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POS0867

ALTERATION OF DUODENAL HISTOLOGY IN SYSTEMIC SCLEROSIS PATIENTS AFTER FECAL MICROBIOTA TRANSPLANTATION

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Background: Systemic sclerosis (SSc) is a complex autoimmune, multi-organ disease with gastro-intestinal tract (GIT) involvement significantly contributing to comorbidity. While understanding of mechanisms behind SSc-related GIT disease is incomplete, recent work shows that altered gut microbiota (dysbiosis) is present in many patients and associates with specific GIT symptoms. Intending to improve dysbiosis, we set up the controlled ReSScue pilot trial, where fecal microbiota transplantation (FMT) was conducted by duodenal infusions of Anaerobic Cultivated Human Intestinal Microbiome (ACHIM) or placebo. The results indicated that FMT by ACHIM induced short-term improvement on patient reported GIT symptoms, as evaluated by the validated UCLA GIT score (1). Duodenal biopsies were taken before and after FMT to assess potential effects of ACHIM on small intestinal mucosa.

Objectives: Assessment of duodenal histology and GIT symptoms before and after FMT by ACHIM compared to placebo.

Methods: In this explorative study, we assessed duodenal biopsies collected prior to first FMT (week 0), prior to second FMT (week 2) and at study end (week 16) from ReSScue trial patients who either received ACHIM (n=5) or placebo (n=4). To examine potential effects of FMT on the duodenal mucosa, we performed immunohistochemistry (IHC) staining on paraffin-embedded tissue samples using the following markers: Sirius red (SIR) for collagen fibers and monoclonal antibodies against gp38 (podoplanin, as marker for lymphatic vessels and fibroblasts), CD38 (as preliminary marker for adaptive immune cells) and CD64 (as preliminary marker for innate immune cells). We determined staining per area in the individual tissue slides for each marker using ImageJ Fiji. The mean total UCLA GIT score for the patients were calculated at week 0, 2 and 16, as well as the mean staining per area of the duodenum biopsies at week 0, 2 and 6 for all the markers. Finally, correlations between mean staining per area and mean total UCLA GIT score were assessed for ACHIM and placebo patient groups by Pearson correlation (r).

Results: All nine patients included in the pilot trial were female and had limited cutaneous SSc. Groups receiving ACHIM and placebo had comparable disease duration (1). We found that relative change in staining per area for SIR from week 0 to week 2 differed between the ACHIM group and the placebo group (Figure 1A, left panel). Similar changes were observed for anti-gp38, anti-CD38 and anti-CD64 (left panel in Figures 1B-D). Strong correlations were found between mean total UCLA GIT score and the mean staining per area of the markers SIR (r=0.98), anti-gp38 (r=0.94), anti-CD38 (r=0.85) and CD64 (r=0.93) in the ACHIM group (Figure 1, A-D). In the placebo group, there was no correlation between the UCLA GIT score and anti-gp38 (r=0.22) and anti-CD64 (r=0.21), however, a strong correlation was observed for SIR (r=0.86) and anti-CD38 (r=0.92) staining (Figure 1A-D, right panel).

Conclusion: This explorative data set indicates different effects of FMT by ACHIM and placebo on the duodenal mucosa of SSc patients with GIT affection. Interestingly, we observed correlations between mucosal markers and improved patient reported GIT symptoms in the ACHIM group.

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Figure 1. Relative staining per area in ACHIM and placebo group (left panel) and correlation between total UCLA GIT score and staining ratios at time point 0, 2 and 16 weeks in patients receiving ACHIM and placebo (right panel).

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POS0868

THE FORMULA TO PREDICT TACROLIMUS CONCENTRATION ACCORDING TO GENOTYPING OF CYP3A5 IS USEFUL FOR EFFECTIVE TREATMENT IN INTERSTITIAL LUNG DISEASE WITH DERMATOMYOSITIS

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Background: Tacrolimus (TAC), an immunosuppressant, can be used in second-line maintenance therapy for interstitial lung disease (ILD) in patients with dermatomyositis (DM) [1]. Although some studies reported the clinical efficacy of initial high-trough levels of TAC in combination with GC and IVCY in induction therapy for severe DM-ILD [2], there have been no useful clinical tools for deciding suitable initial dose of TAC. Genotype of polymorphisms in cytochrome P450 (CYP) 3A5 enzyme was reported to play an important role in pharmacokinetics of TAC [3], and we made a formula for deciding initial dose of TAC according to CYP3A5 genotypes in our previous study.

Objectives: In our previous study (retrospective study), we set the target trough according to the severity for nine DM-ILD patients, six of whom were CYP3A5 *3/*3 and investigated the dose of TAC that could attain the trough using their CYP3A5 genotyping. Using these results, we developed a formula for deciding initial daily dose of TAC (target trough*weight / [(151.1, if CYP3A5 *3/*3) or (86.5, if CYP3A5 *1 allele)]).

