Recombinant α_1-Microglobulin Is a Potential Kidney Protector in ^{177}Lu-Octreotate Treatment of Neuroendocrine Tumors

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Treatment of neuroendocrine tumors with ^{177}Lu-octreotate results in prolonged survival and improved quality of life for the patient. However, the treatment is today limited by side effects on kidney and bone marrow, and complete tumor remission is rarely seen. A possible way to minimize dose-limiting toxicity and to optimize this treatment method is to use radioprotectors in conjunction with radiotherapy. A recombinant form of α_1-microglobulin (rA1M) was recently shown to preserve kidney structure and function after ^{177}Lu-octreotate injection in mice and was suggested as a radioprotector in peptide receptor radionuclide therapy. The aims of this work were to investigate the influence of rA1M on the in vivo biokinetics of ^{177}Lu-octreotate, with a focus on tumor tissue, and to study the impact of rA1M on the therapeutic response in tumor tissue subjected to ^{177}Lu-octreotate treatment. **Methods:** The biodistribution of ^{177}Lu-octreotate was examined in BALB/c nude mice with GOT2 tumors 1–168 h after injection with either ^{177}Lu-octreotate or coadministration of ^{177}Lu-octreotate and rA1M. The effects of rA1M on the tumor response after ^{177}Lu-octreotate treatment were studied in BALB/c nude mice with GOT1 tumors. Three groups of mice were administered rA1M, ^{177}Lu-octreotate, or both. Another group served as untreated controls. Tumor volume was measured to follow the treatment effects. **Results:** No statistically significant difference in biodistribution of ^{177}Lu was observed between the groups receiving ^{177}Lu-octreotate or coinjection of ^{177}Lu-octreotate and rA1M. The therapy study showed a decrease in mean tumor volume during the first 2 wk for both the ^{177}Lu-octreotate group and the coadministration group, followed by tumor regrowth. No statistically significant difference between the groups was found. **Conclusion:** rA1M did not negatively impact absorbed dose to tumor or therapeutic response in combination with ^{177}Lu-octreotate and may be a promising kidney protector during ^{177}Lu-octreotate treatment of patients with neuroendocrine tumors.

Key Words: α_1-microglobulin; somatostatin receptors; GOT1; GOT2; radioprotector

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Targeted radionuclide therapy with somatostatin analogs has been used for more than 2 decades to treat patients with metastasized neuroendocrine tumors (NETs). Currently, the β-emitters ^{90}Y (energy, 0.933 MeV/nuclear transition (*1*)) and ^{177}Lu (energy, 0.148 MeV/nuclear transition (*1*)) are used, of which ^{177}Lu has been found to have superior dosimetric properties for systemic therapy (*2*). Clinical studies with both ^{177}Lu-octreotate and ^{90}Y-octreotate have shown promising results, although mild side effects on bone marrow and kidneys have been reported (*3–6*). Fractionation of the treatment to allow recovery of bone marrow, and use of ^{177}Lu instead of ^{90}Y, have resulted in fewer side effects on normal tissues (*6,7*). Coinfusion with positively charged amino acids, such as lysine and arginine, reduces renal uptake of the somatostatin analog, and coadministration of these amino acids is now routinely used in treatment with ^{177}Lu-octreotate or ^{90}Y-octreotate (*8*). However, despite these efforts to minimize damage to normal tissue, radionuclide therapy with somatostatin analogs is still limited by the assumed risk of kidney toxicity.

