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GRAND ROUND
Cardiac imaging

Genome silencer therapy leading to 'regression' of cardiac amyloid load on cardiovascular magnetic resonance: a case report

Anca Florian [1], Michael Bietenbeck[1], Anna Hüsing-Kabar[2], Matthias Schilling[3], Hartmut H. Schmidt[2], and Ali Yilmaz[1]*

[1]Department of Cardiology I, Division of Cardiovascular Imaging, University Hospital Münster, Albert-Schweitzer-Campus 1, Building A1, 48149 Münster, Germany; [2]Department of Gastroenterology/Hepatology, University Hospital Münster, Münster, Germany; and [3]Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Germany

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Background Hereditary or variant transthyretin amyloidosis (ATTRv) is a progressive disease manifesting with neuropathy and/or cardiomyopathy. An early and accurate diagnosis of cardiac amyloidosis is a pre-requisite for timely and appropriate patient management, including anti-amyloid therapies, as it is associated with heart failure, conduction disease, and arrhythmias, leading to reduced quality of life and early death.

Case Summary We present the case of an ATTRv male patient presenting with a mixed amyloidosis phenotype (neuropathy and cardiomyopathy). Cardiac disease manifestation comprised tachyarrhythmias (atrial fibrillation) and conduction abnormalities (atrio-ventricular block) in addition to segmental left ventricular (LV) hypertrophy (septal wall) due to regionally pronounced amyloid deposits in the basal LV myocardium. Interestingly, by means of serial cardiovascular magnetic resonance (CMR) studies, we were able to demonstrate an impressive and unexpected improvement of cardiomyopathy findings within a relatively short period-of-time after the implementation of genome-silencer therapies.

Discussion This is our second case report that showed ATTRv cardiomyopathy reversal under anti-amyloid therapy—documented by multi-parametric CMR. Our findings support the hypothesis that amyloid infiltration leading to cardiomyopathy is not an irreversible pathological process—but rather a dynamic one, that cannot only be stopped but even reversed (to a certain degree) by currently emerging anti-amyloid therapies. Moreover, the role of serial multi-parametric CMR imaging for surveillance of cardiomyopathy dynamics under these therapies is nicely illustrated.

Keywords ATTR • Amyloidosis • CMR • Case report • LGE • Patisiran • Inotersen

* Corresponding author. Tel: +49-251-83-45185, Fax: +49-251-83-48143, Email: ali.yilmaz@ukmuenster.de
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Learning points

- In a patient at high risk for developing cardiac amyloidosis (e.g. carrier of pathogenic mutations in the transthyretin gene), a definitive diagnosis can usually be achieved non-invasively using imaging techniques such as multi-parametric cardiovascular magnetic resonance (CMR).
- In the era of anti-amyloid—disease-modifying—therapies, serial multi-parametric CMR, including late gadolinium enhancement and T1-mapping techniques, plays an important role not only in the early diagnosis but also in the surveillance of amyloid cardiomyopathy progression.
- Currently emerging anti-amyloid therapies might have the potential not only to stop but even to reverse (to a certain degree) the pathological process of amyloid infiltration leading to cardiomyopathy.

Primary specialties involved other than cardiology

Internal medicine, Hepatology, Neurology

Introduction

Hereditary or variant transthyretin amyloidosis (ATTRv) is an autosomal dominant, multi-systemic disease manifesting with progressive neuropathy and/or cardiomyopathy. Over 130 pathogenic mutations in the gene that encodes transthyretin (TTR) have been identified so far. Accordingly, ATTRv is characterized by a large phenotypic heterogeneity regarding onset, organ involvement, and progression.[1]

Hereditary ATTR-associated cardiomyopathy usually presents with a hypertrophic/restrictive phenotype, conduction disease, and arrhythmias leading to heart failure, reduced quality of life and death.[2] An early and accurate diagnosis of cardiac amyloidosis is a prerequisite for timely and appropriate patient management, including already available as well as upcoming anti-amyloid therapies.[3]

Case presentation

We report the case of a 53-year-old male with ATTRv amyloidosis. A heterozygote mutation in the transthyretin gene (p.Gly67Ala) was known in his family and also confirmed in his case 17 years before. At the index time-point (September 2020), he presented to our outpatient clinic for follow-up cardiac evaluation due to known ATTRv cardiomyopathy.

