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BRIEF REPORT

Application of a Novel CD206+ Macrophage-Specific Arterial Imaging Strategy in HIV-Infected Individuals

Markella V. Zanni,[1,a] Mabel Toribio,[1,a] Moses Q. Wilks,[3,b] Michael T. Lu,[2,b] Tricia H. Burdo,[4,d] Joshua Walker,[4] Patrick Autissier,[4] Borek Foldyna,[2] Lauren Stone,[1] Amanda Martin,[1] Fred Cope,[5] Bonnie Abbruzzese,[5] Thomas Brady,[3] Udo Hoffmann,[2] Kenneth C. Williams,[4] Georges El-Fakhri,[3,c] and Steven K. Grinspoon[1,c]

[1]Program in Nutritional Metabolism and [2]Cardiac MR PET CT Program, and [3]Gordon Center for Medical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston; [4]Biology Department, Boston College, Chestnut Hill, Massachusetts; and [5]Navidea Biopharmaceuticals, Dublin, Ohio

Background. The ability to noninvasively assess arterial CD206+ macrophages may lead to improved understanding of human immunodeficiency virus (HIV)–associated cardiovascular disease.

Methods. We trialed a novel macrophage-specific arterial imaging technique.

Results. We demonstrated colocalization between technetium Tc 99m tilmanocept (^{99m}Tc-tilmanocept) and CD206+ macrophages ex vivo. In vivo application of ^{99m}Tc-tilmanocept single-photon emission computed tomography/computed tomography revealed high-level ^{99m}Tc-tilmanocept uptake across 20.4% of the aortic surface volume among HIV-infected subjects, compared with 4.3% among non–HIV-infected subjects (P = .009). Among all subjects, aortic high-level ^{99m}Tc-tilmanocept uptake was related to noncalcified aortic plaque volume (r = 0.87; P = .003) on computed tomographic angiography, and this relationship held when we controlled for HIV status.

Conclusion. These first-in-human data introduce a novel macrophage-specific arterial imaging technique in HIV.

Clinical Trials Registration. NCT02542371

Keywords. HIV-associated cardiovascular disease; arterial inflammation; atherosclerosis.

Individuals with human immunodeficiency virus (HIV) infection have an increased risk of myocardial infarction [1, 2], thought to be fueled in part by heightened systemic immune activation [3] and downstream arterial inflammation [4, 5]. Development of targeted immunomodulatory strategies to reduce myocardial infarction risk in HIV requires improved understanding of the relationship between systemic immune activation, arterial inflammation, and atherogenesis/plaque remodeling. We previously assessed aortic fluorodeoxyglucose labeled with fluorine 18 (^{18}F-FDG) uptake seen with positron emission tomography (PET)/computed tomography (CT) as a proxy for arterial inflammation, showing increased uptake in HIV-infected individuals compared with matched controls [6]. However, the ^{18}F-FDG PET/CT technique has limitations: although arterial ^{18}F-FDG uptake on PET/CT tends to track with the number of arterial macrophages [7], it reflects the presence of metabolically active cells and not macrophages per se. More specifically, noninvasive molecular techniques are needed to functionally image arterial inflammation in HIV infection.

We tested the degree of colocalization between the radiopharmaceutical technetium Tc 99m tilmanocept (^{99m}Tc-tilmanocept) and CD206+ macrophages in tissue-banked aortic samples of individuals with or without HIV infection. Next, we performed a first-in-human assessment of whether systemic ^{99m}Tc-tilmanocept administration could facilitate noninvasive quantification of aortic ^{99m}Tc-tilmanocept uptake with single-photon emission computed tomography (SPECT)/CT. ^{99m}Tc-tilmanocept (^{99m}Tc-diethylenetriaminepentaacetic acid–mannosyldextran) was synthesized to avidly and specifically bind the macrophage mannose receptor, CD206 [8, 9]. This radiopharmaceutical consists of a dextran backbone supporting amine-terminated molecular leashes, which link with mannose moieties (permitting CD206 binding) and moieties of diethylenetriaminepentaacetic acid (permitting labeling with ^{99m}Tc) [8, 9] (Supplemental Figure 1). Injected peritumorally or intradermally, ^{99m}Tc-tilmanocept has proved useful for preoperative detection of tumor-affected lymph nodes in patients with head and neck cancer [10], breast cancer [11], and melanoma [11]. We hypothesized that subcutaneous administration of ^{99m}Tc-tilmanocept would permit SPECT/CT-based quantification of its aortic uptake.