A strategy to further reduce the risk of toxicity after therapy includes the use of radioprotectors (*9*). α_1-microglobulin (A1M) is a small plasma protein (26 kDa) with the ability to protect normal tissues from oxidative stress by binding and neutralizing free radicals and by reducing oxidants and oxidative lesions (*10,11*). A1M has also been shown to inhibit the propagation of cell death to bystander cells—that is, cells not exposed directly to radiation but residing near irradiated cells (*12*). A recombinant form of human A1M (rA1M) has been proposed as a kidney protector during ^{177}Lu-octreotate treatment of NET (*13*). rA1M, with its antioxidation properties and its similar biodistribution and pharmacokinetics to that of the ^{111}In-labeled somatostatin analog octreotide (*14*), is an interesting candidate for renal protection during treatment with ^{177}Lu-octreotate. Inhibition of renal damage by coadministration with rA1M has recently been studied in non–tumor-bearing mice up to 6 mo after injection of 150 MBq of ^{177}Lu-octreotate (*15*). The results indicate that rA1M could potentially protect kidney tissue from radiation-induced damage, allowing for reduced toxicity or dose escalation. However, adding a radiation-protecting agent, such as an antioxidant, to radionuclide therapy may result in protective effects not only on normal tissue but also on tumor tissue. To the best of our knowledge, this is the first study investigating the potential radioprotective effect of rA1M on tumor tissue.

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The aim of this work was therefore to investigate whether coadministration of ^{177}Lu-octreotate with rA1M impacts, first, the biokinetics of ^{177}Lu, with particular interest on the tumor uptake, and second, the treatment effect of ^{177}Lu-octreotate on tumor tissue.

MATERIALS AND METHODS

Animal Models

Animal experiments were performed on NET-bearing female 4-wk-old BALB/c nude mice (Janvier and Charles River). The animals were kept under a standard laboratory day and night cycle and were given water and food ad libitum. All animal procedures were approved by the Ethics Committee for Animal Research in Gothenburg (approval 107-2015). GOT2 (human medullary thyroid carcinoma) and GOT1 (human small intestine NETs) tumors were transplanted subcutaneously between the shoulders, as described earlier (*16,17*). At the start of the study, the mean tumor volume was 0.5 cm^3 (SEM, 0.1 cm^3); the animals receiving the GOT2 were 13–32 wk old, and the animals receiving the GOT1 tumors were 12–27 wk old.

Radiopharmaceutical

^{177}Lu-octreotate was obtained from the Nuclear Research and Consultancy Group (IDB Holland), and radiolabeling was conducted according to the manufacturer's instructions. The amount of peptide-bound ^{177}Lu in the injection solution was higher than 97%, as shown using instant thin-layer chromatography (Whatman Chromatography paper [3 mm] [GE Healthcare] and 0.1 M sodium citrate [Labservice AB]). After preparation of the ^{177}Lu-octreotate, the stock solution was diluted with saline solution to the desired activity concentration. Syringes containing ^{177}Lu-octreotate (0.1 mL) were prepared from the stock solution. The activity of the syringes were measured before and after injection by a well-type ionization chamber (CRC-15R; Capintec) to determine the amount of injected activity in each animal.

rA1M

Human rA1M (RMC-035; 5.9 mg/mL) was obtained from A1M Pharma AB and was diluted with a solution containing sterile endotoxin-free 10 mM sodium phosphate (pH 7.4), 0.15 M NaCl, and 12 mM histidine (A1M Pharma AB), to an rA1M concentration of 1.1 mg/mL. The mice were weighed, and syringes containing a 5 mg/kg dose of rA1M were prepared for each mouse.

Biodistribution in GOT2-Bearing Mice

The biodistribution of ^{177}Lu-octreotate was studied in female BALB/c mice bearing GOT2 tumors. In total, 32 mice were intravenously injected with 5 MBq (SD, 8%) of ^{177}Lu-octreotate in the tail vein at 3 PM (±1 h). Half of the mice also received an intravenous 5 mg/kg injection of rA1M directly after the ^{177}Lu-octreotate injection. The animals (n = 4/group) were killed by cardiac puncture under anesthesia with sodium pentobarbital (APL) at 1, 24, 72, or 168 h after administration. Samples of blood, lungs, liver, spleen, kidneys, tumor, femur (including bone marrow), adrenal gland, and pancreas were collected and weighed directly after excision. The ^{177}Lu activity in the samples was measured using a γ-counter equipped with a 7.6-cm (3-in) NaI(Tl) detector (2480 Wizard^2; Wallac). The ^{177}Lu activity concentration in the tissue samples, $c_{tissue}(t)$, was calculated as percentage injected activity per gram:

