
Abstract:

Recently, an intra-patient comparison demonstrated that the somatostatin (sst) ligand [(68)Ga]HA-DOTATATE ([(68)Ga]DOTA-3-iodo-Tyr(3)-octreotate) provides PET images comparable to or superior to those obtained with [(68)Ga]DOTATATE. To provide a comprehensive basis for nevertheless observed slight differences in tracer biodistribution and dosimetry, the characteristics of [(68)Ga]HA-DOTATATE were investigated in a detailed preclinical study. Affinities of (nat)Ga-HA-DOTATATE and (nat)Ga-DOTATATE to sst1-5 were determined using membrane preparations and [(125)I]SST-28 as radioligand. Internalization into AR42J cells was studied in dual-tracer studies with [(125)I]TOC as internal reference. Biodistribution was investigated using AR42J tumor-bearing CD1 mice, and specificity of tracer uptake was confirmed in competition studies by coinjection of 0.8 mg TOC/kg. Sst2 affinities (IC50) of [(nat)Ga]HA-DOTATATE (1.4 ± 0.8 nM, logP: -3.16) and [(nat)Ga]DOTATATE (1.2 ± 0.6 nM, logP: -3.69) were nearly identical. Both compounds displayed IC50 > 1 ?M for sst1,3,4, while sst5 affinity was markedly increased for (nat)Ga-HA-DOTATATE (102 ± 65 nM vs > 1 ?M for (nat)Ga-DOTATATE). [(nat)Lu]HA-DOTATATE and [(nat)Lu]DOTATATE showed slightly
lower, identical sst2 affinities (2.0 ± 1.6 and 2.0 ± 0.8 nM, respectively) and sst3 affinities of 93 ± 1 and 162 ± 16 nM. Internalization of [(68)Ga]HA-DOTATATE was tenfold higher than that of [(125)I]TOC but only sixfold higher for [(68)Ga]DOTATATE and [(177)Lu]HA-DOTATATE. While [(68)Ga]HA-DOTATATE and [(68)Ga]DOTATATE had shown similar target- and non-target uptake in patients, biodistribution studies in mice at 1 h post injection (n = 5) revealed slightly increased non-specific uptake of [(68)Ga]HA-DOTATATE in the blood, liver, and intestines (0.7 ± 0.3, 1.0 ± 0.2, and 4.0 ± 0.7 %ID/g vs 0.3 ± 0.1, 0.5 ± 0.1, and 2.7 ± 0.8 %ID/g for [(68)Ga]DOTATATE). However, sst-mediated accumulation of [(68)Ga]HA-DOTATATE in the pancreas, adrenals, and tumor was significantly enhanced (36.6 ± 4.3, 10.8 ± 3.2, and 33.6 ± 10.9 %ID/g vs 26.1 ± 5.0, 5.1 ± 1.4, and 24.1 ± 4.9 %ID/g, respectively). Consequently, tumor/background ratios for [(68)Ga]HA-DOTATATE in the AR42J model are comparable or slightly increased compared to [(68)Ga]DOTATATE. The present preclinical data fully confirm the general biodistribution pattern and excellent in vivo sst-targeting characteristics previously observed for [(68)Ga]HA-DOTATATE in patients. The effect of slightly enhanced lipophilicity on background accumulation and normal organ dose is compensated by the high uptake of [(68)Ga]HA-DOTATATE in tumor. Thus, [(68)Ga]HA-DOTATATE represents a fully adequate, freely available substitute for [(68)Ga]DOTATATE and, given the superb sst-targeting characteristics of [(177)Lu]HA-DOTATATE in vitro, potential applicability for sst-targeted PRRT.

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