METHODS

Ex Vivo Experiments on Tissue-Banked Aortic Samples From Individuals With or Without HIV

Aortic samples from individuals with (n = 10) or without (n = 10) HIV infection were obtained from the National NeuroAIDS Tissue Consortium and National Disease Research Institute. The density of aortic CD206 macrophage infiltration was compared, and the degree of colocalization of tilmanocept-positive and CD206+ macrophages assessed (Supplemental Methods).

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[a]M. V. Z. and M. T. contributed equally to this work.

[b]M. Q. W. and M. T. L. contributed equally to this work.

[c]G. E. F. and S. K. G. contributed equally to this work.

[d]Present affiliation: Department of Neuroscience, Temple University School of Medicine, Philadelphia, Pennsylvania.

Correspondence: S. K. Grinspoon, MD, Program in Nutritional Metabolism, Massachusetts General Hospital, Boston, MA 02114 (sgrinspoon@mgh.harvard.edu).

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Human Subjects Study

Study Design

Six HIV-infected subjects were recruited and enrolled. Major entry criteria included age ≥18 years, documented HIV infection, current use of antiretroviral therapy without regimen changes within the last 3 months, and subclinical atherosclerosis at CT angiography. Major exclusion criteria included known current or prior clinical cardiovascular disease, current treatment with prescription systemic steroids or anti-inflammatory/immunosuppressant medical therapies, any recent statin therapy, and estimated glomerular filtration rate <60 mL/min/1.73 m^2. Subsequently, for comparison, non–HIV-infected subjects without known current or prior clinical cardiovascular disease were recruited. Seven non–HIV-infected subjects were screened to enroll 3 with cardiovascular risk profiles (sex, age, and Framingham risk score) similar to those in the HIV-infected group. These subjects did not have prior CT angiographic data available, but all 3 demonstrated subclinical atherosclerosis at the CT angiography performed as part of the study. Subjects underwent ^{99m}Tc-tilmanocept SPECT/CT, CT angiography, and detailed immune/metabolic phenotyping. The study, approved by Partners HealthCare Institutional Review Board and registered at clinical trials.gov (NCT02542371), began in August 2015 and was completed in July 2016. All subjects provided written informed consent.

^{99m}Tc-Tilmanocept SPECT/CT

^{99m}Tc-tilmanocept SPECT/CT was performed using a Symbia T6 SPECT/CT system (Siemens). A total ^{99m}Tc-tilmanocept dose of <2 mCi (50 μg) (1.37–1.85 mCi) was injected subcutaneously by a physician trained in nuclear medicine. The dose range was derived by subtracting the residual radioactivity in the syringe post injection from the total radioactivity in the syringe prior to injection. The subcutaneous route was chosen because it is a Food and Drug Administration–approved route of administration for this radiopharmaceutical, albeit for a different indication. For details on imaging technique and analysis, see Supplemental Methods. In brief, muscle was chosen as an analytic reference region, owing to low and consistent activity across subjects and groups, to control for nonspecific tissue and blood-pool uptake.