$$c_{tissue}(t) = \frac{A_{tissue}(t)}{A_{inj} \cdot m_{tissue}} \cdot 100\%,$$

where $A_{tissue}(t)$ is the activity in the sample at the time of death, corrected for radioactive decay to time of administration (t = 0), A_{inj} is the injected activity at time t = 0 and m_{tissue} is the mass of the sample. For bone, the ^{177}Lu activity concentration was calculated together with bone marrow.

Therapy Study in GOT1-Bearing Mice

The effect on tumor volume of rA1M alone or rA1M in combination with ^{177}Lu-octreotate treatment was studied in female BALB/c mice bearing GOT1 tumors. The 40 mice were divided into 4 groups (n = 10/group). One group received ^{177}Lu-octreotate (30 MBq), one group received rA1M (5 mg/kg), one group received both, and one group served as untreated controls. The injected ^{177}Lu activity level was chosen to give a limited therapeutic effect (noncurative) to enable detection of differences in tumor volume among the groups (*18*).

The mean tumor volume in the groups at the time of injection (day 0) was approximately 0.5 cm^3: 0.51 cm^3 (SEM, 0.09 cm^3) in the A1M group, 0.50 cm^3 (SEM, 0.08 cm^3) in the ^{177}Lu-octreotate group, 0.47 cm^3 (SEM, 0.07 cm^3) in the coadministration group, and 0.51 cm^3 (SEM, 0.08 cm^3) in the control group.

The tumor response was followed over time by measurement once or twice a week with digital slide calipers. The volume was estimated assuming an elliptic shape:

$$V = \frac{\pi \cdot a \cdot b \cdot c}{6},$$

where a is the longest diameter and b and c are the 2 perpendicular diameters. Tumor response was studied as the tumor volume relative to that at treatment, or as the area under the curve (AUC) for each individual tumor using the trapezoidal rule.

The animals were killed by cardiac puncture under anesthesia with sodium pentobarbital (APL) when the tumor size exceeded 10% of the body weight or the general condition of the mouse was reduced. The mice in the rA1M group were killed and tumor samples collected on day 37 or 44, at the latest. All remaining mice were killed 70 d after the treatment.

Statistical Analysis

In the biodistribution study, 2-way ANOVA was used to determine statistically significant differences between groups. Statistical significance was considered present for probabilities higher than 95% ($P < 0.05$).

In the therapy study, the difference between groups was determined by performing Kruskal–Wallis 1-way ANOVA with pairwise comparison, using IBM SPSS Statistics, version 25, on the AUC calculated up to the time point when the first mouse was killed (day 21). Statistical significance was considered present for probabilities higher than 95%.

RESULTS

Biodistribution Study

The concentration of ^{177}Lu in the investigated organs and tissues at different time points is shown in Figure 1. In almost all organs and tissues, the maximal activity concentration was reached within the first hour after injection for both groups. Thereafter, the ^{177}Lu concentration decreased rapidly. The highest ^{177}Lu activity concentration was observed in the kidneys at 1 h after the injection for both the ^{177}Lu-octreotate group and the coadministration group: 15% (SEM, 2) and 15% (SEM, 1) injected activity per gram, respectively. High concentrations were also obtained for pancreas, adrenals, and GOT2 tumors, all with known expression of somatostatin receptor type 2. The results from the 2-way ANOVA showed no statistically significant differences in ^{177}Lu

