In vivo SPECT imaging of liver inflammation in a murine model of nonalcoholic steatohepatitis.

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Résumé

Introduction. We recently developed 99mTc-cAbVCAM1-5, a single domain antibody (sdAb) derived radiotracer directed against the inflammatory marker Vascular Cell Adhesion Molecule 1 (VCAM-1). This imaging agent has been fully validated for the non-invasive imaging of murine atherosclerotic lesions (1-2), and is currently under clinical translation for this application. However, VCAM-1 is considered as a potent inflammatory marker not only in the field of atherosclerosis, but in several other clinically relevant pathophysiological settings such as chronic liver inflammation. Thereby, 99mTc-cAbVCAM1-5 imaging was here evaluated in a nutritional mouse model of nonalcoholic steatohepatitis (NASH).
Methods. Thirty 12-wks old male C57Bl/6J mice were used (n=10/group). Mice were either fed a standard diet (STD) or methionine and choline deficient diet (MCD) to induce NASH. Longitudinal SPECT imaging was performed at baseline and at 4 wks and 8 wks following diet onset using either the anti VCAM-1 (V) or an irrelevant control sdab (C). Results were expressed as standardized uptake values (SUV). Following the 8 wks time point mice were euthanized and post mortem analysis were performed.

Results. MCD diet induced a 10-fold increase in serum alanine transaminase (ALT) levels both at 4 and 8 wks in comparison to STD diet ($p< 0.001$). Moreover Oil Red O staining showed large lipid vacuoles in the liver of MCD fed mice. Finally, as demonstrated by ELISA, a significant 5-fold increase in the level of hepatic VCAM-1 expression was observed in MCD in comparison to STD fed group (MCD: 5.6±1.7 vs STD: 1.1±0.5 ng/mg, $P< 0.001$).

Robust 99mTc-cAbVCAM1-5 uptake in the liver of MCD fed mice (V-MCD) was readily observable by SPECT at 4 wks and remained unchanged at 8 wks. In comparison, modest liver uptake was found in control group fed a standard diet (V-STD) and in control group injected with the irrelevant control sdab (C-MCD) at all investigated time points. Image quantification further confirmed these results. Indeed 99mTc-cAbVCAM1-5 hepatic uptake significantly increased in MCD fed mice between baseline and 4 wks, and then remained unchanged at 8 wks (SUV = 0.25±0.04; 0.48±0.11 and 0.45±0.10 respectively, $p< 0.001$ vs baseline at 4 and 8 wks), whereas no significant change was found in control groups. Moreover, SPECT imaging quantification performed at 8 wks significantly correlated with ex vivo

*Intervenant

biodistribution and with the level of VCAM-1 expression ($p < 0.001$ for both).

Conclusions. The present data demonstrate that MCD diet increases VCAM-1 hepatic levels in mice. Robust and specific uptake of 99mTc-cAbVCAM1-5 was visible as early as 4 wks following MCD diet onset. 99mTc-cAbVCAM1-5 can therefore be employed for the non-invasive longitudinal imaging of NASH in mice, and further studies are ongoing in order to evaluate the sensitivity of this technique for the monitoring of NASH therapy.

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