For each subject, tilmanocept activity (uptake) was normalized to a mean muscle activity of 1. A CT-guided volume of interest was drawn to cover the entirety of the aorta visible in the SPECT field of view (aortic root, arch, descending aorta to the liver base). To assure specificity of aortic analyses, "high-level" tilmanocept uptake was defined as any voxel with activity (uptake) at ≥5 times muscle activity. This level of tilmanocept uptake was roughly equivalent to the mean activity observed in the liver (Supplemental Figure 2). For each subject, we calculated the total volume within the aortic volume of interest that was at or above the "high-level" activity threshold, along with the percentage of the total volume at or above that level.

CT Angiography

CT angiography of the coronary arteries and thoracic aorta was performed with a Somatom Definition Flash 128-slice dual-source CT scanner (Siemens Medical Solutions), according to Society of Cardiac Computed Tomography guidelines [12] (Supplemental Methods). Techniques for assays and flow cytometric analyses are described in the Supplemental Methods.

Statistical Analysis

For ex vivo experiments, *t* tests were used. For the human study, the primary end point was aortic ^{99m}Tc-tilmanocept uptake at SPECT/CT. Our initial goal was to determine feasibility of ^{99m}Tc-tilmanocept SPECT/CT imaging in humans. A secondary aim was to compare aortic ^{99m}Tc-tilmanocept uptake among HIV-infected versus non–HIV-infected subjects. Continuous parameters were assessed for normality and presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) values. Between-group comparisons were made using *t*, Wilcoxon rank sum, or χ^2 tests, as appropriate. Correlations between aortic ^{99m}Tc-tilmanocept uptake and CT angiographic/metabolic/immune parameters were assessed using Pearson or Spearman correlation coefficients, as appropriate. Statistical tests were 2 sided and performed using JMP software (version 11; SAS Institute).

RESULTS

Ex Vivo Experiments on Tissue-Banked Aortic Samples From Individuals With or Without HIV Infection

The mean number of $CD206^+$ macrophages was significantly higher in aortic sections from individuals with HIV infection than in those from individuals without HIV infection (mean [SD], 30.1 [7.9] vs 14.2 [7.0] macrophages per square millimeter; $P < .001$; Figure 1A). The mean (SD) percentage of $CD206^+$ tilmanocept-positive macrophages in aortic samples from HIV-infected versus non–HIV-infected subjects was 89.1% (6.3%) versus 86.3% (6.8%), respectively, reflecting a high degree of colocalization (Figure 1B). Aortic samples from both groups featured a low percentage of cells that were positive for tilmanocept but negative for CD206 (mean [SD], 3.1% [1.8%] for HIV vs 3.3% [2.1%] for non-HIV).

Human Subjects Study

Baseline Cardiometabolic Parameters

Study subjects were men with a mean (SD) age of 58 (5) years. No subject received statin therapy within 1 year of the study. The Framingham risk score did not differ significantly between groups (9% for HIV vs 8% for non-HIV; $P = .55$). Among HIV-infected subjects, the mean (SD) duration since HIV diagnosis was 23.3 (8.1) years, the median $\log_{10}$ viral load was 1.4 copies/mL (IQR, 1.3–2.8 copies/mL), and the mean (SD) $CD4^+$ cell count was 534/μL (138/μL) (Supplemental Table 1).