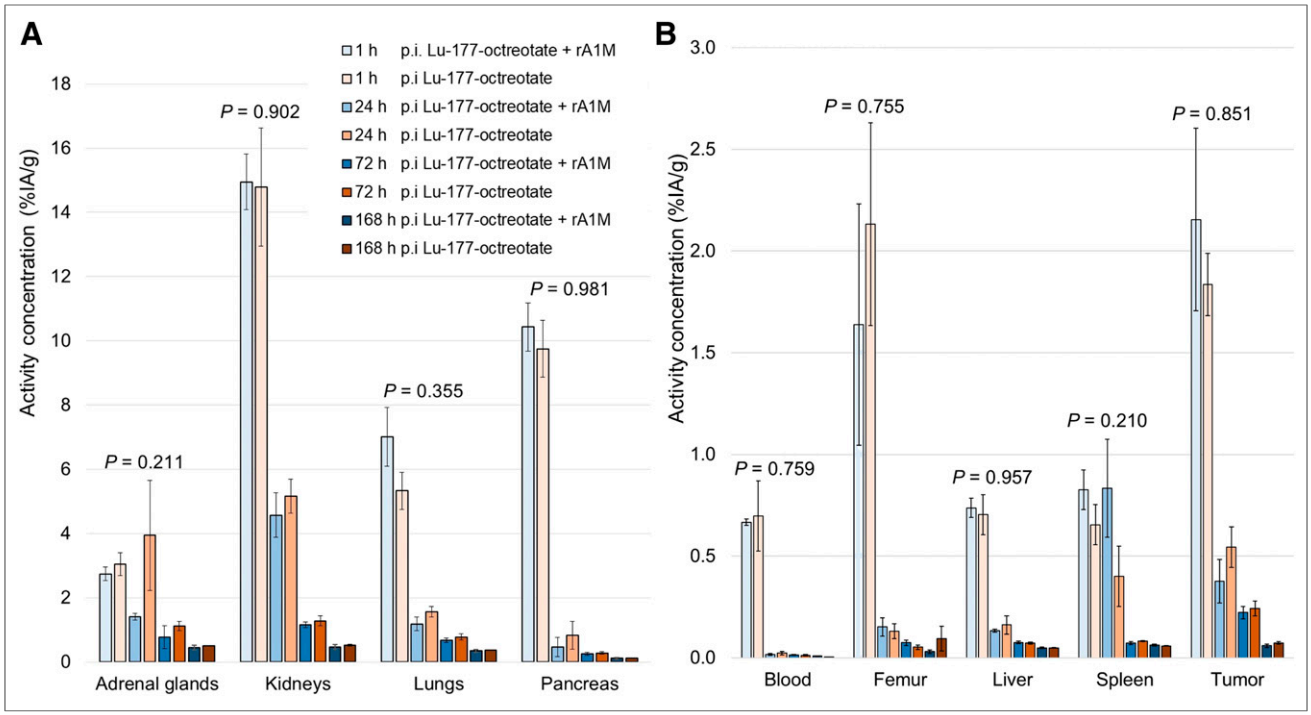

FIGURE 1. Mean ^{177}Lu activity concentration in adrenal glands, kidney, lungs, and pancreas (A) and in blood, femur, liver, spleen, and GOT2 tumors (B) at 1, 24, 72, and 168 h after injection (p.i.) with ^{177}Lu-octreotate (5 MBq) or ^{177}Lu-octreotate (5 MBq) and rA1M (5 mg/kg) (n = 4/group). Error bars show SEM, and P values show results from 2-way ANOVA of interaction of 2 groups over time. Note difference in y-axis scales.

activity concentration with time for any organ or tissue between the 2 groups (Fig. 1).

Therapy Study

The mean tumor volume of GOT1 tumors in the rA1M group and the untreated control group did not decrease over time (Fig. 2). For the ^{177}Lu-octreotate group and the coadministration group, a therapeutic response was observed. The mean tumor volume decreased during the first 14 d, followed by tumor regrowth (Fig. 2).

