Original Article

Intra-arterial PRRT with Lu-177 DOTATATE in Liver-dominant Metastatic Neuroendocrine Tumors: Early Assessment of Efficacy and Toxicity

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Abstract

Purpose: We proposed to administer Lu-177-DOTATATE in intra-arterial (IA) mode for higher first-pass localization to somatostatin receptors, higher residence time in liver metastases, and more radiation to tumor. This study aimed at assessing early hematological, renal and hepatotoxicity; and objective response to IA peptide receptor radionuclide therapy (PRRT). **Materials and Methods:** Fourteen patients (4 females and 10 males) were prospectively assessed. 5/14 patients underwent 2 cycles, whereas 3/14 underwent 3 cycles, and 6/14 received 1 cycle of IA PRRT. 200 mCi of Lu-177-DOTATATE was administered in 15–20 min by IA route under angiographic guidance. Patients were asked to follow-up at 4 and 8 weeks with hematological, liver, and renal functional parameters, and Ga-68 DOTATATE positron emission tomography/computed tomography (PET/CT) after 8 weeks. Response was assessed using RECIST 1.1 and EORTC PET criteria. **Results:** *Safety:* 2/14 patients had high total and direct bilirubin, which reverted to normal after IA PRRT. Three patients had low albumin, which improved after 1 cycle. Nine patients showed no worsening of liver function. Two patients showed Grade 1 hematotoxicity which reverted to normal. Five patients showed high creatinine, but preserved glomerular filtration rate and EC clearance. On follow-up at 8 weeks, serum creatinine reverted to normal. *Efficacy:* In five patients who underwent 2 cycles of IA PRRT, 3 showed partial response (PR) on RECIST 1.1 and partial metabolic response (PMR) on EORTC criteria, whereas 2 showed stable disease (SD). In patients who underwent 3 cycles, 1 showed SD, whereas other patient showed PMR on DOTANOC PET/CT, with PR in size. Among the remaining seven patients, 5 showed PMR, whereas the other 2 showed SD. Thus 9/14 patients showed PR, whereas 5 showed SD on metabolic and size criteria. **Conclusions:** IA PRRT is a safe and efficacious approach for the treatment of liver dominant metastatic neuroendocrine tumors.

Keywords: *Intra-arterial, liver metastases, neuroendocrine, peptide receptor radionuclide therapy*

Introduction

Trans-arterial approach provides several diverse options in the treatment of neuroendocrine liver metastases. There are multiple modalities of treatment which ranges from arterial embolization resulting in local ischemia at tumor site to delivery of high doses of chemotherapy to the tumor and selective internal radiotherapy using yttrium-90 microspheres. However, multiple recurrences in liver are known to occur, for which multiple treatment sessions are required, which not just adds to the cost but also to toxicity to normal liver parenchyma.[1] Lu-177 DOTATATE is a receptor-specific treatment, directed toward overexpressed somatostatin receptors (SSTR). It has resulted in better progression-free survival (PFS) in metastatic neuroendocrine tumors (NETs) in patients who have failed first-line therapy.[2] In spite of this, it has been observed that the most common reason for failure or progression following peptide receptor radionuclide therapy (PRRT) is high liver tumor burden. Kwekkeboom *et al*. reported that a high hepatic tumor burden significantly reduced the median disease-specific survival from more than 48 months to only 25 months.[3] In line with their results, Ezziddin *et al*. reported a median overall survival (OS) of 43 months in patients with a hepatic tumor burden of more than 25%, while median OS was not reached (>70 months) in patients with a hepatic tumor burden <25%.[4] Hence,

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if the same receptor specific treatment is administered in an intra-arterial (IA) mode, it shall lead to higher residence time of tracer in the liver metastases and more radiation delivered to the tumor sparing the normal liver parenchyma.[5] Conceptually, the approach has shown promising results; however, the clinical parameters of outcome like toxicity and early response to this therapeutic approach have not been studied so far, which was the rationale behind conducting this study.

Materials and Methods

This prospective, observational study was approved by the Institutional Ethics Committee (Project No 3881) and was conducted in accordance with the Declaration of Helsinki and guidelines of Good Clinical Practice. Written informed consent was taken. We analyzed the early toxicity and treatment response to IA PRRT in a prospective cohort of 14 patients studied between July 1, 2020, and October 31, 2021.

