[Sn-117m]-DOTA-annexin V treatment of carotid and coronary plaque in apo-e mice

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Abstract:

OBJECTIVES: A novel systemic therapy using a mouse model of inflammatory coronary and carotid plaque using a targeted Sn-117m compound.

METHODS: Sn-117m was coupled to aminobenzyl-DOTA and purified using HPLC. Conjugation of the chelate to annexin V-128 [Sn-117m]-DOTA-annexin V was accomplished by preparing the isothiocyanate version of the chelate and then reacting it with lysine residues on the annexin for 90 mins at 37°C. Nine week old apo-E -/- mice were were fed normal chow during a 3 week acclimation period. At 12 weeks of age, the animals were started on a Harlan Western Rodent Diet TD.88137 for another 6 weeks. At 18 weeks of age, [Sn-117m]-DOTA-annexin V or saline were injected into 4 groups of mice - Group 1 (control using saline), Group 2 (low dose: 1.0 µCi), Group 3 (middle dose: 1.7 µCi) and Group 4 (high dose: 3.4 µCi) with 9 to 12 mice per group. All animals were sacrificed 8+1 weeks after injection. The cardiovascular tree, including the heart, aortic arch and carotid arteries were removed and preserved in 3% neutral buffered formalin (NBF) or equivalent. The liver and one kidney were also harvested and preserved in 3% NBF or equivalent for examination of potential toxicity. All tissue was sent to an independent laboratory for thin sectioning and staining with Movat, H&E, MAC-3, a-SMA and apoptosis. The brachiocephalic (carotid) vessels were sectioned beginning at the most proximal end nearest the aortic arch for H&E, modified Movat Pentachrome, and immunohistochemistry for macrophages and smooth muscle cells. The heart was sectioned serially (10 µm intervals) for H&E and modified Movat Pentachrome, and representative sections with the greatest plaque area within the brachiocephalic arteries and at sinotubular (coronary) junction were selected respectively from each animal for immunohistochemistry for macrophages and smooth muscle cells. Lesions were classified on histologic sections of brachiocephalic and sinotubular arteries of the heart and immunohistochemistry was performed for macrophages, and smooth muscle cells. Additionally collagen qualitative and quantitative assessment was also performed based on the polarized light microscopic images. Apoptosis staining for apoptotic nuclei were identified in select lesions by in situ end labeling (ISEL) DNA fragmentation staining.

RESULTS: ApoE mouse vascular histopathology treated with [Sn-117m]-DOTA-annexin V revealed macrophage apoptosis leading to increased fibroatheromatous smooth muscle, increase collagen and reduced apoptotic bodies.

CONCLUSION: [Sn-117m]-DOTA-annexin V treated ApoE mice resulted in plaque stabilization and has the potential to be used as a therapy for stabilizing coronary and carotid plaque.