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CORRESPONDENCE

Research Correspondence

Peptide Receptor–Targeted Radionuclide Therapy Alters Inflammation in Atherosclerotic Plaques

To the Editor: In recent years, various techniques to identify high-risk atherosclerotic plaques have been introduced (1). But development of therapies targeted at plaque vulnerability is lagging behind. The theranostic approach, in which the same molecule is used for diagnosis and subsequent therapy, is increasingly being used in oncology. In neuroendocrine tumors, e.g., expression of somatostatin receptor subtype-2 (SSTR-2) is visualized by ^{68}Gallium-[1,4,7,10-tetraazacyclododecane-N,N′,N,N′-tetraacetic acid]-D-Phe^{1},Tyr^{3}-octreotate (^{68}Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT), and often followed by peptide receptor radionuclide therapy (PRRT) with DOTATATE bound to the beta-emitter ^{177}Lutetium (2). SSTR-2 is also overexpressed on activated macrophages (3). ^{68}Ga-DOTATATE uptake has been reported in coronaries (4) and large arteries (5), where it correlates with established risk markers. We speculated that SSTR-2 may provide a theranostic opportunity to characterize and modulate atherosclerotic plaque biology, and we sought to collect initial evidence from a retrospective analysis of oncology patients.

Of 165 consecutive patients undergoing PRRT, we identified 11 patients (9 male subjects, 2 female subjects; mean age 60 ± 13 years) who had 3 successive ^{68}Ga-DOTATATE PET/CT scans and received their first PRRT according to standard protocol (2) after disease progression was confirmed by the second scan. The median number of days between scans 1 and 2 was 347 (range 99 to 945); between scan 2 and PRRT, it was 28 (range 14 to 89); and between PRRT and scan 3, it was 105 (range 76 to 131). Exclusion criteria included medical history of vasculitis, rheumatoid disease, cardiovascular events within 5 years before scan 1, or systemic chemotherapy from 4 weeks before scan 1 until end of imaging. Four patients took vasoactive medication (statins, n = 1; antihypertensive agents, n = 3), the dosages of which remained stable. Standard whole-body images were acquired 30 ± 10 min after intravenous injection of 73 ± 13 MBq ^{68}Ga-DOTATATE, using a Biograph Duo PET/CT (Siemens Medical Solutions, Erlangen, Germany). The mean effective dose per PET scan was 1.88 mSv (6). Mean therapeutic activity of ^{177}Lu-DOTATATE was 7.5 ± 0.3 GBq. Scans 1 and 2 were used to estimate whether vessel wall uptake was stable over time. Scan 3 was used to identify PRRT-related changes. Focal vessel wall DOTATATE uptake was measured in 6 arterial segments (carotids; aortic arch; ascending, descending, and abdominal aorta; iliac arteries). Target-to-background ratio was determined by dividing the maximal standardized uptake value of a vessel focus by the mean standardized uptake value of 5 regions of interest in the superior vena cava, which represented the mean blood pool uptake. Overall vessel uptake was determined as the sum of target-to-background-ratios in all vascular segments of each scan. CT was used to detect calcified plaque, with a cutoff of 130 Hounsfield units. Continuous variables, expressed as mean ± SD, were compared by using analysis of variance and post-hoc Bonferroni-corrected *t* tests. The relationship between variables was determined by using Pearson's correlation coefficient. The Mann-Whitney *U* test was used to compare subgroups with and without hypercholesterolemia or calcification. A p value <0.05 was considered significant.

Focal ^{68}Ga-DOTATATE vessel wall uptake was detectable in all patients (Fig. 1A). At baseline, overall vessel uptake correlated significantly with cardiovascular risk factors (patient age, $r = 0.76$, $p < 0.01$ [Fig. 1B]; number of calcified plaques, $r = 0.84$, $p < 0.001$). In the presence of hypercholesterolemia, overall vessel uptake was significantly higher (71.6 ± 3.9 with vs. 35.0 ± 18.3 without; $p = 0.04$). No significant difference in overall vessel uptake was found between scans 1 and 2 (42 ± 23 vs. 41 ± 26; $p = 0.8$). After PRRT, however, a significant reduction was observed in scan 3 (30 ± 19; $p = 0.003$ and $p = 0.012$ vs. scans 1 and 2) (Figs. 1C and 1D). Of note, the number of calcified plaques remained stable over time. When analyzed on a lesion-by-lesion basis, PRRT-related reduction of DOTATATE uptake was more pronounced in noncalcified versus calcified active plaque (9.6 ± 7.1 vs. 2.1 ± 3.2; $p = 0.047$). Analysis on a segment-by-segment basis found that changes in the 6 different vascular beds mostly paralleled the overall vessel uptake change.