Patient selection

All patients underwent a baseline Ga-68-DOTANOC positron emission tomography/computed tomography (PET/CT) study to confirm SSTR expression, which was performed not beyond 2 weeks before treatment. Patients with Krenning score of 3 or 4 were and with liver lesion/s more than 30 mm measured on contrast CT component of DOTA PET/CT were selected for IA approach. None of the patients had extrahepatic metastatic disease. Exclusion criteria for PRRT were as follows: hemoglobin level of <8.0 g/dl, red blood cell count not <300,000/mm^3, white cell count of <2000/mm^3, platelet count of <75,000/mm^3, total bilirubin level of more than 3 times the upper limit of the normal range, and serum creatinine level of more than 1.6 mg/dl or a creatinine clearance of <50 mL/min. Patients with portal vein thrombosis, any contraindication to hepatic arteriography, and an anticipated life expectancy of <3 months were not included. Patient characteristics are shown in Table 1.

Table 1: Patient characteristics

	Number of patients
Site of primary	
Pancreas	5
Small bowel	4
Rectum	2
Liver	2
Colon	1
Number of liver lesions	
1	2
2–3	3
>3	9
Size of liver lesions (cm)	
3–4	7
4–5	6
>5	1
Number of cycles of IA PRRT	
1	7
2	5
3	2
Prior treatment	
Octreotide LAR	5
IV PRRT	6
Chemotherapy	3
WHO grade	
I	4
II	10

IV: Intravenous, PRRT: Peptide receptor radionuclide therapy, IA: Intra-arterial

Intra-arterial peptide receptor radionuclide therapy procedure

Patients were admitted to radionuclide therapy ward on the day of procedure. After premedication, intravenous (IV) amino acid solution containing 25 g of lysine and 25 g of arginine diluted in 2 L of normal saline was administered over 4 h. Patient was then shifted to an interventional radiology facility. During angiography, the allocated hepatic artery (i.e., left or right) was catheterized via a femoral or radial approach. A nuclear medicine physician and interventional radiologist determined the final injection position during angiography. In the angiographic procedure, a cone-beam computed tomography (CBCT) scan was performed with a catheter position identical to the injection position. The CBCT confirmed the target tumor's arterial blood supply and demonstrated the arteries' perfusion territory. Following heparinization of the catheter and sheath, 180–200 mCi (6.6–7.4 GBq) of 177 Lu-DOTATATE was administered in 15–20 min. Patient was then shifted to the nuclear medicine facility for posttherapy scanning. Tracer localization was confirmed at desired site on gamma camera imaging at 4 h posttreatment.

Follow-up

Patients were asked to follow-up at 4- and 8 weeks following completion of treatment with hematological, liver function, and renal functional parameters (serum creatinine, glomerular filtration rate [GFR] on Tc-99m-DTPA scan, and EC clearance on Tc-99m EC scan). Ga-68 DOTATATE PET/CT was performed at 8 weeks. Response was assessed using RECIST 1.1 and EORTC PET criteria.

Results

Safety

2/14 patients had high total bilirubin levels, which reverted to normal levels following IA PRRT. Both patients had lesions more than 5 cm in size and received 2 cycles, and as the lesions regressed, the bilirubin levels reverted to normal. Three patients had low albumin levels, which improved following therapy. Two of these three patients also had deranged bilirubin levels. The remaining

11 patients had preserved liver functional parameters. Liver enzymes and alkaline phosphatase were within normal limits for all patients. Table 2 mentions the details about hepatic function parameters.

Two patients showed Grade 2 thrombocytopenia which reverted to normal range within 8 weeks. Anemia or derangement in white blood cell counts was not seen in any of the patients.

At 4 weeks, two patients showed mildly raised creatinine levels (1.7 and 2.0 mg/dl), but normal GFR and EC clearance. On follow-up at 8 weeks, all renal functional parameters reverted to normal.