The AUC for each individual tumor from a plot of relative tumor volume versus time after treatment was calculated with a normalized time-axis (Fig. 3); a tumor with no change in volume during the integrated time would have an AUC of 1, and a nonresponding tumor with an increase in tumor volume would have a value greater than 1. The 1-way ANOVA showed that the mean AUCs (calculated from day 0 to day 21) for the rA1M group (1.4; SEM, 0.2) and the control group (1.6; SEM, 0.1) were significantly higher than those for the ^{177}Lu-octreotate group (0.84; SEM, 0.09) and the coadministration group (0.79; SEM, 0.07). AUC did not significantly differ between the ^{177}Lu-octreotate group and the coadministration group or between the control group and the rA1M group.

DISCUSSION

Higher amounts of ^{177}Lu-octreotate can be administered to patients with NET if the risk of side effects on normal tissues can be reduced. rA1M is a new, promising candidate for renal protection in radiation therapy. However, when radiation-protecting agents are used, it is essential that the radiobiologic effect on tumor tissue is not reduced. In this study, we investigated whether coadministration of rA1M and ^{177}Lu-octreotate in NET-bearing mice affected the biokinetics of ^{177}Lu and the change in tumor volume, compared with corresponding data after injection of ^{177}Lu-octreotate alone.

The result showed no statistically significant difference in biodistribution of ^{177}Lu-octreotate over time in GOT2-bearing mice with or without coadministration of rA1M. Of special interest is that there was no reduction of uptake in tumor tissue and no increased uptake in kidneys and bone marrow (femur), which are the 2 main organs at risk in ^{177}Lu-octreotate treatment. Thus, coadministration with rA1M will not influence the absorbed dose delivered to tumor or normal tissues from ^{177}Lu-octreotate exposure. Furthermore, no statistically significant difference in the therapeutic effect of ^{177}Lu-octreotate was observed in GOT1-bearing mice with or without coadministration of rA1M. No statistically significant difference in tumor growth was observed between GOT1-bearing mice injected with rA1M and controls.

Both animal tumor models used in this study, GOT1 and GOT2, are relevant for this type of study, as the basis for future clinical trials. They are human NETs and show a close resemblance to the clinical situation, with a slow tumor growth rate and preserved neuroendocrine features. In the biodistribution study, the impact of change in tumor volume over time was reduced using GOT2, which has a lower uptake of and a lower therapeutic response to ^{177}Lu-octreotate than GOT1. GOT1 expresses all subtypes of somatostatin receptors and especially high amounts of somatostatin receptor subtype 2 (*17*) and was chosen for the therapy study. Since initial tumor size may influence the uptake of ^{177}Lu-octreotate, as we have observed in another model (*19*), efforts were made to minimize the variation in size of the tumors on day 0 both within and between the groups. The fact that more than one GOT1 transplantation donor was used in this study may also contribute to the difference in biologic response between mice.

