^{89}Zr-Labeled *N*-succinyldesferrioxamine-ranibizumab

[^{89}Zr]-Ranibizumab

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Chemical name:	^{89}Zr-Labeled *N*-succinyldesferrioxamine-ranibizumab	
Abbreviated name:	[^{89}Zr]-Ranibizumab	
Synonym:		
Agent Category:	Antibody	
Target:	Vascular endothelial growth factor-A (VEGF-A)	
Target Category:	Antigen	
Method of detection:	Positron emission tomography (PET)	
Source of signal / contrast:	^{89}Zr	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

The vascular endothelial growth factors (VEGF) are a family of mitogenic glycoproteins (designated VEGF-A thru VEGF-E) that promote angiogenesis by the activation of the VEGF receptors (VEGFR) *via* a tyrosine kinase (TK) signaling pathway. These growth factors are known to assist in the survival and promotion of malignant tumors by increasing the abnormal neovascularization of the lesions (1). As a result, anti-angiogenic therapy with bevacizumab, a humanized anti-VEGF monoclonal antibody (mAb), its Fab fragment ranibizumab, and small molecule VEGFR TK inhibitors such as sorafenib and sunitinib are often used to treat various types of cancer (2) and other VEGF-related health

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conditions (3). However, these therapies are not entirely effective due to the development of resistance to the treatments as discussed in detail elsewhere (4). In addition, the efficacy of an anti-angiogenic therapy cannot be reliably assessed with either invasive (e.g., biopsy to measure different histochemical vascular markers) or non-invasive (imaging with $[^{15}O]H_2O$, ultrasound, optical probes, or magnetic resonance) methods (4). Radiolabeled VEGF or anti-VEGFR antibodies have been used to study the VEGF/VEGFR expression profiles of angiogenic tumors with single-photon emission computed tomography or positron emission tomography (PET) imaging in preclinical studies; however, because the expression level of these molecules in the tumor changes with the tumor's development stage, data obtained from these studies often yields inconclusive results (4).

PET imaging with ^{89}Zr-labeled bevacizimab (^{89}Zr-bevacizimab; molecular weight ((mol. wt.) ~150 kDa) was recently shown to be suitable for the determination of VEGF levels in xenograft tumors on athymic nude mice and to predict tumor response to VEGF-dependent anti-angiogenic therapy (5). The physical half-life of ^{89}Zr is ~78.5 h. The main limitation of this imaging agent is its long circulating serum half-life (21 days), and the maximum signal was observed only 4–7 days postinjection (p.i.) of the radiolabeled mAb. In an effort to develop an imaging agent superior to ^{89}Zr-bevacizimab to predict the effectiveness of anti-VEGF therapy, ranibizumab (mol. wt. ~40 kDa) was labeled with ^{89}Zr (^{89}Zr-ranibizumab). For the development, characteristics, and clinical application of ranibizumab, see Ferrara et al. (6). The biodistribution and possible utility of ^{89}Zr-ranibizumab as a tumor-imaging agent to determine the efficacy of sunitinib was investigated in athymic mice bearing SKOV-3 (a human adenocarcinoma cell line), A2780 (a human ovarian cancer cell line), or Colo205 (a human colorectal adenocarcinoma cell line) xenograft tumors (7).

Other Sources of Information

Other VEGF (or related) chapters in MICAD

Chapters on anti-angiogenic agents in MICAD

Human VEGF-A protein sequence and mRNA transcript variant 1 (gene ID: 7422)

VEGF-A in OMIM (Online Mendelian Inheritance in Man)

VEGF related clinical trials

VEGF pathways related to hypoxia and angiogenesis (from NCI/Nature Pathways Interaction Database)

Synthesis

[PubMed]

The source and ^{89}Zr-labeling of ranibizumab was performed as described by Nagengast et al. (7). The radiochemical yield (RY) of ^{89}Zr-ranibizumab was >95%, and the specific activity (SA) of the final product was 1,500 MBq/mg (40.5 mCi/mg). The radiochemical

purity (RP) of the labeled mAb was not reported. ^{89}Zr-ranibizumab was stable in serum for at least 24 h at 37°C (source of serum not mentioned).