In summary, our results show the feasibility of ^{68}Ga-DOTATATE PET/CT for characterizing biological activity of atherosclerotic plaque via SSTR-2 expression. Vessel wall lesions were observed reproducibly without treatment over a longer period of time that was driven by clinical criteria in this retrospective analysis. Although histopathologic proof of plaque vulnerability and data on short-term reproducibility are still missing and should be the subject of subsequent work, our initial observations in oncology patients suggest that DOTATATE-based, SSTR-2–targeted PRRT results in a reduction in atherosclerotic plaque activity. Other limitations of this work, such as retrospective design, small sample size, and concomitant oncologic disease, need to be considered. Nevertheless, our results may serve as a stimulus for further prospective exploration of radionuclide-based antiatherosclerotic molecular interventions. Ultimately, such therapies (which may also be catheter-based and targeted to specific vascular regions) might be used to lower the degree of inflammation in high-risk atherosclerosis.

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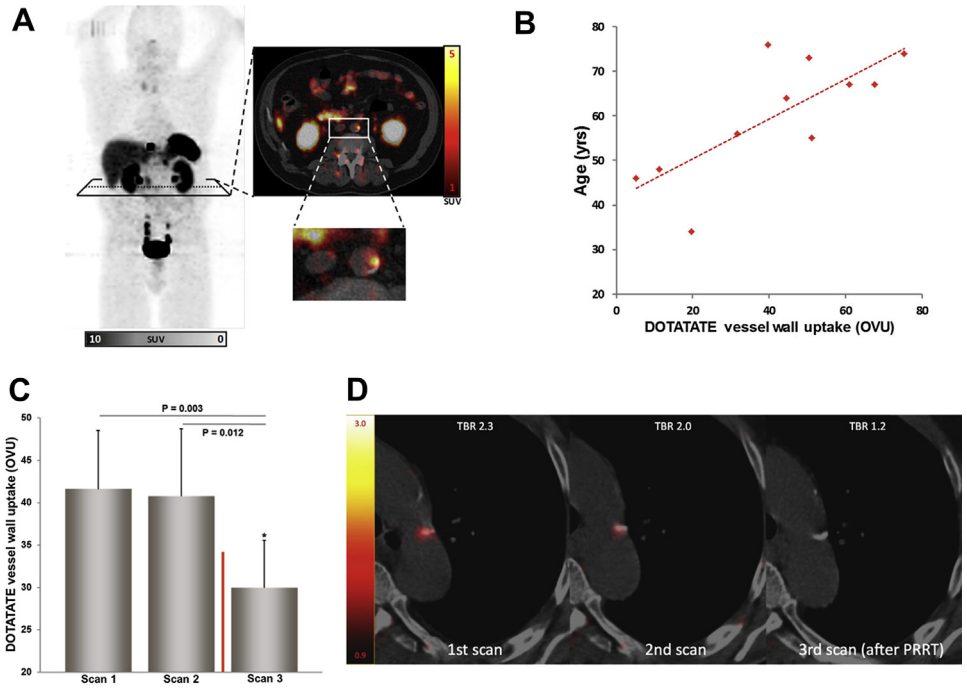

Figure 1 Somatostatin Receptor Subtype-2–based PET/CT Imaging of Atherosclerosis

(A) Whole-body imaging by ^{68}Gallium-[1,4,7,10-tetraazacyclododecane-N,N′,N,N′-tetraacetic acid]-D-Phe^{1},Tyr^{3}-octreotate (^{68}Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT) of a patient with metastatic neuroendocrine tumor. Maximum intensity projection **(left)** shows DOTATATE biodistribution. Transaxial fused PET/CT scan **(right**; full image and magnification) at the location of the lower kidneys shows plaque, with focal uptake in the abdominal aorta, partially calcified on the CT scan. **(B)** Regression plot for DOTATATE overall vessel uptake (OVU) index and patient age at the time of scan 1. **(C)** Group results of OVU at the time of 3 scans **(red bar** indicates timing of peptide receptor radionuclide therapy [PRRT]). **(D)** Representative example of a calcified and initially DOTATATE-avid aortic arch plaque showing stable target-to-background ratio (TBR) between scans 1 and 2. It declined after PRRT.

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Letters to the Editor

Diagnosis of "Paradoxical" Low-Gradient Aortic Stenosis Patients

The report by Lauten et al. (1) investigates a very important clinical presentation—"paradoxical" low-gradient aortic stenosis (PLG AS). This is a diagnostic challenge, and their work definitely improves our understanding of this problem. However, we found multiple inconsistencies and unclear explanations that we wish to highlight.

First, the authors compared echocardiographic and catheterization data in PLG AS to evaluate errors and bias of echocardiography measurements. Unfortunately, this inherently assumes that catheterization measurements represent a veritable "gold-standard" measurement. Cardiac catheterization has inherent errors and uncertainties, including uncertainty in measuring stroke volume, errors in pressure measurements, and assumption of identical hemodynamic conditions between catheterization and echocardiography. A bench-top in vitro study might provide