The patient had been suffering from a slowly progressive polyneuropathy for the past 8 years, for which he received therapy with tafamidis for 82 months (February 2012 to October 2018), followed by inotersen (November 2018 to May 2019). Since neuropathic symptoms did not change during inotersen therapy, starting in June 2019 and continuing until present, the patient was treated with patisiran. Already in August 2017, the patient had been listed for liver transplantation (LTx). In addition, the patient suffered from bilateral carpal tunnel syndrome. The patient had no other past medical history and had as a unique cardiovascular risk factor, active smoking (30 pack-years).

Regarding cardiac history, over the years no special cardiac symptoms were recorded. Annually performed transthoracic echocardiography (2013–18) had shown slightly progressive LV hypertrophy,

Timeline

2003	**Heterozygote pathologic mutation in the transthyretin gene (p.Gly67Ala) confirmed.**
2012	Onset of variant transthyretin amyloidosis (ATTRv) neuropathy symptoms.
February 2012 to October 2018	Tafamidis therapy for neuropathy.
2013–18	Annually repeated transthoracic echocardiography depicting progressive septal left ventricular (LV) hypertrophy and mild diastolic dysfunction.
2017–18	Cardiovascular magnetic resonance (CMR) depicting non-ischaemic late gadolinium enhancement in the septum and basal LV myocardium suggestive of cardiac amyloidosis.
November 2018 to May 2019	Inotersen therapy for neuropathy.
June 2019—Present	Patisiran therapy for neuropathy.
July 2019	Occurrence of symptomatic, paroxysmal, tachycardic atrial fibrillation.
July 2019	Repeated CMR (with vasodilalator–stress perfusion) showing no progression of cardiomyopathy and excluding myocardial ischaemia. No coronary stenosis on invasive angiography.
July 2019	Implantation of a dual-chamber, MRI-conditional pacemaker (Medtronic Ensura DR MRI) due to a marked first-degree atrio-ventricular block (AV-block) (PQ interval up to 500 ms) with intermittent second-degree AV-block (2:1 conduction) under beta-blocker therapy.
September 2020 (Present)	Index cardiac evaluation, including CMR showing a relatively accelerated and unexpected improvement of cardiomyopathy findings.

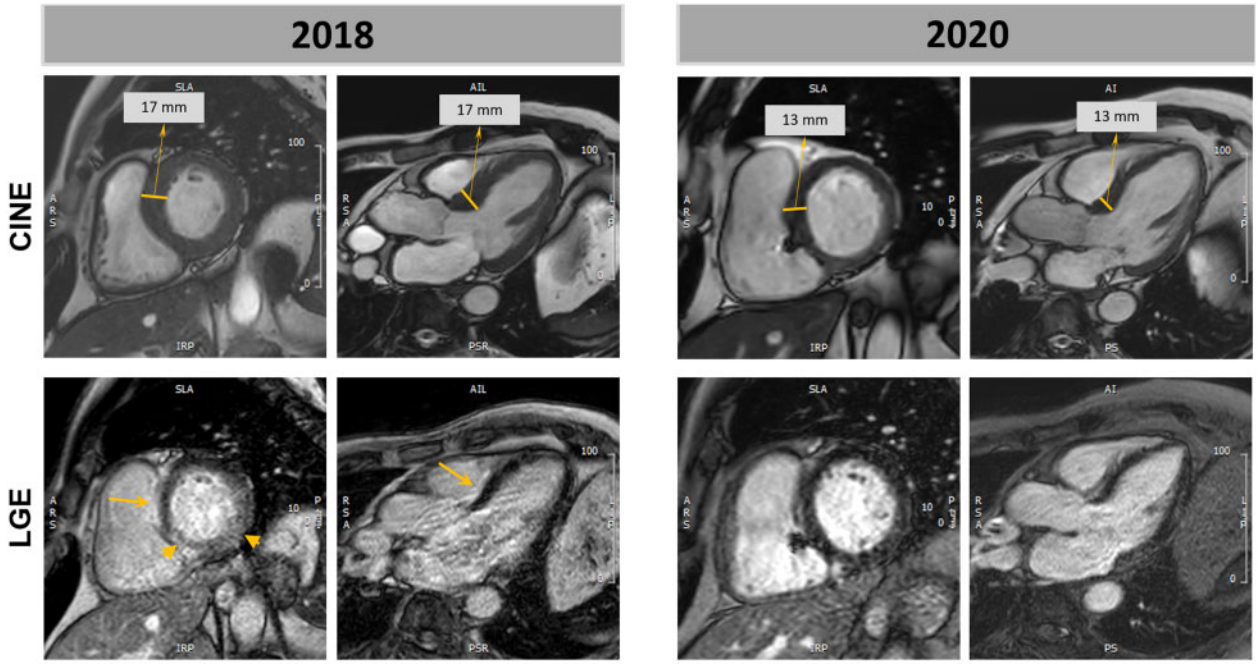
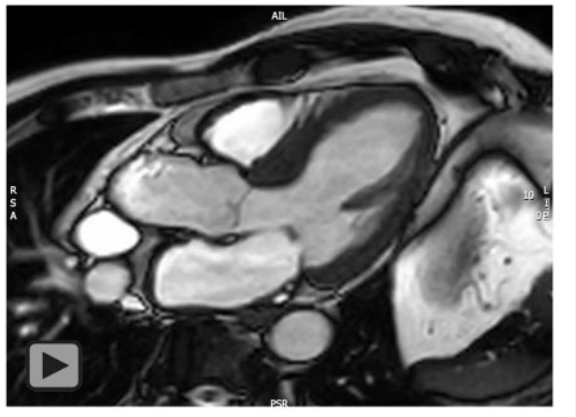
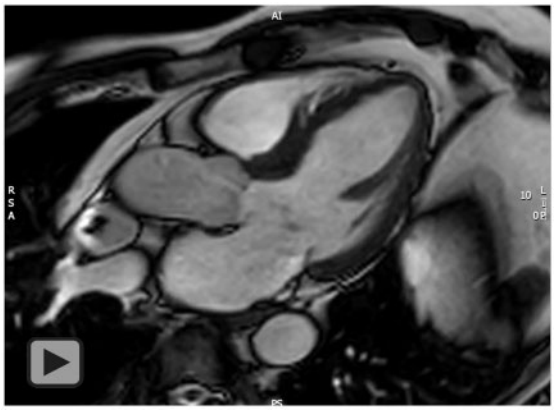