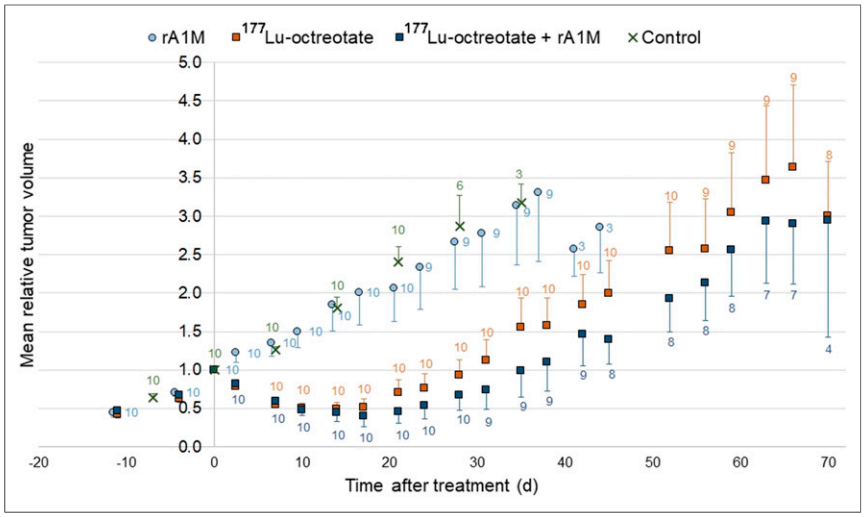

FIGURE 2. Mean relative volume of GOT1 tumors in BALB/c nude mice vs. time after injection (or study start) for control mice and mice injected with rA1M (5 mg/kg), ^{177}Lu-octreotate (30 MBq), or both rA1M (5 mg/kg) and ^{177}Lu-octreotate (30 MBq). Data labels represent number of animals, and vertical error bars indicate SEM.

However, no relationship between transplantation donor and uptake of ^{177}Lu-octreotate or therapeutic response was seen.

The findings in the biodistribution study are well in line with published results from the GOT2 animal model (*20*), but with a few exceptions: in the present study, the ^{177}Lu concentration was slightly higher in adrenal glands and spleen and lower in pancreas 24 h after injection. It is known that parameters such as the amount of activity and the sex may affect the result (*21,22*), and the low administered amount of ^{177}Lu-octreotate in the present study was chosen with consideration of previous studies to avoid, for example, receptor saturation (*18,21*). In this study, the mice were purchased from 2 different suppliers: Charles River in Germany and Janvier in France. The relatively large variations observed for spleen and adrenal glands may be due to differences in mice obtained from different suppliers.

In the therapy study, the response of GOT1 tumors in the mice receiving ^{177}Lu-octreotate with or without rA1M can be divided into 2 phases: a reduction phase during which the tumor volume is smaller than the volume at treatment, and a regrowth phase during which the tumor has regrown and increased above the volume at treatment (Fig. 2). A similar response of GOT1 tumors to ^{177}Lu-octreotate and coadministration treatments was observed, especially during the reduction phase. There was a tendency toward delayed regrowth in the coadministration group compared with the ^{177}Lu-octreotate group, but the difference was not statistically significant. As expected, a differential response was observed between the rA1M group and the groups receiving ^{177}Lu-octreotate (alone or together with rA1M), with the exception of one tumor that had an unexpectedly strong therapeutic response. The mean tumor size in the rA1M group increased over time, resembling the behavior of the untreated tumors in the control group.

The results from the therapy study are consistent with a previous study of response in GOT1 after treatment with 30 MBq of ^{177}Lu-octreotate (*18*). The therapeutic response was almost immediate and lasted for about 38 d for the coadministration group and 31 d for the ^{177}Lu-octreotate group. The therapeutic effect of ^{177}Lu-octreotate was quite variable between individuals: the mean maximal decrease in tumor volume was about 50% (Fig. 2), but for some tumors the response was much stronger. Although the amount of ^{177}Lu-octreotate was deliberately chosen to induce a moderate remission, some tumors had a period when they were not visible to the unaided eye. A few of these tumors never entered the regrowth phase before the end of the study. When these mice were killed, the skin where the tumors had been located was removed, and no signs of the tumors were visible. This was also the case for one tumor in the rA1M group that had a therapeutic response. The fact that this tumor was slightly smaller than the mean volume in this group at the start of the study, at 0.18 cm^3 versus a mean of 0.54 cm^3 (SEM, 0.09 cm^3), may have contributed to the observed effect.