Efficacy

Patients underwent Ga-68-DOTATATE PET/CT, with triphasic CT of the liver, which was reported by two independent reviewers. In five patients who underwent 2 cycles of IA PRRT, three patients showed partial response (PR) on RECIST 1.1 and partial metabolic response (PMR) on EORTC criteria [Figure 1], whereas the other two patients showed stable disease (SD) on RECIST 1.1 and PMR [Figure 2]. In patients who underwent 3 cycles, one patient showed SD on CT and DOTANOC PET, whereas other patient showed PMR on DOTANOC PET/CT, with partial regression in size. Among the remaining seven patients who received 1 cycle, five patients showed regression in size (PR) with interval regression in metabolic activity [Figure 3], whereas other two patients showed SD with regression in metabolic activity. Thus, 13/14 patients showed PMR, whereas on RECIST 1.1, five patients showed SD, and nine patients showed PR.

Dosimetric assessment

The mean absorbed dose to kidneys, spleen, liver, and lungs was 1.22 ± 0.64, 2.09 ± 6.71, 0.72 ± 0.50, and 0.03 ± 0.007 Gy, respectively, in IA PRRT treatment. The mean absorbed dose received by tumor site was 15.37 ± 13.64 Gy.

Discussion

Lu-177-DOTATATE significantly increases PFS and OS, with limited toxicity, compared to high-dose somatostatin analogs in patients with advanced stage NET.[2,6-9] However, patients with liver metastases have a significantly lower PFS,[2] and among those, patients with diffuse and bulky liver metastases have worse prognosis and lower disease control rate after treatment with PRRT,[4] which leaves room for further improvement of PRRT. The *post hoc* analysis of the NETTER-1 trial reported that the presence of bulky disease significantly limits median PFS after treatment with Lu-177-DOTATATE to 28 months, while the median PFS was not reached in 5 years of follow-up in patients with no bulky disease.[10] Hence, to increase the concentration of Lu-177-DOTATATE in intrahepatic tumors, IA administration has emerged as a relatively easy improvisation to the established PRRT regimen. There is high first-pass hepatic circulation of radiotracer, which leads to maximum saturation of SSTRs leading to higher dose delivery. This has resulted in higher dose deposition in liver lesions, thus sparing the normal liver parenchyma, as has been shown in a preclinical rat liver metastasis model by Pool *et al*.[11] Kratochwil *et al*.[12] demonstrated a strong first-pass effect of IA Ga-68-DOTATOC using dynamic PET imaging and it to IA use of therapeutic radio-isotopes 90Y-and 177 Lu-DOTATOC. This was objectively confirmed by Thakral *et al*.,[13] in a study of 29 patients, wherein the dose per activity to normal hepatic parenchyma was much lesser during IA

Table 2: Serum bilirubin and albumin levels at baseline and after IA peptide receptor radionuclide therapy

Patient number	Baseline		4 weeks (post 1#)		8 weeks (post 1#)		4 weeks (post 2#)		8 weeks (post 2#)	
	Total bilirubin	Albumin	Total bilirubin	Albumin	Total bilirubin	Albumin	Total bilirubin	Albumin	Total bilirubin	Albumin
1	0.3	4.09	0.25	4.15	0.34	4.3				
2	0.59	4.5	0.67	4.65	0.72	5.1	0.71	4.6	0.75	4.3
3	0.69	3.72	0.63	3.81	0.67	3.6				
4	0.47	4.22	0.5	4.19	0.52	4.2				
5	0.68	3.87	0.65	3.8	0.65	3.4				
6	0.72	3.77	0.75	3.95	0.76	3.7	0.77	3.7	0.56	3.5
7	0.41	4.16	0.45	4.3	0.44	4.4				
8	0.54	2.2	0.54	3.23	0.55	3.4	0.56	3.6	0.63	3.3
9	0.46	4.19	0.48	4.2	0.47	3.9				
10	1.54	2.8	1.23	2.9	0.86	3.2	0.77	3.9	0.78	3.7
11	0.72	4.28	0.54	3.48	0.76	3.6				
12	0.24	4.06	0.33	4	0.27	4.2				
13	1.42	3.1	1.12	3	0.95	3.3	0.87	4.1	0.79	4.1
14	0.89	3.67	0.15	3.5	0.71	3.5				

