Regression of Bone-Tracer Uptake in Cardiac Transthyretin Amyloidosis

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Published in:
Mayo clinic proceedings

DOI:
10.1016/j.mayocp.2019.10.036

Publication date:
2020

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To The Editor: Hereditary transthyretin (ATTRv) amyloidosis is a progressive disease caused by mutations in the transthyretin (*TTR*) gene.[1] Bone scintigraphy is recognized as a useful noninvasive diagnostic modality for cardiac involvement in ATTR amyloidosis.[2] However, its utility in evaluating treatment efficacy remains undetermined.[3] We report on the use of ^{99m}Tc-labeled hydroxymethylene diphosphonate bone scintigraphy to evaluate treatment efficacy in a patient with ATTRv amyloidosis in whom serum TTR levels were effectively reduced by gene-silencing.

A 68-year-old white man was diagnosed with ATTRv amyloidosis, caused by the *TTR* p.Val50Met variant, in September 2009. Echocardiography did not suggest cardiac involvement (mean left-ventricular wall thickness measured 9 mm, interventricular septum 10

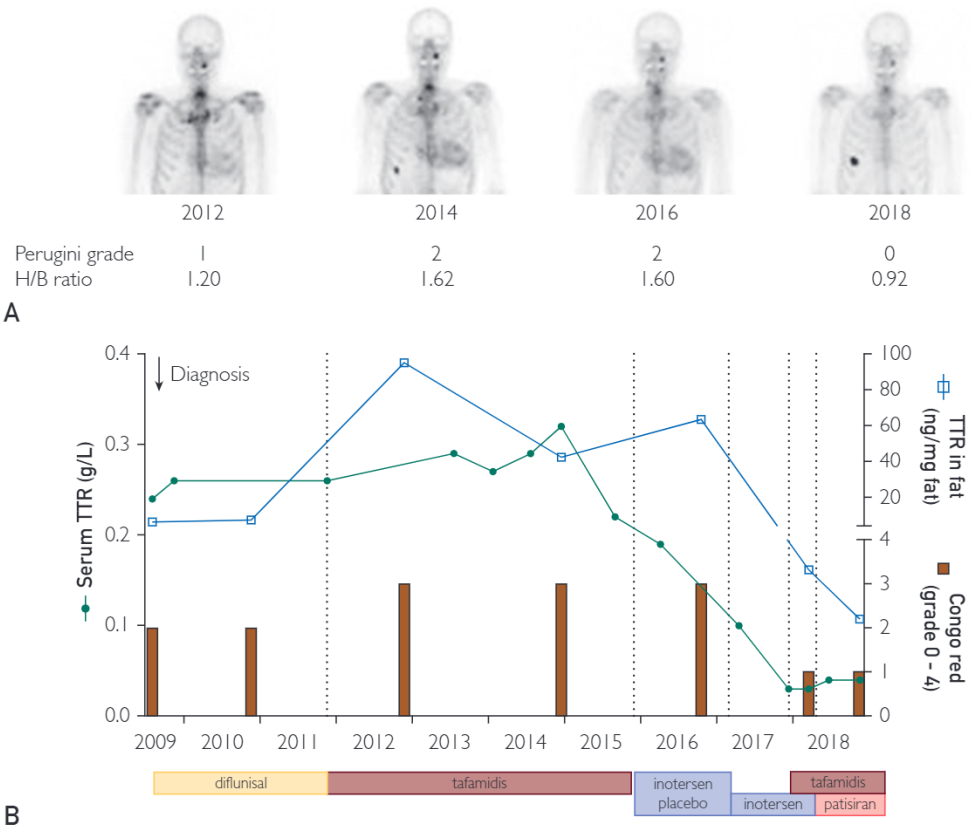

FIGURE. Assessment of cardiac involvement with bone scintigraphy and laboratory parameters during treatment with gene-silencing. **A,** Bone scintigraphy demonstrating increased cardiac ^{99m}Tc-labeled hydroxymethylene diphosphonate uptake, grade 1, according to Perugini[2] (2012). Follow-up revealed a visible increase in myocardial tracer uptake on consecutive scans in 2014 (grade 2) and 2016 (grade 2). After 21 months of treatment with gene-silencing therapeutics, a normalized cardiac pattern was observed in 2018, without bone-tracer uptake (grade 0). Of note, there was a costal fracture on the right side (2014 and 2018). In all images, the heart-to-background (H/B) ratio was calculated by placing regions of interest over the heart and ribs, after which the average of counts for each region of interest were established. **B,** Course of laboratory parameters before and during treatment with gene-silencing therapeutics. Serum transthyretin (TTR) levels as well as the grade of amyloid deposition and the corresponding TTR concentrations in adipose tissue biopsies are shown. Subcutaneous abdominal adipose tissue samples were stained with alkaline Congo red and semiquantitatively graded: 0 (negative, no amyloid), 1+ (minute, <1% of inspected area), 2+ (little, 1% to 10%), 3+ (moderate, 10% to 60%), 4+ (abundant, >60%). The quantitative amount of TTR was measured using an enzyme-linked immunosorbent assay, with non-ATTR amyloid reference values <7 ng TTR/mg wet adipose tissue. Treatment periods are shown on the bottom legend. The vertical dotted lines indicate the start of a different treatment.

mm, left-ventricular posterior wall 8 mm). TTR-stabilizing treatment was started, and he returned to our center every 6 months.