Figure 1 End-diastolic cine (upper panels) and late gadolinium enhancement (lower panels) cardiovascular magnetic resonance images in basal short-axis and three-chamber views acquired in 2018 and at present evaluation (2020). In 2018, marked septal hypertrophy (max. 17 mm) as well as non-ischaemic late gadolinium enhancement, with a sub-epicardial distribution in the basal antero-septum (arrows) together with a diffuse, intramural late gadolinium enhancement in the basal inferoseptal, inferior and inferolateral segments (arrow heads) can be seen. At present evaluation, an obvious decrease in the extent of hypertrophy (max. 13 mm) as well of late gadolinium enhancement is noted together with a pace-maker lead in the right ventricle.



Video 1 Cine CMR loop in three-chamber view acquired in 2018 showing septal hypertrophy and a non-dilated, normokinetic left ventricle.



Video 2 Cine CMR loop in three-chamber view acquired at present time (2020) showing regression of septal hypertrophy.

predominantly involving the basal septum (max. thickness: 14 mm in 2013 and increase to 16 mm in 2017 and 17 mm in 2018), normal left ventricular ejection fraction (LVEF) and mild diastolic dysfunction without signs of increased filling pressures, including no atrial dilatation. Subsequently, repeated cardiovascular magnetic resonance (CMR) studies (2017 and 2018)—at that time still on tafamidis therapy—had shown a non-ischaemic pattern of late gadolinium enhancement (LGE) with a sub-epicardial distribution in the basal and mid-ventricular septal wall and a rather diffuse, intramural LGE in the basal inferior and inferolateral segments (*Figure 1*, Supplementary material online, *Video S2*). In addition, septal hypertrophy (max. 17 mm) with a non-dilated, normokinetic LV could be confirmed (*Videos 1* and *3*). Natriuretic peptide concentration at the time of second