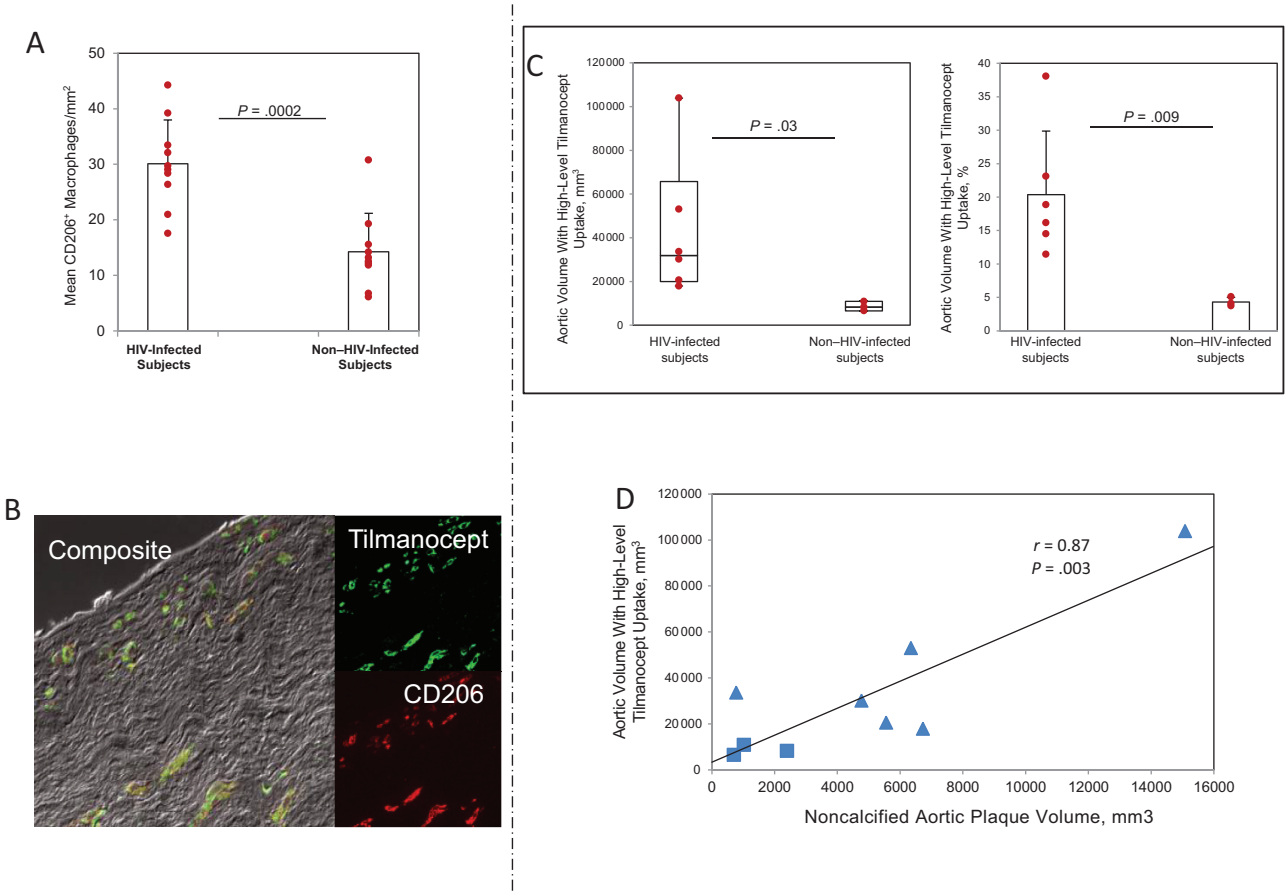

Figure 1. Ex vivo experiments on tissue-banked aortic samples from individuals with or without human immunodeficiency virus (HIV) infection and in vivo aortic high-level technetium Tc 99m tilmanocept (^{99m}Tc-tilmanocept) uptake and relationship to aortic noncalcified plaque in both groups of subjects. *A,* In tissue-banked aortic samples, the mean number of CD206$^+$ macrophages per square millimeter was significantly higher among HIV-infected individuals (n = 10) than among non–HIV-infected individuals (n = 10) (*P* = .0002). *B,* Double-label immunofluorescence using a CD206 antibody and tilmanocept-Alexa Fluor 488 revealed a high and similar degree of colocalization of tilmanocept and CD206 in sections from HIV-infected (n = 10) and non–HIV-infected (n = 10) subjects (mean [standard deviation (SD)], 89.1% [6.3%] vs 86.3% [6.8%], respectively). The mean (SD) percentages of CD206$^+$ tilmanocept-negative macrophages and CD206$^-$ tilmanocept-positive macrophages in HIV-infected (n = 10) versus non–HIV-infected (n = 10) subjects were 7.8% (7.0%) versus 10.4% (6.2%) and 3.1% (1.8%) versus 3.3% (2.1%), respectively. *C,* Aortic volume with high-level ^{99m}Tc-tilmanocept uptake was significantly increased in HIV-infected (n = 6) compared with non–HIV-infected (n = 3) subjects (*P* = .03). Results represent medians and interquartile ranges, with whiskers showing minimum and maximum values. Aortic volume with high-level ^{99m}Tc-tilmanocept uptake is shown to facilitate assessment of the relationship with total noncalcified coronary atherosclerotic plaque volume. The percentage of aortic volume with high-level ^{99m}Tc-tilmanocept uptake was significantly increased among HIV-infected (n = 6) compared with non–HIV-infected (n = 3) subjects (*P* = .009). Results represent means