Patients 10 and 13 had deranged baseline bilirubin and albumin levels, which reverted to normal values over 2 cycles of IA PRRT. Patient 8 had low albumin level, which reverted to normal. IA PRRT: Intra-arterial peptide receptor radionuclide therapy

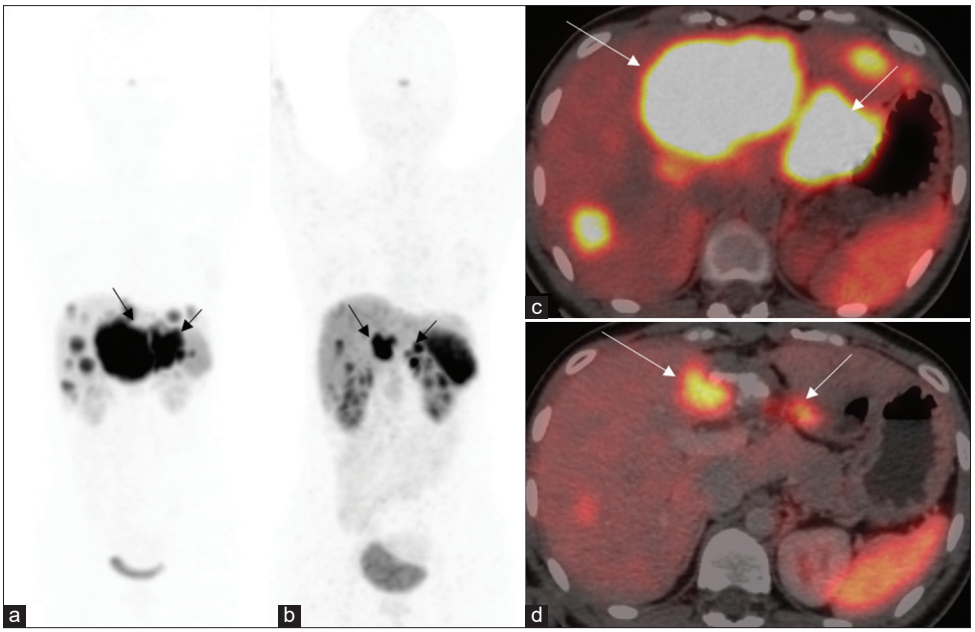

Figure 1: A 28-year-old female, case of WHO Grade 2 NET of liver with extensive disease involvement on baseline Ga-68 DOTATATE PET/CT, which shows bilateral lobar involvement, with dominant lesion in segments II (a and c: block arrow) and IVA (a and c: arrow) of liver and multiple focal liver lesions in rest of hepatic parenchyma. Two cycles of IA PRRT was administered. After 8 weeks following the 2nd cycle, Ga-68 DOTATATE PET/CT was performed. Compared to baseline, there is significant response seen in segment II (b and d-block arrow) and IV A (b and d: arrow) lesions. Also, there was complete metabolic regression in the majority of the focal liver lesions. Patient is now being considered for hepatic transplantation. PET/CT: Positron emission tomography/computed tomography, IA PRRT: Intra-arterial peptide receptor radionuclide therapy, NET: Neuroendocrine tumor

