IMPACT OF JAK INHIBITORS ON MACROPHAGE POLARISATION: PERSPECTIVES FOR SYSTEMIC SCLEROSIS

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Background: Macrophage can adopt various phenotypes and activation states according to their surrounding microenvironment. M1 or inflammatory macrophages are generated under IFNγ/LPS signaling and express the states according to their surrounding microenvironment. M1 or inflammatory macrophages (generated under IL-1β/IL-13 signaling) and characterized by a high expression of CD206 and pro-fibrotic properties and, M2c macrophages (generated under IL10 and/or glucorticoid signaling), considered as anti-inflammatory resolving macrophages. There is growing interest in the role of macrophages in the pathogenesis of Systemic Sclerosis (SSc).

Recent studies highlight that macrophages from fibrotic tissues such as lung or skin from SSc patients have a M2 phenotype whereas, in blood-monocytes derived macrophages (MDM), SSc MDM have a mixed signature associating M1 and M2 characteristics. Jak inhibitors are treatments used in rheumatoid arthritis and that can variously target signals that could be involved both in M1 and in M2 polarisation.

Methods: Blood monocytes form healthy donors (HD) were differentiated with M-CSF (for 7 days) in MDM and pre-treated by ruxolitinib (Jak2-Jak1 inhibitor) or tofacitinib (Jak3 inhibitor), or itacitinib (Jak1 inhibitor) (1µM for all). They were then polarised into M1 (IFNγ, 20µg/mL), M1i (IFNγ+LPS, 20µg/mL), M2a (IL-4+IL13, 20µg/mL), M2c (IL-10, 20µg/mL) and M2c(dex) (IL10+dexamethasone, 10µM). The impact of each Jak inhibitor on phenotype (flow cytometry), gene expression (qPCR) and cytokine secretion (ELISA) was evaluated in each polarisation state.

Results: Concerning phenotypes, all Jak inhibitors reduced the expression of the M1 and M1i marker CD86, but ruxolitinib had a higher effect. Only ruxolitinib reduced the expression of the M1 marker MHCII. All Jak inhibitors reduced the expression of CD206 in M2a. They had no impact on the expression of CD163, CD204 in any M2 conditions. Key M1 genes were repressed by all Jak inhibitors, such as CXCL10, IL6 or TNFα with a more significant effect of ruxolitinib. All Jak inhibitors reduced the gene expression of CXCL13 and SOCS3 in M2c. Secretion levels of IL6 and CCL18 were also repressed, with a more significant effect of ruxolitinib.

Conclusion: Jak inhibitors can limit M1 and M2 polarisation state in vitro, with a more significant effect of the Jak2-Jak1 inhibitor ruxolitinib. The relevance of these results in MDM from SSc patients and in vivo models of SSc is still to be determined.

CARDIAC AUTONOMIC NEUROPATHY PREVALENCE IN A COHORT OF SYSTEMIC SCLEROSIS (SSc) PATIENTS

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Background: Systemic sclerosis is a rare disease determining a damage to the connective tissue and, consequently, an involvement of several organs. Besides the damage of the connective tissue, preminent is also the small vessels injury, detectable by videocapillaroscopy. Some authors report that the vascular damage may be also responsible of a cardiovascular impairment as cardiac autonomic disease (CAN) and heart rate variability [1].

Methods: This is a pilot prospective cohort study. We enrolled 28 patients in a period of six months, from May 2019 to November 2019, afferent to the study. Inclusion criteria were: diagnosis of SSc, median age of 58.5 years [IQR: 49-64.8 yrs.] and a median duration of the disease of 4 years [IQR 2-13 yrs.]. The observed prevalence of NAC was equal to the 46.4% (13 cases). In addition, we evaluated the potential association of NAC with age, duration of disease, gastrointestinal dysmotility, sicca syndrome, cutaneous involvement and type of videocapillaroscopy pattern, from which no statistically significant result emerged. Hence, a further analysis, by using a time-dependent Cox regression model (with the duration of disease as time covariate), was performed on the same variables. From this model a