with SDs. *D,* Regression analysis demonstrating a significant relationship between aortic volume with high-level ^{99m}Tc-tilmanocept uptake at single-photon emission computed tomography/computed tomography and noncalcified aortic plaque volume (Pearson correlation coefficient [*r*] = 0.87; *P* = .003). HIV-infected subjects (n = 6) are represented as triangles, and non–HIV-infected control subjects (n = 3) as squares.

Areas of ^{99m}Tc-Tilmanocept Uptake at SPECT/CT

Among all subjects, significantly increased ^{99m}Tc-tilmanocept uptake (relative to muscle) was visualized in the kidneys, liver, and aorta (Supplemental Figure 2). ^{99m}Tc-tilmanocept is known to be renally cleared. Liver uptake was similar among HIV-infected and non–HIV-infected subjects (median [IQR] liver-to-muscle ratio 5.7 [5.5–8.1] vs 5.1 [4.2–5.8], respectively; *P* = .37).

Aortic ^{99m}Tc-Tilmanocept Uptake at SPECT/CT

Among all study subjects, aortic ^{99m}Tc-tilmanocept uptake was observed (Figure 2). Overall, the aortic volume with high-level ^{99m}Tc-tilmanocept uptake was significantly higher in the HIV-infected than in the non–HIV-infected subjects (median uptake [IQR], 31 910 [19 922–65 745] vs 8276 [6574–10 890] mm^3; *P* = .03), as was the percentage of aortic volume with high-level ^{99m}Tc-tilmanocept uptake (mean [SD], 20.4% [9.5%] vs 4.3% [0.7%]; *P* = .009; Figure 1C).

Aortic ^{99m}Tc-Tilmanocept Uptake in Relation to Atherosclerotic Plaque at CT Angiography

HIV-infected subjects had an increased volume of total aortic plaque (mean [SD], 10 623.2 [6746.7] vs 2271.3 [1148.5] mm^3; *P* = .03) and noncalcified aortic plaque (attenuation <130 HU) (6541.0 [4697.3] vs 1371.0 [900.2] mm^3; *P* = .04), compared with age-matched non–HIV-infected subjects with similar Framingham risk scores. Among all study subjects, there was a

