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THE POTENTIAL ROLE OF IL13 IN VASCULOPATHY IN SYSTEMIC SCLEROSIS PATIENTS

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Background: Systemic sclerosis (SSc) is a heterogeneous disease characterized by fibrosis, vasculopathy and autoimmunity. Dysfunctions causing disease pathology are characterized by the activation and recruitment of immune cells, as well as the formation of autoantibodies and cytokines. Profibrotic cytokines, such as interleukin-(IL)13, IL4 or IL6 play a crucial role in collagen production and fibrosis development [1]. Preliminary data reveal IL13 as a main driver for obliterative vasculopathy characterized by severe Raynaud phenomenon, acral ulcers and pulmonary arterial hypertension (PAH). Particularly acral ulcerations lead to a severe impairment in functional capacity in everyday life. In addition, pulmonary arterial hypertension is one of the main causes of the high mortality rate in SSc [2].

Objectives: To prove the impact of IL13 in the pathogenesis of systemic sclerosis and thus provide the rationale for the identification of a potential new therapeutic target, we investigated IL13 expression in CD4 and CD8 T cells in patients suffering from systemic sclerosis compared to healthy controls.

Methods: Peripheral blood mononuclear cells (PBMC) obtained from systemic sclerosis (SSc, n=31) patients and healthy controls (HC, n=13) were cultured without or in the presence of phorbol myristate acetate and ionomycin to activate T cells for cytokine production. Brefeldin A was used as an inhibitor of cytokine secretion. The intracellular IL13 and IL4 expression of CD4 and CD8 positive T cells were measured by flow cytometry and were compared between the investigated subgroups.

To identify a disease phenotype mediated by IL13, the expression levels in the SSc group were correlated to clinical, laboratory and apparatus parameters assessing organ dysfunction.

Results: While there were no significant differences in IL4 expression between healthy and diseased individuals, analyses of IL13 positive CD4 and CD8 T cells showed significant differences compared to HC (CD8+IL13 p=0.048; CD4+IL13 p=0.0046) revealing the functional differences though high structural homology of the two interleukins. The increased expression of IL13 in T cells from patients with systemic sclerosis further supports the assumption of an interleukin mediated pathomechanism. Considering the IL13-mediated clinical phenotype, high levels were detected in patients showing signs for vasculopathy, correlation with sPAP (CD8+IL13 p=0.0392), NTproBNP (CD4+IL13 p=0.0461), creatinine (CD4+IL13 p=0.0227), angiotensin II receptor type I and endothelin receptor type A antibodies (CD4+IL13 p=0.0105, p=0.0042) was demonstrated. In addition, patients in the fourth quartile of CD4+IL13 expression showed a higher incidence of acral ulcers and pits than patients with low interleukin levels. Moreover, this group of patients had an increased cardiovascular comorbidity including atherosclerosis, coronary heart disease and arterial hypertension.

Conclusion: Increased IL13 levels could be detected in patients with SSc, especially in patients with the phenotype of an obliterative vasculopathy. This indicates preliminary evidence for the use of IL13 blockers as a new therapeutic approach in systemic sclerosis.

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Vasculitis - Large vessel vasculitis

POS0336

PATTERNS OF LARGE-VESSEL LESIONS AND POOR TREATMENT OUTCOMES IN PATIENTS WITH LARGE-VESSEL GIANT CELL ARTERITIS

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Background: Giant cell arteritis (GCA) is characterized by cranial symptoms and large-vessel lesions (LVL) in the aorta or its branches. We retrospectively analyzed the Japanese patients newly diagnosed as GCA between 2007 and 2014, and subsequently treated with glucocorticoid (GC). The imaging studies revealed that LVLs were observed in approximately half of the GCA patients, and the LVLs were significantly associated with the increased probability of poor treatment outcomes (1).

Objectives: The objective of this study is to evaluate whether the distribution of LVLs of GCA was associated with poor treatment response.

Methods: In a retrospective, multi-centric, nationwide registry of GCA patients treated with GCs between 2007 and 2014, 68 newly-diagnosed GCA with LVLs by imaging were detected. All investigators were members of Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis (JPVAS). Poor treatment outcomes (non-achievement of clinical remission by week 24 or relapse during 104 weeks) were primarily evaluated. Cumulative rates and median time to the first event were analyzed by the Kaplan-Meier method and the log-rank test. Associated factors with the outcomes were analyzed by using the Cox proportional hazard model.

Results: The mean age was 70.5 years, and 70.6% were women. Twenty-seven (39.7%) of the 68 patients were diagnosed as having GCA by both positive temporal artery biopsy and positive imaging, and 41 (60.3%) by positive imaging. Aortic lesions were detected in 72.1% (group 2, n=49) of the 68 GCA patients with LVLs. Patients without aortic lesions were categorized into two phenotypes: large-vessel GCA with subclavian lesions (group 1, n=9) and atypical large-vessel GCA without subclavian lesions (group 3, n=10). Cranial lesions were observed in 66.7%, 55.1%, and 80.0% in the group 1, 2, and 3, respectively. The initial mean dose (SD) of prednisolone was 0.74 (0.26) mg/kg/day, and 20.6 % received methotrexate for remission induction therapy. Baseline dose of GCs and mean time to achievement of low-dose GCs (prednisolone ≤ 5 mg/day) was not significantly different among the three groups.

Overall, 35 (51.5%) of the 68 patients had the event of poor treatment outcomes. Eleven patients were not able to achieve clinical remission by week 24. Relapse after achievement of clinical remission was reported in total of 24 patients; 9 between week 0 and 24, 12 between week 24 and 52, 3 between week 52 and 104. The cumulative rate of events of poor treatment outcomes over the two years was 11.1% in patients with group 1, 55.3% in those with group 2, and 88.0% in those with group 3. Mean time to events was significantly different among the three groups. Multivariable analysis showed the risk of poor treatment outcomes was likely to decrease in the group 1 (hazard ratio 0.14 [95% CI 0.02-1.03], p=0.054), while it increased in the group 3 (hazard ratio 2.22 [95% CI 1.06-4.68], p=0.035).

Conclusion: The distribution of LVLs were associated with poorer treatment outcomes. A half of the patients with aortic lesions had poor treatment outcomes while subclavian arteritis without aortic lesions had better clinical outcomes. Atypical large vessel-GCA without the aortic and subclavian artery involvement