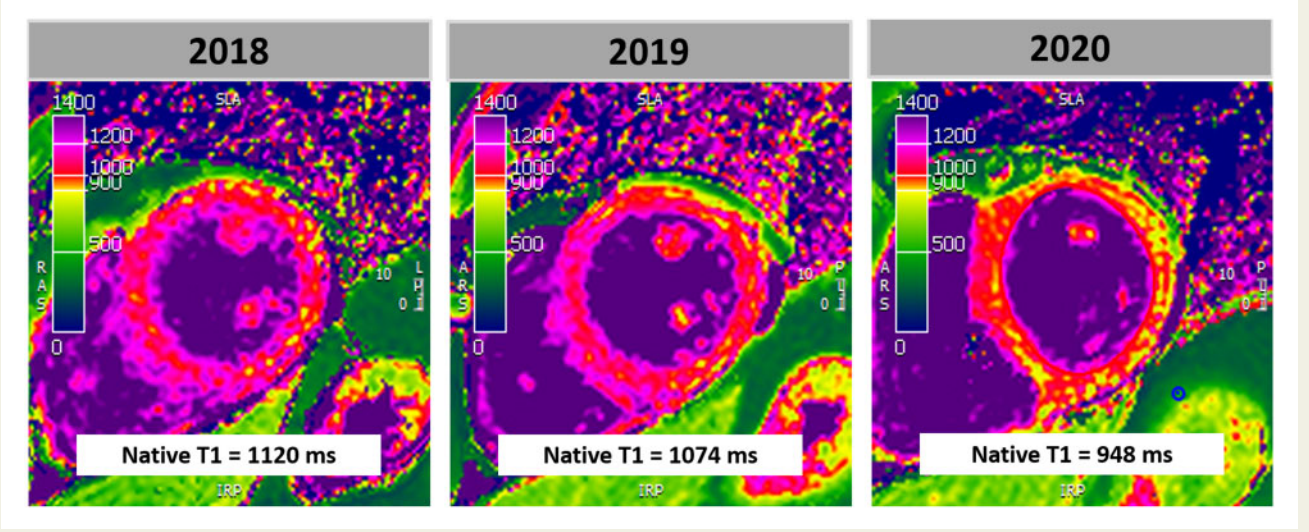
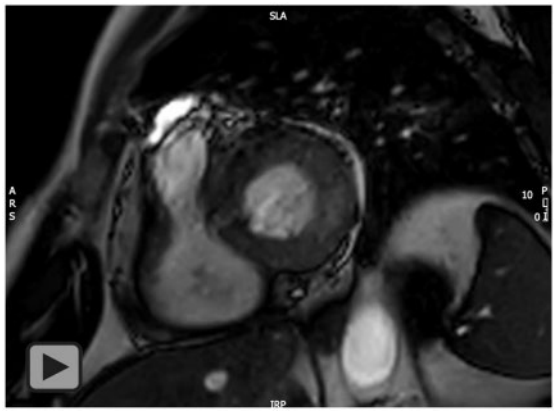


Figure 2 Native T1 maps in mid-ventricular short-axis view acquired in 2018, 2019, and at present evaluation (2020). An elevated averaged native myocardial T1 time for the whole slice was measured in 2018 with normalization in 2020.



Video 3 Cine CMR loop in a basal short-axis view, acquired in 2018, showing septal hypertrophy and normal systolic function.

CMR (2018) was only slightly elevated [N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) = 191 pg/mL, normal < 172 pg/mL].

In July 2019, after the patient had started complaining of palpitations accompanied by dyspnoea, paroxysmal tachycardic atrial fibrillation was diagnosed. In the same month, a dual-chamber, MRI-conditional pace-maker (Medtronic Ensura DR MRI) was implanted due to a marked first-degree atrio-ventricular block (AV-block) (PQ interval up to 500 ms) with intermittent second-degree AV-block (2:1 conduction) under beta-blocker therapy. Repeated CMR before implantation excluded myocardial ischaemia (hyperaemic stress) as well as a progression of cardiomyopathy. At the same time, invasive coronary angiography revealed coronary plaques without relevant stenoses.

At the present cardiac examination, the patient was in good general condition, fully mobile, and without any overt cardiac symptoms. He had stopped smoking and started exercising with improved endurance and muscle strength. Besides ATTRv disease-modifying therapy (patisiran), current medication comprised a beta-blocker (bisoprolol, 2.5 mg o.d.), a diuretic (torasemide, 5 mg o.d.), a statin (simvastatin, 20 mg o.d.), and aspirin (100 mg o.d.). Clinical examination of the cardiovascular system was unremarkable. No signs of systemic or lung congestion were present. Twelve-lead resting electrocardiogram showed sinus rhythm (70 b.p.m.), first-degree AV-block (PQ interval 300 ms), with no further abnormalities (QRS duration 80 ms; QRS axis 60°; QTc 420 ms). No overt low QRS voltage in the limb leads (<5 mm) was present. Pacemaker interrogation revealed a very low pacing activity (<1%), intermittent second-degree AV-block with no further recorded arrhythmias. Repeated transthoracic echocardiography showed an unclear reduction in LV hypertrophy with no relevant change in the other, above-mentioned parameters. Blood analysis was unremarkable, with normal natriuretic peptide levels (NT-proBNP = 73 pg/mL).

