recently diagnosed pSS patients. ILC3 might play a pathogenic role in the development of T and B lymphocyte infiltrates in the early stages of pSS.

REFERENCES

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POSO814

UNTARGETED METABOLOMICS ANALYSIS OF SEBUM: A NON-INVASIVE STRATEGY TO SHOW POTENTIAL TO IDENTIFY NEW BIOMARKERS IN PRIMARY SJÖGREN’S SYNDROME AND SYSTEMIC SCLEROSIS

Keywords: Biomarkers, Sjögren syndrome, -omics

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Background: Saliva and tears are easy accessible fluids for biomarker analyses, but a major drawback is that a substantial proportion of patients with primary Sjögren’s syndrome (pSS) suffers from severe dryness, with limited or no saliva or tear to donate. Thus, novel non-invasive strategies applying state-of-the-art technologies should be welcomed.

Objectives: To evaluate if metabolome analysis of sebum can be used as a non-invasive method to identify skin metabolic signatures in patients with primary Sjögren’s syndrome (pSS) as compared to healthy controls and other systemic autoimmune diseases.

Methods: Untargeted metabolomics of sebum samples collected from sebutapes placed on the forehead for 5 minutes was performed using mass spectrometry. Sebum metabolomes of healthy controls (HCs, n=17) and 32 pSS patients were compared (for this abstract only ions from the negative ionization mode are discussed, for the positive ionization mode similar results were found). Additionally, the metabolomes of two other systemic autoimmune diseases, i.e. systemic sclerosis (SSc, n=21) and systemic lupus erythematosus (SLE, n=8), were compared to pSS and HCs. The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.

Results: Modest significant differences were observed between the sebum metabolome of pSS patients as compared to HCs. Unsupervised dimensionality reduction using UMAP showed no strong differences between metabolic signatures of pSS patients and HCs. However, correlation analyses of metabolic changes and disease activity markers did identify several metabolite ions with a good correlation with disease activity. A total of 335 metabolite ions significantly correlated to the European Sjögren’s Syndrome Disease Activity Index (ESSDAI) score, 13 metabolite ions correlated with sIgG and 41 metabolite ions with lymphocytic focus scores (LFS, all spearman r < 0.50 or >0.50, p<0.05). To understand if pathways in disease activity-associated metabolites may underlie the observed changes we performed pathway enrichment analyses to investigate potential group function of the metabolite ions identified in these comparisons. Two significantly enriched pathways were identified correlating to the ESSDAI score: alpha-aminobutyric acid metabolism and phenylalanine metabolism. More robust significant differences were identified in patients with systemic sclerosis as compared to healthy controls, indicating metabolites significantly enriched for pathways associated with neurotransmission, including metabolite ions with annotations as L-glutamic acid, noradrenaline, dopamine and 3’-AMP. Interestingly, when analyzing differentially expressed metabolite ions of pSS and SSc patients relative to HCs highly significant and strong correlations were observed (R=0.78 for negative ionization mode), indicating that these diseases might have common metabolic dissimilarities.

Conclusion: This pilot study demonstrates that sebum metabolomics might be a novel strategy to identify biomarkers in pSS and other (systemic) autoimmune diseases. Larger follow-up studies using more targeted metabolomics strategies that take into account potential confounding factors and optimize sebum collection should demonstrate the feasibility of this novel non-invasive monitoring method in molecular profiling of disease.

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POSO815

CD40L BLOCKADE WITH DAZODALIBEP (VIB4920/ HZN4920) REDUCES BLOOD BIOMARKERS OF T AND B CELL COSTIMULATION IN SUBJECTS WITH SYSTEMIC SJÖGREN’S SYNDROME

Keywords: Sjögren syndrome, Randomized control trial, Biomarkers

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Background: Dazodalibep (DAZ) is a non-antibody biologic antagonist of CD40L. In several autoimmune diseases, the CD40/CD40L pathway is activated on a variety of cell types, including T cells, B cells, and antigen-presenting cells. DAZ blocks costimulatory signals between T cells and CD40-expressing B cells, disrupting the development of germinal centers, pathogenic B cells, plasma cells, and autoantibodies that are hallmarks of Sjögren’s Syndrome (SS).

Objectives: To evaluate the impact of DAZ on blood biomarkers of T and B cell costimulation in adult SS subjects with moderate-to-high systemic disease activity.

Methods: This was a randomized, double-blind, placebo-controlled, crossover study to evaluate DAZ therapy in adult SS subjects with moderate-to-high systemic disease activity, as defined by a EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) score ≥ 5. Subjects were randomized 1:1 to receive intravenous DAZ 1500 mg or placebo (PBO) Q4W x 3 doses, then Q4W x 4 additional doses (Stage 1). Starting on Day 169, subjects initially randomized to DAZ received PBO Q4W x 5 doses and subjects initially randomized to PBO received DAZ Q4W x 5 doses and were then followed for 12 weeks (Stage 2). B cell subsets downstream of T cell stimulation (Ki67+CD27+, memory CD27 high CD38 high plasmablasts, and CD11c high atypical memory cells) were assessed via FACS throughout the study period. Serum CXCL13 concentrations, a chemokine essential for GC formation produced by activated follicular T cells, and rheumatoid factor (RF) autoantibodies were also measured.

Results: Concomitant with DAZ-related reductions in ESSDAI observed at Stage 1, significant and rapid reductions were observed in Ki67+CD27+ memory B cells, plasmablasts, CD11c+ CD27− memory B cells, CXCL13 and RF antibodies from day 15 onwards in subjects who received DAZ as compared to PBO. In Stage 2, similar reductions were observed in these biomarkers when PBO-treated subjects were transitioned to DAZ treatment. In DAZ-treated subjects who were transitioned to PBO in stage 2, these biomarkers returned to baseline values while sustained reductions were observed in ESSDAI from baseline through the duration of stage 2.

Conclusion: CD40/CD40L blockade with DAZ in patients with SS reduces systemic disease activity by inhibiting T and B cell costimulation, as evidenced by treatment-related reductions in blood biomarkers downstream of these pathways.

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