It was recently shown that coadministration with rA1M could inhibit renal damage in non–tumor-bearing mice up to 6 mo after injection of 150 MBq of ^{177}Lu-octreotate (*15*). In the present study, we found that coadministration with rA1M did not prevent

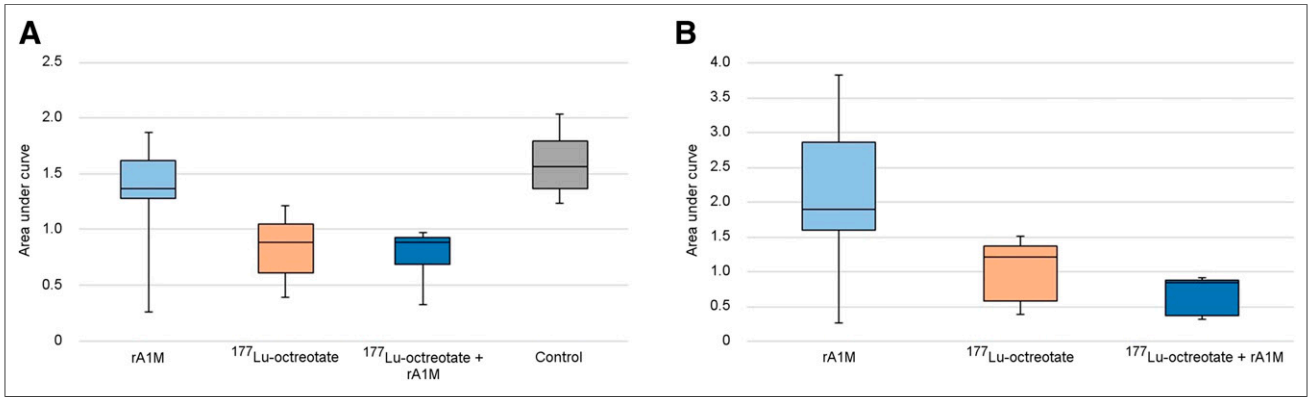

FIGURE 3. Response of GOT1 tumors in BALB/c nude mice injected with rA1M (5 mg/kg), ^{177}Lu-octreotate (30 MBq), or ^{177}Lu-octreotate (30 MBq) and rA1M (5 mg/kg) or untreated control, determined as AUC, from individual data behind Figure 2. (A) AUC calculated from day 0 to day 21, when all mice remained in study. (B) AUC calculated from day 0 to day 37 for mice still followed on day 37. AUC of 1 corresponds to no net change in tumor volume during period. Box plots show interquartile range (Q1–Q3) with median value, and whiskers show range from minimum to maximum.

^{177}Lu-octreotate from inducing remission of tumors in vivo. Why does rA1M protect the kidneys, but not the tumors, from ^{177}Lu-octreotate–induced damage? A plausible explanation may be that, like ^{177}Lu-octreotate, rA1M is colocalized to the renal cortex (*14*), whereas A1M did not to influence the radiobiologic effects on NETs. The mechanisms behind these findings should be explored further.

CONCLUSION

No difference in the biodistribution of ^{177}Lu in NET-bearing mice was found after coadministration of rA1M and ^{177}Lu-octreotate, compared with administration of ^{177}Lu-octreotate alone. rA1M had no negative effects on the therapeutic response of NET after exposure to ^{177}Lu-octreotate. Together with results from previous studies demonstrating reduced radiobiologic effects on the kidneys when ^{177}Lu-octreotate is combined with rA1M, we conclude that coadministration of rA1M could be a potential possibility for improving ^{177}Lu-octreotate therapy by reducing the side effects to the kidneys.

DISCLOSURE

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KEY POINTS

QUESTION: Does the potential kidney protector rA1M affect the therapeutic response of ^{177}Lu-octreotate?

PERTINENT FINDINGS: No differences in biodistribution of ^{177}Lu-octreotate were observed between mice with human neuroendocrine tumors with or without coadministration with rA1M. Therapeutic response of ^{177}Lu-octreotate was also not affected by coadministration with rA1M.

IMPLICATIONS FOR PATIENT CARE: Coadministration of rA1M could allow for a better kidney protection during ^{177}Lu-octreotate therapy, while keeping the tumor treatment efficacy. This would increase the therapeutic window, and thus allow for higher administered activity and enhanced cure rate.

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