Methods: We introduced TAC for new six DM-ILD patients who visited our hospital between November 2019 and May 2020 (prospective study). The starting dose of TAC was decided by using the formula. We assessed the association between predicted and observed trough concentration of TAC at first measurement date (from day 2 to day4), using linear regression analysis. We also assessed the days for attaining the target trough concentration between the patients using the formula (prospective group) and six patients with CYP3A5 *3/*3 (retrospective group).

Results: CYP3A5 genotype of all six DM-ILD patients were *3/*3 and underwent the TAC treatment by using the formula. The predicted and observed trough concentration of first measurement date were significantly correlated in the patients ($r = 0.897$, $p = 0.0041$) (Fig.1). Compared with our retrospective study, target trough was more quickly attained in patients of the prospective study (Fig.2).

Conclusion: The formula which we made for attainment target trough concentration based on CYP3A5 genotype was useful for deciding the starting dose of TAC. We also showed that we could attain the target trough concentration at early stage of initial treatment by using the formula.

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Figure 1. Correlation of predicted and observed tacrolimus trough concentration at first measurement in the prospective study

Figure 2. Days to attain the target trough concentration of tacrolimus in the prospective group and the retrospective group

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POS0869

PREDICTIVE VALUE OF ANTI-INTERFERON-INDUCIBLE PROTEIN 16 ANTIBODIES FOR DIGITAL ULCERS OF SYSTEMIC SCLEROSIS

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Background: Interferon-inducible protein 16 (IFI-16) is constitutively expressed in vascular endothelial cells and can inhibit the proliferation of human endothelial cells and the formation of capillary-like structures *in vitro*. Anti-IFI-16 antibodies were reported in 21%-29% of patients with systemic sclerosis (SSc) and were associated with digital vascular events in a few retrospective studies.

Objectives: To evaluate the presence and the clinical implication of anti-IFI-16 antibodies in Chinese SSc cohort, focusing on the associations with vasculopathy indexes, and to investigate the predictive value of anti-IFI-16 antibodies for the development of digital ulcers (DUs) in SSc prospectively.

Methods: Patients with SSc presenting to our center between July 2018 and September 2018 were prospectively enrolled. Serum from 42 SSc patients and 42 age- and sex-matched healthy controls were analyzed for anti-IFI-16 antibodies by enzyme-linked immunosorbent assay (ELISA), and was considered positive if the optical density (OD) value was above the mean OD of controls plus two standard deviations. Tissue immunofluorescence was used to evaluate the expression of IFI16 in skin biopsy samples obtained from SSc patients and normal controls. At baseline, nailfold video-capillaroscopy was performed to assess nailfold capillary density of SSc patients. Power Doppler ultrasound was used to grade finger pulp blood flow (0-no observed flow; 1-decreased flow; 2-normal flow), and to measure ulnar and radial artery blood flow and resistive index (RI). All patients were followed up for 6 months to see whether they experienced new onset or recurrent DUs. The association of anti-IFI-16 antibodies with DUs was analyzed using logistic regression.

Results: Of the 42 SSc patients, 8 (19.0%) were positive for anti-IFI-16 antibodies. Immunofluorescence of skin biopsy samples from SSc patients exhibited enhanced staining of IFI-16 in the dermis, and colocalization with endothelial marker CD31. SSc patients who were positive for anti-IFI-16 antibodies showed higher ulnar artery RI at baseline (0.95 ± 0.09 vs. 0.86 ± 0.09 , $p = 0.015$), while no significant differences were found for other vascular parameters, nor for clinical or demographic profiles. Within 6-month follow-up, 14 (33.3%) patients experienced new-onset or recurrent DUs. Univariate logistic regression revealed the presence of DUs at enrollment ($p = 0.009$), anti-IFI-16 antibody ($p = 0.012$), finger pulp blood flow ($p = 0.027$), and ulnar artery RI ($p = 0.008$) could be the predictors for the development of DUs. Multivariate analysis further identified DUs at enrollment (odds ratio [OR]: 10.85; 95% confidence interval [CI]: 1.61-73.18; $p = 0.014$) and anti-IFI-16 antibody (OR: 15.00; 95% CI: 1.13-199.18; $p = 0.040$) as independent risk factors. Among patients without DUs at enrollment, new-onset ulcers occurred in 80% (4/5) and 4.5% (1/22) of those with and without anti-IFI-16 antibody, respectively ($p = 0.001$).

Conclusion: Anti-IFI-16 antibody is associated with vasculopathy in SSc and could be used as a novel biomarker for indicating the development of DUs.

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Figure 1. Multivariate logistic analysis for new or recurrent digital ulcers.

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POS0870

CLINICAL CHARACTERIZATION OF PORTUGUESE PATIENTS WITH ANTISYNTHEASE SYNDROME

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