European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:691–694
https://doi.org/10.1007/s00259-023-06576-8

EDITORIAL

Treatment response assessment in transthyretin-related cardiac amyloidosis: an emerging clinical indication of bone-seeking radiopharmaceuticals?

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Published online: 19 December 2023

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a severe and progressive restrictive infiltrative cardiomyopathy caused by the deposition of misfolded amyloid fibrils in the myocardium. Cardiac SPECT or SPECT/CT using ^{99m}Tc-radiolabeled bone-seeking radiopharmaceuticals complements echocardiography and cardiac magnetic resonance and has revolutionized the management of patients with suspected ATTR-CM. In particular, cardiac SPECT with bone-seeking radiopharmaceuticals allows to obtain a non-biopsy diagnosis of ATTR-CM with high accuracy if a plasma cell dyscrasia is excluded according to current international guidelines [1–5]. The possibility of reaching the diagnosis of ATTR-CM diagnoses non-invasively and the increased awareness of physicians of clinical and imaging "red flags" associated with ATTR-CM in recent years have resulted into a substantial increase in the number of patients diagnosed with ATTR-CM. Patients with ATTR-CM are now diagnosed earlier in the disease process and benefit from improved outcome thanks to the development of new treatments [6, 7].

Furthermore, incidental myocardial uptake of bone-seeking radiopharmaceuticals for non-cardiac indications is present in a not negligible percentage of cases, necessitating further clinical investigations for cardiac amyloidosis, which contributes to the early diagnosis of this condition [8].

Beyond the well-established role of SPECT or SPECT/CT with bone-seeking radiopharmaceuticals for the diagnosis of ATTR-CM, several recent studies evaluated the possible role of bone-avid scintigraphy in evaluating treatment response in ATTR-CM (Table 1) [9–16]. The introduction of novel therapies aimed to either silence TTR production or stabilize TTR has shown to reduce heart failure hospitalizations and to improve clinical outcome in ATTR-CM patients [17]. The increasing availability of novel ATTR-targeted treatments concurs with a growing interest for early quantitative markers to assess treatment response in ATTR-CM. There are currently no specific biomarkers to directly assess early response to targeted ATTR treatments and SPECT or SPECT/CT with bone-seeking radiopharmaceuticals could fill this gap by providing (semi-)quantitative estimates.

The recent article published by Tingen and co-authors is the last published study on serial bone-seeking tracer cardiac planar scintigraphy or SPECT before and after treatment with TTR gene silencers or TTR-stabilizers for ATTR-CM [16]. The authors demonstrated that changes in the intensity of myocardial uptake of bone-seeking tracers after treatment differed significantly between ATTR-CM patients treated with TTR gene silencers and those treated with TTR-stabilizers. As a matter of fact, during treatment with a TTR gene silencer (Patisiran), a median decrease in heart-to-whole

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Table 1 Clinical studies about the role of scintigraphy with bone-seeking radiopharmaceuticals in treatment response monitoring in patients with ATTR-CM (case reports are not reported)

Authors	Publication year	Country	Bone-seeking radiopharmaceutical/scintigraphic imaging acquisition	No. of ATTR-CM treated patients and timing of treatment response assessment	Main findings
Fontana et al. [9]	2021	UK	[^{99m}Tc]Tc-DPD/planar, SPECT, and SPECT/CT	16 patients evaluated at 1 year after treatment with Patisiran	Reduction in cardiac uptake of [^{99m}Tc]Tc-DPD (expressed as percentage of the injected dose) of 19.6% (IQR, 9.8 to 27.1%) was reported in 15/16 (94%) treated patients and the remaining patient showed no change.
Doumas et al. [10]	2022	Greece	[^{99m}Tc]Tc-DPD or [^{99m}Tc]Tc-HMDP/planar and SPECT	5 patients evaluated at 1 year after treatment with Tafamidis	Reduction in cardiac uptake of [^{99m}Tc]Tc-DPD (expressed as heart-to-thigh uptake ratio) was shown in 4/5 (80%) treated patients The patient evaluated by [^{99m}Tc]Tc-HMDP exhibited minimal cardiac uptake reduction.
Lee et al. [11]	2023	Taiwan	[^{99m}Tc]Tc-PYP/planar, SPECT, and SPECT/CT	3 patients evaluated at a median time of 1043 days after treatment with Tafamidis	Reduction in cardiac uptake of [^{99m}Tc]Tc-PYP (expressed as heart-to-contralateral lung uptake ratio) was observed in 3/3 (100%) treated patients.
Papathanasiou et al. [12]	2023	Germany	[^{99m}Tc]Tc-DPD/planar, SPECT, and SPECT/CT	14 patients evaluated at a median time of 44 months after treatment with Tafamidis	Reduction in cardiac uptake of [^{99m}Tc]Tc-DPD (expressed as heart-to-contralateral lung uptake ratio or SUVmax) was shown in the majority of treated patients (from 77 to 86% based on the index used). Regression of Perugini visual score was observed in 5/14 (36%) treated patients, whereas it was unchanged in 9/14 (64%) patients.
Rettl et al. [13]	2023	Austria	[^{99m}Tc]Tc-DPD/planar, SPECT, and SPECT/CT	40 patients evaluated at a median time of 9 months after treatment with Tafamidis	Reduction in cardiac uptake of [^{99m}Tc]Tc-DPD (expressed as SUV retention index) was shown in the majority of treated patients.
Rettl et al. [14]	2023	Austria	[^{99m}Tc]Tc-DPD/planar, SPECT, and SPECT/CT	9 patients evaluated at 12 months after treatment with Patisiran or Inotersen	Reduction in cardiac uptake of [^{99m}Tc]Tc-DPD (expressed as SUV retention index) was observed in the majority of treated patients (78%).
Garcia-Pavia et al. [15]	2023	Different countries	Not reported	40 patients evaluated at 4 and 12 months after infusions of either an experimental antibody (NI006) or placebo	In patients treated with NI006, the median cardiac uptake of bone-seeking radiopharmaceuticals (expressed as heart-to-whole body ratio) decreased after treatment whereas the same value increased in patients treated with placebo.