In November 2012, bone scintigraphy showed moderate myocardial tracer uptake (grade 1)[2] (Figure), indicating cardiac involvement, despite absence of substantial changes on echocardiography compared with 2009. However, in December 2014, echocardiography revealed diastolic dysfunction, thickening and sparkling of the interventricular septum (13 mm), and left-ventricular posterior wall (13 mm) and cardiac bone-tracer uptake had also increased (grade 2) (Figure), confirming progression of cardiac involvement. A subsequent bone scintigraphy in December 2015 still demonstrated marked cardiac radiotracer uptake (grade 2) (Figure). At that moment, the patient enrolled in a TTR gene-silencing study of inotersen in ATTRv amyloidosis (NCT01737398),[4] during which TTR-stabilizing treatment was discontinued. Considered in retrospect, the patient received placebo. In March 2017, the patient continued in the open-label extension study (NCT03400098) and received the active compound. Serum TTR levels consequently decreased (Figure). In December 2017, TTR-stabilizing treatment was resumed. In April 2018, inotersen was discontinued, and treatment with patisiran was started upon the patient's request. After 14 months of inotersen and 7 months of patisiran, cardiac bone-tracer uptake had completely disappeared (grade 0) (Figure). Echocardiography revealed that thickness of both the interventricular septum and the left-ventricular posterior wall had decreased 1 mm and 3 mm, respectively, compared with 2014. Moreover, ATTR amyloid deposition in abdominal adipose tissue had decreased from grade 3+ (64 ng TTR/mg tissue) before the start of gene-silencing therapy to grade 1+ (2 ng TTR/mg tissue). Patient's complaints had disappeared, and overall status had improved.

Our findings agree with recent evidence showing improved echocardiographic parameters after treatment with patisiran.[5] More importantly, they extend previous literature by demonstrating that effective reduction of serum TTR levels by means of gene-silencing may reverse the formerly inexorably progressive amyloid deposition seen in ATTR amyloidosis, as shown by the regression of cardiac radiotracer uptake on bone scintigraphy and the substantial reduction of ATTR amyloid deposition in subcutaneous adipose tissue. As signs of cardiac involvement on bone scintigraphy preluded confirmation by echocardiography, we propose that bone scintigraphy be investigated in a long-term study for monitoring disease status and treatment efficacy in patients with cardiac ATTR amyloidosis.

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Potential Competing Interests: Drs. Nienhuis and Hazenberg have received consultancy fees from Pfizer and Alnylam. The other authors report no competing interests.

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