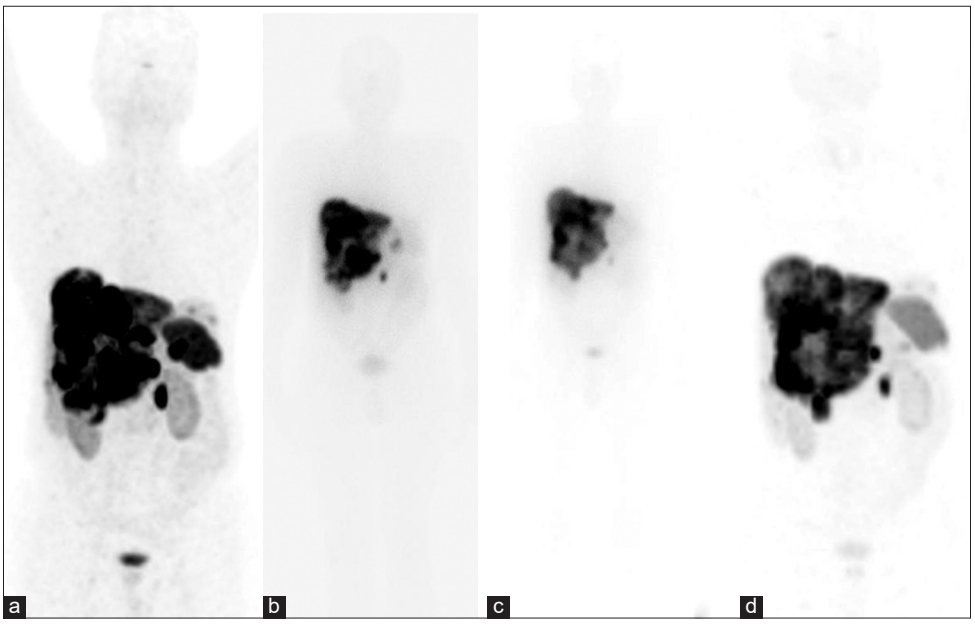

Figure 2: A 73-year-old male, case of WHO Grade 2 NET of pancreatic tail with large liver metastases involving both lobes of liver. Baseline Ga-68 DOTATATE PET/CT was done. MIP (a) shows intense tracer localisation in both lobes of liver. Patient received 2 cycles of IA PRRT. Anterior images of post therapy Lu-177 DOTATATE planar images following first (b) and second (c) cycles of IA PRRT shows visually appreciable reduction in intensity of tracer uptake on second posttherapy scan (c). This was confirmed on the MIP image of Ga-68 DOTATATE PET/CT (d). However, based on RECIST on EORTC criteria, it was interpreted as stable disease. Patient showed improvement in quality of life and with normal liver function parameters. PET/CT: Positron emission tomography/computed tomography, IA PRRT: Intra-arterial peptide receptor radionuclide therapy, NET: Neuroendocrine tumor, MIP: Maximum intensity projection

administration than IV administration. Although the technical studies have shown promise, this needs to translate into good treatment response and less toxicity. Hematologic toxicity is the most common adverse event and Grade 3–4 toxicity, most often thrombocytopenia, has been observed in 10%–15% of patients treated with PRRT. Studies have shown that the dose delivered to marrow is equivalent during IA and IV administration.[13] The fact that maximum dose delivery occurs

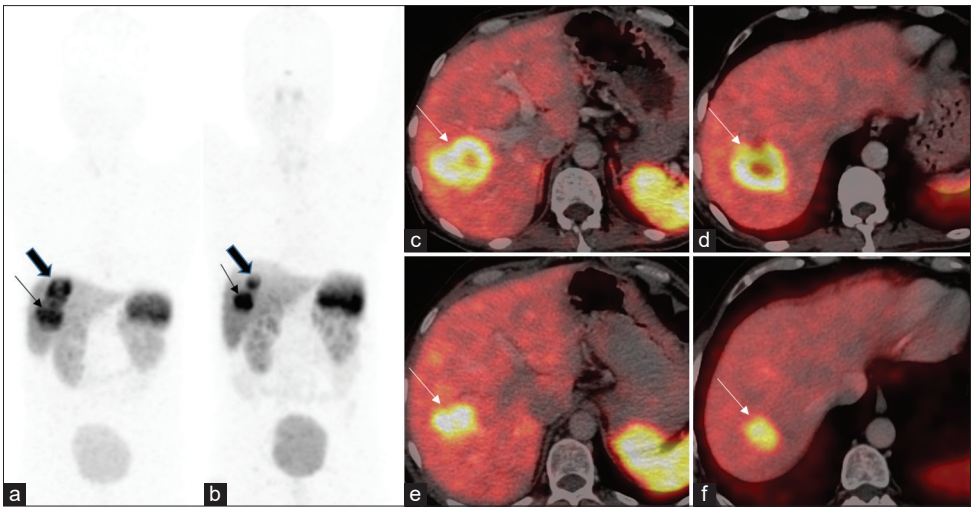

Figure 3: A 54-year-old male presented with two large discrete liver lesions, biopsy was suggestive of WHO Grade 1 NET. Baseline Ga-68 DOTATATE PET/CT showed two tracer avid lesions in segments VII (a: block arrow) and V (a: arrow) on MIP image, which was confirmed on axial PET/CT images (c and d: arrows). Patient was treated with 1 cycle of IA PRRT, and at 8 weeks, Ga-68 DOTATATE PET/CT was done for assessing response. MIP image (b: block arrow and arrow) shows reduction in extent and intensity of uptake in both lesions, which corresponded to reduction in size and metabolic activity of liver lesions (e and f). PET/CT: Positron emission tomography/computed tomography, IA PRRT: Intra-arterial peptide receptor radionuclide therapy, NET: Neuroendocrine tumor