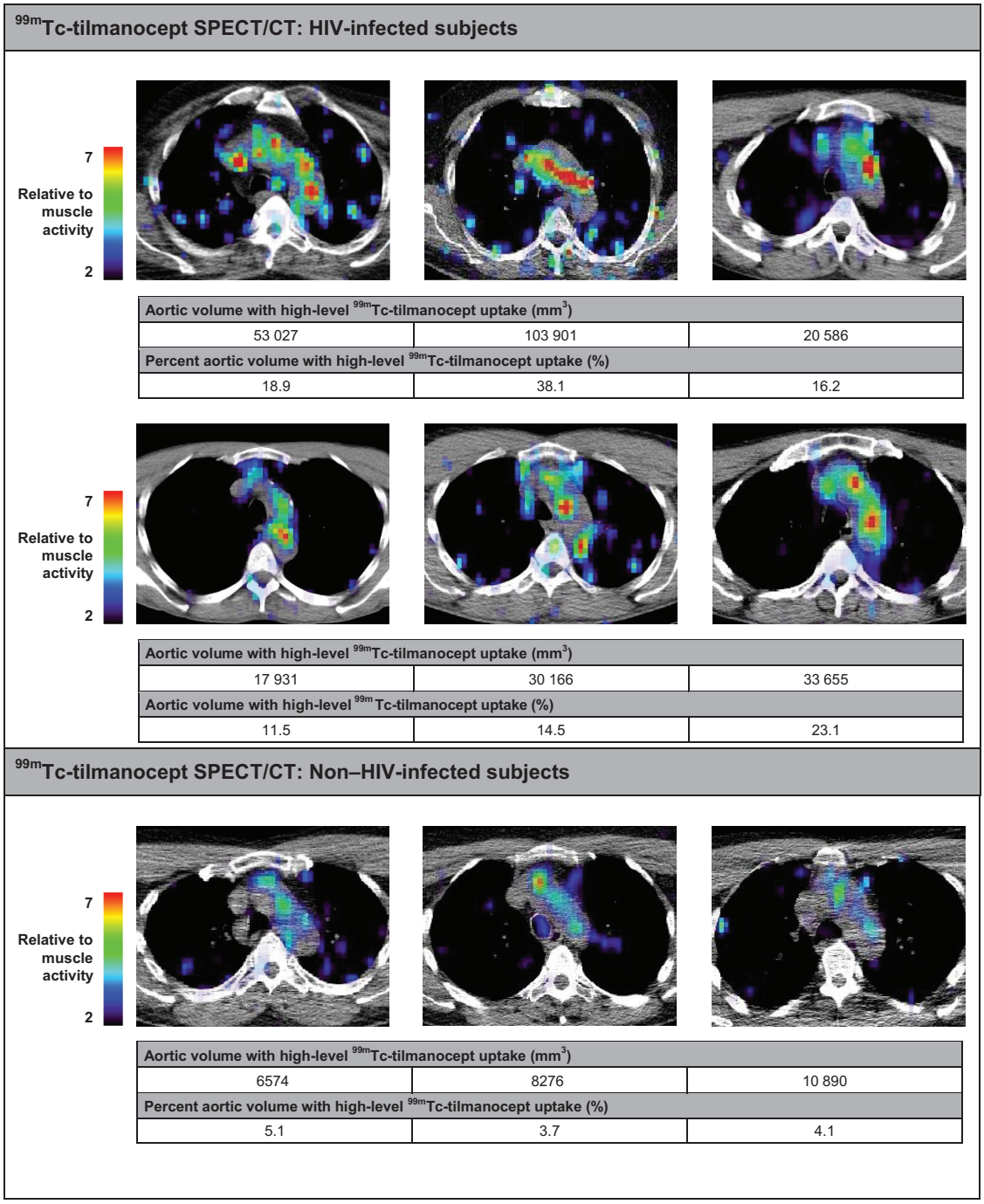

Figure 2. Aortic technetium Tc 99m tilmanocept (^{99m}Tc-tilmanocept) single-photon emission computed tomography (SPECT)/computed tomography (CT) in human immunodeficiency virus (HIV)–infected and non–HIV-infected subjects. Axial cross-sections of the aorta from ^{99m}Tc-tilmanocept SPECT/CT scans are shown for HIV-infected (n = 6) and non–HIV-infected (n = 3) subjects. Aortic volume and the percentage of aortic volume with high-level ^{99m}Tc-tilmanocept uptake (>5 times muscle ^{99m}Tc-tilmanocept uptake) are displayed for each subject. The adjacent color scale indicates aortic ^{99m}Tc-tilmanocept uptake relative to muscle ^{99m}Tc-tilmanocept uptake, with red representing areas of high relative ^{99m}Tc-tilmanocept uptake. Abbreviation: ^{99m}Tc, metastable technetium isotope.