For use as a control, a human immunoglobulin G (IgG) Fab fragment (size is comparable to ranibizumab and has no affinity for VEGF-A) was also labeled with ^{89}Zr as described (7). The RY, RP, and SA of this labeled control were not reported.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) and [^{18}O]H_2O were produced for PET imaging as detailed elsewhere to compare PET images obtained with ^{89}Zr-ranibizumab (7).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The percent binding of ^{89}Zr-ranibizumab to VEGF was reported to be comparable to the unlabeled version of the mAb as determined with an enzyme-linked immunosorbent assay (7). The VEGF binding of the labeled mAb was shown to decrease with increasing concentrations of unlabeled ranibizumab.

Animal Studies

Rodents

[PubMed]

The biodistribution of ^{89}Zr-ranibizumab was studied in nude mice bearing SKOV-3 cell xenograft tumors as described by Nagengast et al. (7). Animals were injected with the radiolabeled mAb or with ^{89}Zr-Fab-IgG through the penile vein. Mice were euthanized at 1, 3, 6, and 24 h p.i. (number of animals used per group was not reported), and radioactivity incorporated in the major organs, including tumors, was determined. Data were presented as percent of injected dose per gram tissue (% ID/g). With ^{89}Zr-ranibizumab, the amount of radioactivity in the blood was shown to decrease from 8.44 ± 2.19% ID/g at 1 h p.i. to 0.38 ± 0.38% ID/g at 24 h p.i., indicating that there was a rapid clearance of the ^{89}Zr from circulation. The amount of label detected in the heart, lung, liver, muscle, and bone was reported to be between ~1.0% ID/g (muscle) and ~5.0% ID/g (lungs) at 1 h p.i. and between ~0.5% ID/g (muscle) and ~4.0% ID/g (liver) at 24 h p.i. During the same period, the incorporation of radioactivity in the tumors from the labeled mAb increased from ~2.0% ID/g at 1 h p.i. to ~4.0% ID/g. With ^{89}Zr-Fab-IgG, the amount of radioactivity in the tumor was reported to be ~1.5% ID/g at 24 h p.i. Increasing doses of unlabeled ranibizumab given to the mice were reported to decrease the tumor uptake of ^{89}Zr-ranibizumab to the background levels observed with the radiolabeled Fab-IgG.

In another study, microPET imaging of mice bearing A2780 or Colo205 cell xenograft tumors (number of animals used per group was not reported) injected with either ^{18}F-FDG or [^{18}O]H_2O (imaging performed at 1 h p.i.) or ^{89}Zr-ranibizumab (imaging performed at 24 h p.i.) showed that the tumor could be clearly visualized on the animals

with all the tracers (7). Treatment of the animals with sunitinib for a week followed by imaging showed that, in both cell type tumors, there was an ~45% and ~20% reduced uptake of the labeled mAb in the tumor center and the rim, respectively, compared with the tumor uptake in animals given no drug treatment. ^{18}F-FDG imaging of animals treated the TK inhibitor showed that the label was present uniformly across the lesion; in imaging with ^{18}O, only the tumor rim was clearly visible while the center was not visible. Compared with untreated mice, tumors on the sunitinib-treated animals showed a minimal change in uptake of the Fab-IgG. PET imaging in mice one week after stopping sunitinib treatment showed an increased tumor uptake of ^{89}Zr-ranibizumab in both tumor models (7). The increase was ~70% and ~35% higher ($P = 0.056$) compared to the 7-day sunitinib treatment and the baseline, respectively. Histological staining of tumors obtained from the sunitinib-treated animals showed that there was increased vascularization and expression of VEGFR on the tumor rim compared with the tumor center; these studies also confirmed the differential uptake of ^{89}Zr-ranibizumab observed at the tumor center and the rim during the PET imaging studies (7).

From these studies, the investigators concluded that PET imaging with ^{89}Zr-ranibizumab is suitable to visualize and possibly quantify VEGF signaling in cancerous tumors and has a potential application to monitor anti-cancer therapy (7).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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