For a more detailed assessment of potential cardiac disease progression, follow-up CMR was performed. Surprisingly, when compared to the examinations from the previous years, the current study revealed a regression of the aforementioned septal LV hypertrophy (from max. 17 mm to 13 mm) with a consecutive decrease in absolute (161–129 g) and indexed (76–59 g/m^2) LV mass and constantly preserved biventricular systolic function (LVEF 65%; right ventricular ejection fraction 61%) (*Figure 1*, *Video 2*, Supplementary material online, *Video S1*). In addition, there was an improvement in feature-tracking based global peak longitudinal strain in comparison to 2018 (-13% to -17%). Most surprisingly, in the post-contrast sequences, there was a clear decrease in the extent of the aforementioned LGE pattern—most impressive in the basal myocardial segments, particularly in the anteroseptal wall—when compared to previous studies from 2018 to 2019 (Supplementary material online, *Video S3*). Moreover, T1-mapping images revealed a marked decrease in the myocardial native T1-time in comparison to 2018 (1120–948 ms), as

measured in the mid-ventricular short-axis slice (*Figure 2*). Considering this improvement in the ATTRv disease course, the present medication was continued and further periodic cardiological follow-up studies including regular pacemaker controls were scheduled.

At the last available follow-up (April 2021), the patient was feeling well, exercising regularly, and was free of cardiac symptoms. Cardiovascular evaluation showed no changes. He recently had undergone bilateral carpal tunnel surgery with consecutive relief of his respective symptoms. Neurological evaluation showed stable polyneuropathy findings.

Discussion

In this report, we describe the case of a ATTRv patient presenting with a mixed phenotype (neuropathy and cardiomyopathy). Cardiac disease manifestation comprised tachyarrhythmias (atrial fibrillation) and conduction abnormalities (AV-block) in addition to segmental LV hypertrophy (septal wall) due to regionally pronounced amyloid deposits in the basal LV myocardium. Interestingly, by means of serial CMR studies, we were able to demonstrate an impressive and unexpected improvement of cardiomyopathy findings within a relatively short period-of-time after implementation of genome-silencer therapies (inotersen and patisiran).

In a patient at risk for cardiac amyloidosis (e.g. ATTRv), a definitive diagnosis can usually be achieved non-invasively through the use of imaging techniques, such as bone scintigraphy and/or multiparametric CMR.[3,4] In the present case, after cardiac amyloidosis was suspected on transthoracic echocardiography, CMR was further performed—due to its unique tissue characterization capabilities—in order to confirm the diagnosis and assess the extent of cardiac amyloid load.[5] On CMR, typical LGE patterns of cardiac amyloidosis include diffuse sub-endocardial as well as sub-epi- and sub-endocardial septal hyperenhancement with a dark mid-wall (zebra pattern). With more advanced amyloid infiltration, a progression to transmural and/or global hyperenhancement patterns can be seen on LGE images.[5,6] Importantly, the presence of LGE is a strong predictor of mortality in cardiac amyloidosis, with transmural LGE carrying the worst prognosis.[6] In our patient, the pattern of LGE initially depicted was rather atypical, with limited, non-transmural extension (only basal LV myocardium), suggesting an early stage of cardiomyopathy that was also supported by asymmetric hypertrophy of the septal wall and only mild diastolic dysfunction on echocardiography. In addition, parametric T1-mapping with extracellular volume fraction (ECV) quantification has recently evolved as a powerful diagnostic and prognostic tool in cardiac amyloidosis, with the potential to elegantly quantify the absolute extent of myocardial amyloid load and to longitudinally monitor disease progression.[6,7] Hence, in our patient, the regression of LGE was paralleled by a relevant decrease in myocardial native T1-time, from a pathologic value (>1100 ms) to a normal one (between 900 and 1000 ms).[8]

Remarkably, after being on tafamidis therapy for more than 6 years—with the echocardiography-based progression of cardiac disease during that time, an impressive regression of septal hypertrophy as well as decrease in LGE extent was documented by follow-up CMR studies just within 21 months of therapy with novel genome silencers (inotersen and patisiran). Besides liver transplantation (LTx), approved disease-modifying (anti-amyloid) therapies in ATTRv amyloidosis include:[1] TTR stabilizers, including tafamidis and diflunisal and[2] TTR gene-silencing, including the antisense nucleotide inotersen and the small-interfering RNA patisiran.[1,9,10] Among these drugs, only tafamidis is currently approved for the therapy of ATTRv-associated cardiomyopathy in the absence of polyneuropathy.