significant relationship between aortic volume with high-level ^{99m}Tc-tilmanocept uptake and noncalcified aortic atherosclerotic plaque volume ($r = 0.87$; $P = .003$), and this relationship held when HIV status was controlled for (overall model, $R^2 = 0.76$; overall $P = .01$; $P = .02$ for noncalcified plaque volume; Figure 1D).

Aortic ^{99m}Tc-Tilmanocept Uptake in Relation to Immune Phenotype

HIV-infected subjects, in general, had higher levels of systemic monocyte activation markers, as well as higher absolute numbers of monocyte subsets, higher absolute CD8$^+$ T-cell counts, and relatively lower absolute CD4$^+$ T-cell counts (Supplemental

Table 2, Supplemental Table 3). Among all subjects, aortic volume with high-level ^{99m}Tc-tilmanocept uptake related to levels of soluble CD14 (P = .72; P = .03), absolute number of CD14$^+$CD16$^-$ monocytes (P = .77; P = .02), absolute CD8$^+$ T-cell count (P = .73; P = .02), and absolute CD8$^+$PD1$^+$ T-cell count (P = .70; P = .04). In analogous univariate analyses performed separately among HIV-infected and non–HIV-infected subjects, relationships between these systemic immune parameters and aortic volume of high-level ^{99m}Tc-tilmanocept uptake did not achieve statistical significance.

DISCUSSION

We present first-in-human data applying a novel CD206$^+$ macrophage-specific arterial imaging strategy, ^{99m}Tc-tilmanocept SPECT/CT, among individuals with HIV. Given the tilmanocept specificity for binding CD206$^+$ macrophages confirmed in our ex vivo studies, aortic ^{99m}Tc-tilmanocept uptake quantified by SPECT/CT may be inferred to reflect in situ arterial CD206$^+$ macrophage density. In our subjects, systemic administration of ^{99m}Tc-tilmanocept via subcutaneous injection resulted in markedly increased ^{99m}Tc-tilmanocept uptake in the aorta, liver, and kidneys. Aortic uptake of ^{99m}Tc-tilmanocept was particularly striking. Indeed, among the HIV-infected subjects with low Framingham risk score, high-level ^{99m}Tc-tilmanocept uptake was detectable across 20.4% of the aortic surface volume. In contrast, among non–HIV-infected subjects with similar Framingham risk scores, high-level ^{99m}Tc-tilmanocept uptake was detectable across only 4.3% of the aortic surface volume. Moreover, we show that aortic volume with high-level ^{99m}Tc-tilmanocept uptake relates robustly to noncalcified aortic atherosclerotic plaque volume, even after controlling for HIV status, highlighting a potential link between arterial CD206$^+$ macrophage density and atherogenesis.

Recent research lends biologic plausibility to the hypothesis that CD206$^+$ macrophages, such as those tagged by ^{99m}Tc-tilmanocept, are relevant to atherogenesis. Indeed, analysis of coronary artery sections from sudden cardiac death victims has revealed that CD206$^+$ macrophages are particularly abundant in "unstable" thin-capped fibroatheromas [13]. The traditional macrophage classification paradigm (developed from in vitro studies) sorts CD206$^+$ macrophages into the M2 phenotype—an "alternatively activated" class working to counterbalance the proinflammatory effects of "classically activated" M1 macrophages. However, macrophage behavior in vivo defies rigid classification. Significant heterogeneity exists *within* the canonical M1/M2 macrophage categories, including, for example, a subclass of M2 macrophages, M2b, producing high-levels of proinflammatory cytokines [14]. Moreover, macrophages demonstrate plasticity in vivo, switching phenotypes in response to locally encountered microenvironmental cues [14]. Our findings suggest a greater relative abundance of CD206$^+$ macrophages in the aortas of HIV-infected versus non–HIV infected individuals, and further highlight a relationship between aortic high-level tilmanocept uptake and aortic noncalcified atherosclerotic plaque. Further research is needed to elucidate whether arterial CD206$^+$ macrophages contribute to or compensate for in situ arterial inflammation/atherogenesis in HIV infection.

