXOSOME S100A8/A9 INHIBITS ANGIOGENESIS IN SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy, inflammation, and extensive fibrosis of the skin and organs. Exosomes (EXOs) are cell-derived vesicles 30-150 nm in size that contain various mRNAs, microRNAs and proteins.

Objectives: Here, we aimed to investigate the roles of EXOs in SSc pathogenesis, especially in angiogenesis.

Methods: EXOs were respectively isolated from plasma, cultured peripheral blood mononuclear cells (PBMCs) and neutrophil supernatants, and were identified by transmission electron microscopy. The expression of S100A8/A9 was measured by real-time PCR and ELISA. Proliferation, migration and scratch assays in human dermal microvascular endothelial cells (HDMECs) were used to study the influence of neutrophil EXOs and neutrophil EXOs S100A8/A9. We also performed a genome-wide transcriptome analysis on PBMCs from 19 SSc patients and 18 matched normal controls (NC) using Illumina BeadChip arrays. The ingenuity pathway analysis (IPA) tool and Database for Annotation, Visualization and Integrated Discovery (DAVID) were used for bioinformatics analysis.

Results: Plasma EXOs and neutrophil EXOs from SSc patients suppressed the proliferation and migration of HDMECs. Using a microarray analysis we found 28% genes upregulated in PBMCs could exist in EXOs, especially the S100 protein family, including S100A8/A9. High levels of S100A8/A9 were consistently verified in SSc plasma, PBMCs, plasma EXOs, PBMC EXOs and neutrophil EXOs. Particularly, S100A8/A9 expression in neutrophil EXOs was distinctly higher than that in PBMC EXOs in SSc patients. Furthermore, we found that neutrophil EXOs S100A8/A9 inhibit the proliferation and migration of HDMECs, and that might through Toll-like receptor 4 (TLR4) pathway.

Conclusion: S100A8/A9 is one of components of neutrophil EXOs that regulates vascular endothelial cell angiogenesis in SSc patients, most likely by activating the TLR4 signalling pathway.

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AB0212

LONG-TERM TREATMENT WITH RITUXIMAB IN SYSTEMIC SCLEROSIS MANAGEMENT: AN OVERVIEW OF THE CLINICAL EXPERIENCE FROM A REAL-LIFE SETTING

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Background: The treatment of systemic sclerosis (SSc) is a clinical challenge because of its complex pathogenesis. The rationale for the use of rituximab (RTX), able to downregulate the B-cell over expression, is demonstrated in different autoimmune diseases, some reports have suggested its key role in regulating both vascular, fibrotic, and immune T- and B-lymphocyte-mediated alterations that characterize several SSc manifestations. According to our previous experience with RTX [1], we suggested a possible therapeutic role of RTX in SSc, along with its good safety profile.

Objectives: To investigate the role and efficacy of RTX in our SSc patients' series.

Methods: A series of 24 SSc patients (M/F 7/17, mean age 55.2 ± 14.7SD years, mean disease duration 11.7 ± 7.3SD years, L/D cutaneous subsets 11/13) were treated with one or more cycles of RTX (4 weekly infusions of 375 mg/m²) and evaluated during a mean follow-up period of 12.3 ± 6.6SD years, range 2-26 years. The indications to RTX were interstitial lung disease, cutaneous, articular manifestations, evaluating its effects after 6 months of the first cycle and at the end of follow-up.

Results: After the first 6 months the extent of skin sclerosis measured with modified Rodnan skin score (mRSS) significantly improved (from 16.3 ± 9.8 to 12.3 ± 7.1; p < 0.0001), and remained stable at the end of the

follow-up (11.0 ± 6.9; p = 0.105). The effect on skin sclerosis was more evident in patients with diffuse cutaneous SSc (n = 13) showing a significant decrease of mRSS after the first 6 months (from 24.3 ± 5.4 to 17.9 ± 4.3; p = 0.006) and at the end of the follow-up period (17.8 ± 5.7; p = 0.005). Similarly, a valuable improvement of other skin manifestations, namely hypermelanosis (17/20 pts), pruritus (18/21 pts), digital ulcers (8/18 pts) and calcinosis (6/3 pts), was observed. Moreover, arthritis revealed a good response to RTX treatment leading to a clear-cut reduction of swollen (from 2.0 ± 2.8 to 0.3 ± 1.3; p < 0.0001) and tender joints (from 5.2 ± 4.0 to 0.9 ± 2.5; p < 0.0001) in 20/24 patients. Finally, lung fibrosis detected in 19/24 on chest-CT remained stable during the entire follow-up, as well as pulmonary function tests (PFTs). These positive clinical changes were mirrored by the subjective improvement of patients' well being in all subjects (HAQ from 1.04 ± 0.55 to 0.85 ± 0.38; VAS from 71.0 ± 15.2 to 28.0 ± 10.3, p < 0.0001). No significant side effects were observed during the entire follow-up. Only in one patient a severe urinary tract infection leading to the discontinuation of the treatment was detected.

Conclusion: The present study reinforces the previous trials and our preliminary researches on this topic, showing the efficacy of RTX in the management of SSc with good safety profile. The specific therapeutic role of RTX on B-cell-driven autoimmunity, might explain its beneficial effects on some SSc clinical alterations. The improvement of skin sclerosis, articular symptoms and the stabilization of lung involvement were identified as the main results. Further exploration of the potential clinical efficacy of RTX in SSc with multicentre, double blind, controlled study is needed.

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AB0213

RELATED FACTORS TO RENAL INVOLVEMENT IN SYSTEMIC SCLEROSIS PERUVIAN PATIENTS

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Background: Systemic sclerosis (SSc) can affect multiple organ systems including the kidney. Renal disease, especially chronic kidney disease (CKD), remains an important cause of morbidity and mortality in SSc. The spectrum of renal complications in SSc include scleroderma renal crisis (SRC), normotensive renal crisis, antineutrophil cytoplasmic antibody associated glomerulonephritis, penicillamine-associated renal disease, and reduced renal functional reserves. Furthermore, subclinical renal impairment affects approximately 10-55% of SSc patients and might be associated with other vascular manifestations. However, the available evidence on CKD in patients with SSc residing in low-middle income countries (LMIC) is scarce. Because the health system of LMIC, and especially Peru, could have great differences in access to diagnosis and management of SSc, it is important to identify which clinical factors would be associated with CKD in patients with this autoimmune disease.

Objectives: To identify the associated factors to renal involvement in Peruvian patients with SSc.

Methods: We analyzed the associated factors to renal involvement in SSc patients at Hospital Nacional Edgardo Rebagliati Martins Lima-Peru, a national reference hospital in Peru. Between June 2001 and December 2018, we included ambulatory patients, older than 18-year-old with SSc that met the ACR-EULAR classification criteria. In patients who accepted to get informed consent, a complete clinical assessment and a sociodemographic survey were done. Additional clinical data were collected from their clinical records. Multiple Poisson regression with robust standard errors was used to identify significant and independently associated factor. Two models were estimated: one based on theoretically selected variables and another parsimonious model based on variables that was selected using a manual backward selection procedure with a predetermined alpha of 0.2. Adjusted prevalence ratio (aPR), 95% confidence interval and p-values were reported.

Results: One hundred and five patients with SSc were included in this study, 15.1% had chronic kidney disease. The average age was 57.8