Targeting mannose receptor expression on macrophages in atherosclerotic plaques of apolipoprotein E-knockout mice using \((111)\text{In-tilmanocept.}\)

Abstract:

Atherosclerotic plaque phenotypes are classified based on the extent of macrophage infiltration into the lesions, and the presence of certain macrophage subsets might be a sign for plaque vulnerability. The mannose receptor (MR) is over-expressed in activated macrophages. Tilmanocept is a tracer that targets MR and is approved in Europe and the USA for the detection of sentinel lymph nodes. In this study, our aim was to evaluate the potential of \((111)\text{In-labelled tilmanocept for the detection of MR-positive macrophages in atherosclerotic plaques of apolipoprotein E-knockout (ApoE-KO) mouse model.}

Tilmanocept was labelled with \((111)\text{In. The labelling stability and biodistribution of the tracer was first evaluated in control mice (n = 10) 1 h post injection (p.i.). For in vivo imaging studies, (111)In-tilmanocept was injected into ApoE-KO (n = 8) and control (n = 8) mice intravenously (i.v.). The mice were scanned 90 min p.i. using a dedicated animal SPECT/CT. For testing the specificity of (111)In-tilmanocept uptake in plaques, a group of ApoE-KO mice was
co-injected with excess amount of non-labelled tilmanocept. For ex vivo imaging studies, the whole aortas (n = 9 from ApoE-KO and n = 4 from control mice) were harvested free from adventitial tissue for Sudan IV staining and autoradiography. Cryosections were prepared for immunohistochemistry (IHC). [111]In radiolabelling of tilmanocept provided a yield of greater than 99%. After i.v. injection, [111]In-tilmanocept accumulated in vivo in MR-expressing organs (i.e. liver and spleen) and showed only low residual blood signal 1 h p.i. MR-binding specificity in receptor-positive organs was demonstrated by a 1.5- to 3-fold reduced uptake of [111]In-tilmanocept after co-injection of a blocking dose of non-labelled tilmanocept. Focal signal was detected in atherosclerotic plaques of ApoE-KO mice, whereas no signal was detected in the aortas of control mice. [111]In-tilmanocept uptake was detected in atherosclerotic plaques on autoradiography correlating well with Sudan IV-positive areas and associating with subendothelial accumulations of MR-positive macrophages as demonstrated by IHC. After i.v. injection, [111]In-tilmanocept accumulated in MR-expressing organs and was associated with only low residual blood signal. In addition, [111]In-tilmanocept uptake was detected in atherosclerotic plaques of mice containing MR-expressing macrophages suggesting that tilmanocept represents a promising tracer for the non-invasive detection of macrophages in atherosclerotic plaques.