in the liver, with minimal dose entering systemic circulation for localization in marrow, reduces the risk of potential hematotoxicity. One patient with platelet count of 86,000/m^3 had extensive hepatic tumor burden, with 3 lesions, 2 of which were more than 5 cm in size. Patients also had deranged total bilirubin and albumin levels; however, after receiving 2 cycles of IA PRRT, platelet counts increased to 112,000 and there was reduction in size and receptor expression in liver lesions. Moreover, the improvement in platelet count was due to significant reduction in liver disease burden. Kidneys are the critical organ for Lu-177-DOTATATE and hence there is a high chance of renal functional deterioration. Since the high tumor volume in liver consumed the maximum dose delivered and small dose entered systemic circulation and in turn reached the excretory pathway, neither the GFR nor EC clearance was affected. In three patients in whom GFR was reduced at 4 weeks after IA PRRT, the percentage reduction was 8%–10% of baseline value, which reverted to normal 4 weeks later. Acute reduction in creatinine levels is known with angiographic contrast, which often reverts to normal within 6–8 weeks, with hydration, which was eventually seen in both these patients.[14] It is interesting to note that the most common site of failure following PRRT was progression in liver metastases, as was seen in 31% of patients in the study by Rudisile *et al*.[15] If these lesions are targeted upfront with maximum dose delivery with IA PRRT, it can potentially lead to better outcomes. The inherent vascularity of tumor and large size of lesions are the two most important factors for high dose delivery to liver lesions. It has been shown that for the same administered activity, the tumor would absorb a radiation dose three times greater through transhepatic infusion than after IV administration. Most objective parameter for assessing dose delivery is tumor absorbed dose. Studies have shown that absorbed doses more than 100 Grays are necessary for objective treatment response.[16] Thakral *et al*.[13] demonstrated increased retention time of the tracer resulting in tumor absorbed radiation dose of 4.18 ± 5.6 mGy/MBq in the hepatic lesions treated with IA administration, which was significantly higher that the IV administration arm (2.68 ± 2.89 mGy/MBq). We thereby decided to look at early response on DOTA PET/CT as well as CT, and as we had expected, there was partial metabolic and morphological response seen in nine patients, with no documented progression at scans performed at 8 weeks following IA PRRT. The study has inherent limitations, one being the small patient cohort and other being the short duration of follow-up. This invasive approach to PRRT is being attempted at many centers recently; our study with its encouraging early results will further pave the way for it becoming the therapy for choice for liver-dominant metastatic NETs.

Conclusions

1. Selective liver-directed approach with IA PRRT delivers higher radiation dose to liver, and its early results have shown that there is no damage to normal liver parenchyma
2. In view of higher first-pass localization at tumor sites in the liver, early results have shown good response to treatment.

Authors contributions

- Ameya D Puranik: Concept, design, data analysis, manuscript writing
- Venkatesh Rangarajan: Concept and design
- Nitin S Shetty, Kunal Gala, Suyash Kulkarni: Interventional procedure of intra-arterial PRRT
- Shailesh V Shrikhande, Vikram Chaudhari, Manish Bhandare: Neuroendocrine tumor clinic-clinical assessment and referral

- Ashish Mohite, Mandar Marotkar, Yogesh Gawale, Indraja D Dev, Suchismita Ghosh: PRRT Procedure – Patient preparation, dosimetric evaluation, data collection and patient scanning protocols following IA PRRT
- Anant Ramaswamy, Vikas Ostwal: Neuroendocrine tumor clinic-clinical assessment and patient follow-up
- Archi Agrawal, Sneha Shah, Sayak Choudhury, Nilendu C Purandare: Scan Interpretation following IA PRRT, and interpretation using RECIST 1.1 and EORTC criteria.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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