For almost 7 years, until late 2018, our patient received tafamidis due to leading symptoms of polyneuropathy. Tafamidis acts as a TTR stabilizer and was shown to slow the progression of ATTR polyneuropathy, being approved for its treatment in numerous countries.[9] In the Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy Trial (ATTR-ACT) trial, tafamidis was associated with lower all-cause mortality and rates of cardiovascular hospitalizations in ATTR cardiomyopathy patients and gained European approval for expanded use in treating adults with wild-type (wt)- or ATTRv cardiac amyloidosis in February 2020.[11] Importantly, the ATTR-ACT study failed to show a significant difference in baseline vs. 30 months LV wall thickness or LVEF on echocardiography between the tafamidis and placebo groups.[11]

Subsequently, our patient received inotersen for 6 months, an antisense oligonucleotide inhibitor of the hepatic production of TTR that was shown to improve the course of neurologic disease and quality-of-life in ATTRv and therefore approved since 2018 for the treatment of polyneuropathy in these patients.[12] In a recent study focusing on cardiomyopathy, inotersen resulted in a decrease in LV mass of 8.4% in patients with wt- and ATTRv in addition to an increase in exercise tolerance by 20.2 m based on a 6-min walk-test.[13]

Following the rather short period of inotersen therapy, our patient received patisiran for the past 15 months (until present). During the time period of genome silencer therapy, a regression of cardiomyopathy was documented based on CMR findings. Similar to inotersen, patisiran is a synthetic, small-interfering RNA that specifically inhibits hepatic synthesis of TTR and consecutively reduces circulating mutant and wild-type transthyretin levels.[14] In The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis (APOLLO) trial, patisiran significantly improved neuropathy in patients with ATTRv amyloidosis and subsequently received European approval in August 2018.[14] Noteworthy, in a sub-population of patients from the APOLLO trial with echocardiographic evidence of amyloid cardiomyopathy, patisiran decreased mean LV wall thickness, improved global longitudinal strain, decreased NT-proBNP levels, and reduced adverse cardiac events compared with placebo at Month 18, suggesting that patisiran may not only stop but also reverse the progression of ATTRv cardiac disease manifestations.[15]

This case report is the second one from our group documenting ATTRv cardiomyopathy reversal based on CMR data. Previously, we have shown in a female patient carrying the same rare ATTRv mutation (p.Gly67Ala), and also with predominant neuropathic manifestations, an impressive regression of non-invasive CMR imaging findings within a 5-year-follow-up time. The respective patient had also been receiving several anti-amyloid therapies (tafamidis and inotersen) in addition to orthotopic liver transplantation.[16] These data are further supported by a recent publication from Fontana *et al.*,[17] which shows a regression of cardiac amyloid—documented by reductions in ECV on CMR, in a proportion of patients with ATTRv cardiomyopathy

receiving patisiran. Noteworthy, despite being the only CMR imaging parameter showing a significant change, the reduction in ECV was associated with a fall in NT-pro-BNP concentrations and an increase in 6MWT distances at 12 months of therapy.[17] Hence, a decrease in cardiac amyloid load during specific genome silencer therapy, as supported by LV mass and LGE regression, could be documented by native T1-mapping data for the first time in the present report.

To conclude, the findings of this case report further support our previously suggested hypothesis that amyloid infiltration leading to cardiomyopathy is not an irreversible pathological process—but rather a dynamic one, that cannot only be stopped but even reversed (to a certain degree) by currently emerging anti-amyloid therapies. Moreover, this report nicely illustrates the role of serial multiparametric CMR imaging for surveillance of cardiomyopathy dynamics in patients receiving specific disease-modifying therapies.

Lead author biography

Anca Florian is a Romanian born and trained cardiologist specialized in non-invasive cardiac imaging and cardiovascular magnetic resonance imaging. Since 2013, she is part of the cardiac imaging division of the University Hospital of Muenster, Germany.Her research topics of interest include imaging of genetic cardiomyopathies and cardiac involvement in neuromuscular diseases.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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