Recognizing the potential importance of CD206$^+$ (mannose receptor–bearing) macrophages to atherogenesis, Tahara et al [13] previously applied 2-deoxy-2-18F-fluoro-D-mannose (^{18}F-FDM) PET in a study of rabbits with or without atherosclerosis. Increased in vivo aortic ^{18}F-FDM uptake was demonstrated in atherosclerotic animals. Among the atherosclerotic rabbits, this uptake was highest in aortic regions featuring vulnerable atherosclerotic plaque and was correlated with density of arterial macrophages, characterized by staining with RAM-11 (a monoclonal antibody reacting with a rabbit macrophage cytoplasmic antigen). The ^{18}F-FDM technique, to date trialed only in animals, differs from our technique insofar as it probably characterizes predominantly cellular mannose uptake [13], whereas ours characterizes cells bearing the mannose receptor. Comparative studies of ^{18}F-FDM PET and ^{99m}Tc-tilmanocept SPECT/CT are required to establish the relative merits of each technique, including sensitivity and specificity for quantifying arterial CD206$^+$ macrophage infiltration in humans.

This proof-of concept study has limitations, including lack of aortic tissue from the same human subjects who underwent in vivo ^{99m}Tc-tilmanocept SPECT/CT and a small sample size (precluding intragroup analyses of correlations between aortic high-level tilmanocept uptake and systemic immune parameters). Study strengths include the first-in-human application of a novel, noninvasive molecular imaging technique targeting CD206$^+$ arterial wall macrophages. This technique may be usefully applied in larger cohorts to provide insights into specific systemic inflammatory pathways promoting in situ arterial inflammation and atherogenesis in HIV infection and to track arterial responses to targeted systemic anti-inflammatory therapies.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. V. Z. and S. K. G. designed the overall study, and M. Q. W., T. B., and G. E. F. contributed to the design and analyses of the data from ^{99m}Tc-tilmanocept SPECT/CT. M. T. L., B. F., and U. H. provided CT data. T. H. B. provided enzyme-linked immunosorbent assay data on immune markers. T. H. B., J. W., P. A., and K. C. W. provided flow cytometric data. J. W. and K. C. W. provided data from experiments on banked aortic samples. M. T. and A. M. recruited the subjects and performed study visits. M. V. Z, M. T., L. S., and S. K. G. performed primary study analysis. F.

C. and B. A. contributed to discussions about optimal dosing and administration of ^{99m}Tc-tilmanocept. S. K. G. had full access to the data in the study and had final responsibility for the decision to submit the manuscript for publication.

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Potential conflicts of interest. M. V. Z. participated in a scientific advisory board meeting for Roche Diagnostics and received grant support from Gilead Sciences, both unrelated to this study. U. H. has received grant support from HeartFlow, Siemens Healthcare, Genzyme, and the American College of Radiology Imaging Network and personal fees from the American Heart Association, all unrelated to this study. K. C. W. served on the scientific advisory board and was paid by Macrophage Therapeutics, unrelated to this study. S. K. G. served as a paid consultant to Gilead Sciences, Theratechnologies, Bristol-Myers Squibb, NovoNordisk, Merck, Navidea, and AstraZeneca and received grant support from Amgen, Bristol-Myers Squibb, Gilead Sciences, Kowa Pharmaceuticals, and Theratechnologies, all unrelated to this study. F. C. and B. A. are employees of Navidea Biopharmaceuticals. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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