Table 1 (continued)

Authors	Publication year	Country	Bone-seeking radiopharmaceutical/scintigraphic imaging acquisition	No. of ATTR-CM treated patients and timing of treatment response assessment	Main findings
Tingen et al. [16]	2023	Netherlands	[^{99m}Tc]Tc-HDP/planar and SPECT	20 patients evaluated at 29 months after treatment with Patisiran and 12 patients evaluated at 24 months after treatment with TTR-stabilizer	In patients treated with Patisiran, the median cardiac uptake of [^{99m}Tc]Tc-HDP (expressed as heart-to-whole body ratio) decreased after treatment whereas the same value increased after treatment in patients treated with a TTR-stabilizer.

Legend: *SUV* standardized uptake value, *PYP* pyrophosphate, *DPD* 3,3-diphosphono-1,2-propanodicarboxylic acid, *HMDP* hydroxymethylene diphosphonate, *HDP* hydroxydiphosphonate, *[^{99m}Tc]Tc* Technetium-99m, *SPECT* single-photon emission computed tomography, *CT* computed tomography, *TTR* transthyretin, *ATTR-CM* transthyretin amyloid cardiomyopathy

body (H/WB) uptake ratio of − 0.58 was observed, whereas an increase of + 0.38 was observed in patients treated with a TTR-stabilizer (Tafamidis) [16]. Conversely, NYHA class, cardiac biomarkers, and parameters on echocardiography did not change significantly during treatment in both groups. These results suggest that myocardial uptake of bone-seeking radiopharmaceuticals may help detect at an earlier stage the impact of treatment on disease progression as compared to conventional follow-up parameters used in ATTR-CM patients, confirming the findings of previous studies [8–14].

However, several key questions remain to be elucidated when using bone-seeking tracer cardiac scintigraphy in ATTR-CM. First of all, the exact binding mechanism of these tracers (DPD, PYP, and HMDP) is unclear and several mechanisms have been proposed such as binding to microcalcifications and to components of the interstitium or amyloid-associated molecules [18]. As long as the binding mechanism is not completely identified, it remains difficult to consider changes in the intensity of myocardial uptake of these tracers directly correlated to the evolution of the amyloid load. The study by Fontana et al. showed that a decrease in cardiac uptake was associated with a decrease in extracellular volume on cardiac magnetic resonance imaging, but without changes in echocardiographic parameters [9]. Recently, Rettl et al. reported an improvement in CMR-derived left ventricular ejection fraction in the patient cohort with a significant improvement in tracer retention index [13]. The study by Tingen et al. also demonstrated a reduction in the H/WB ratio without concomitant changes on echocardiography [16]. Of note, only patients with mixed variant ATTR polyneuropathy and cardiomyopathy were included in this study, which may explain differences in outcome compared to previous studies. Indeed, patients were treated with 20 mg Tafamidis as opposed to 61 mg daily for the indication of cardiomyopathy (mainly in wild-type ATTR-CM). It is yet to be elucidated whether variant disease and wild-type disease behave and respond similar to the type of treatment. Nevertheless, all studies hint towards the hypothesis that molecular and structural changes precede alteration in myocardial contraction.

Secondly, what is the best parameter to evaluate serial changes on bone-seeking tracer cardiac scintigraphy in ATTR-CM? Even if changes of cardiac tracer uptake may be detected also visually on planar or SPECT images, they are not recommended because of their non-quantitative and subjective nature. The available studies on treatment response assessment of ATTR-CM with bone-seeking radiopharmaceuticals have used both semi-quantitative and quantitative estimates of myocardial tracer uptake (Table 1). To this regard, quantification through SPECT/CT in ATTR-CM should be preferred and different metrics have been proposed such as SUVmax, SUV retention index, or % injected activity [19]. However, no data are available on test-retest

measurement variability, which is crucial to distinguish a clinically significant change in myocardial tracer uptake/retention from measurement variability.

Overall, the recently published studies show the potential of scintigraphy, SPECT, or preferably SPECT/CT with bone-seeking radiopharmaceuticals in assessing another domain of response during treatment of ATTR-CM patients. Beyond existing therapies, next-generation ATTR-targeted and fibril-directed therapies will most likely result in more significant changes in amyloid burden, hence improvements in cardiac function. Therefore, it is expected that the role of quantitative imaging to assess treatment response will continue to increase, but the clinical impact of bone-seeking radiopharmaceuticals in monitoring ATTR-CM warrants further studies before it becomes a well-established tool in the management of ATTR-CM and part of the updated expert consensus recommendations [20].

Author contribution All authors contributed to the manuscript writing. All authors read and approved the final manuscript.

Declarations

Competing interests OG received fees for consulting: Pfizer.

AM received research grants from Pfizer, Ionis, Attralus, and Cytokinetics. Personal fees for consulting and steering committee membership from Cytokinetics, BMS, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Haya, BioMarin, Alexion, and Tenaya.
SD received research grants from Pfizer, Attralus, Siemens, and Philips and fees for consulting from Pfizer, Novo Nordisk, and AstraZeneca/Alexion.
GT and FH have no competing interests.

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