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GUIDELINES

Targeted disease-specific therapy for patients with hereditary transthyretin amyloidosis and cardiac involvement after orthotopic liver transplantation. Consensus from the Working Group on Myocardial and Pericardial Diseases of the Portuguese Society of Cardiology and National Reference Centers for Familial Amyloidosis

Terapêutica específica para doentes com amiloidose por transtirretina hereditária com envolvimento cardíaco após transplante hepático ortotópico. Consenso do Grupo de Estudo de Doenças do Miocárdio e Pericárdio da Sociedade Portuguesa de Cardiologia e dos Centros de Referência Nacionais para a Amiloidose Familiar

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Introduction

Hereditary transthyretin amyloidosis (ATTRv) is characterized by the deposition of amyloid fibrils in different organs, mainly the heart and the somatic and autonomic peripheral nervous systems.[1] Variants in the gene encoding transthyretin (TTR) are inherited in an autosomal dominant pattern and heterozygous carriers produce a mixture of variant and wild-type TTR. Mutated TTR is prone to destabilization of the tetrameric structure with consequent dissociation into monomers, misfolding and formation of amyloid fibril aggregates.[2] The p.Val50Met variant (previously designated Val30Met) is the best-known TTR gene mutation, and is the most common variant in Europe, South

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America, and Japan.[3] In Portugal, there is an endemic focus of the p.Val50Met variant and the mean incidence rate of ATTRv amyloidosis due to this variant reaches 0.87/100 000 (95% confidence interval [CI]: 0.68–1.10), which corresponds to 71 new patients per year in the country. In 2016, the prevalence of ATTRv amyloidosis due to the p.Val50Met variant in Portugal was 22.93/100 000 adult individuals (95% CI: 21.90–23.99).[4]

Orthotopic liver transplantation (OLT) was the first available treatment for ATTRv amyloidosis, eliminating production of the amyloidogenic mutated TTR. However, after OLT, some patients still develop cardiac amyloidosis due to the continued deposition of wild-type TTR amyloid fibrils in the heart.[5]

In recent years, several targeted disease-specific therapies have been developed and included in the armamentarium for the management of the disease.[6] However, post-OLT patients were excluded from clinical trials on these therapies,[7–9] which made an argument for the controversy on the use of specific treatment to patients with post-OLT cardiac amyloidosis. As a result, there are now several patients with ATTRv amyloidosis in Portugal with post-OLT cardiac amyloidosis, for whom a targeted disease-specific therapy is not available.

Considering this to be an important issue in the management of Portuguese ATTRv amyloidosis patients and in order to make access to treatment more uniform in the country, the Working Group on Myocardial and Pericardial Diseases of the Portuguese Society of Cardiology and the heads of the two national reference centers for familial amyloidosis wrote the present position statement, which addresses the diagnosis and treatment of post-OLT cardiac amyloidosis in patients with ATTRv amyloidosis.

Cardiac amyloidosis after orthotopic liver transplantation

In ATTRv amyloidosis, cardiac involvement is more severe in patients with type A fibrils (a mixture of full-length and fragmented short haphazard and weakly congophilic fibrils) than in those with type B fibrils (full-length long parallel and highly congophilic fibrils).[10,11] As patients with late-onset V50M disease mainly present type A fibrils, cardiac involvement is more common and more severe in these patients than in those with the early-onset V50M phenotype, who present mainly type B fibrils.[11–14]

After OLT, pre-existing amyloid deposits of mutated TTR act as a substrate, priming new deposits of wild-type TTR in various organs, including the kidneys and nerves, but preferentially the heart.[15] Post-OLT cardiac amyloidosis is thus more frequent in patients with pre-existing cardiac involvement, i.e., those with type A fibrils and with late-onset V50M disease.[11,16] Furthermore, wild-type fibrils seem to be more easily incorporated in type A than in type B fibrils and liver transplantation may accelerate this cardiac amyloidosis process, as it provides a greater quantity of wild-type amyloid fibrils.[6] Cardiac events, mainly end-stage heart failure but also sudden death, are the main cause of death in ATTRv amyloidosis patients after the year following OLT, accounting for about 38% of all deaths in follow-up.[17]

Diagnosis of post-orthotopic liver transplantation cardiac amyloidosis

To aid the early diagnosis of post-OLT cardiac amyloidosis in ATTRv amyloidosis patients, periodic cardiac evaluation is advisable, based on clinical assessment, electrocardiogram (ECG), echocardiogram, N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin levels, and Holter monitoring.[18]

If cardiac amyloidosis is suspected, single-photon emission computed tomography (SPECT) with ^{99m}technetium (^{99m}Tc)-pyrophosphate (PYP), 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or hydroxymethylene diphosphonate (HMDP) scintigraphy should be performed, and clonal dyscrasia should be excluded by performing serum free light chain assay and serum and urine protein immunofixation.[19,20] In patients with the p.Val50Met variant, scintigraphy may not show myocardial radiotracer uptake, especially in patients with early-onset disease, because they present mainly type B fibrils, which produce false negative results on scintigraphy.[21] In such cases, an endomyocardial biopsy should be performed to confirm the presence of TTR amyloid fibrils[19,20,22,23] (Figure 1).

Cardiac magnetic resonance imaging plays a less important role in the diagnosis of cardiac amyloidosis, although it could be useful to determine the amyloid burden at baseline.[23,24]

Table 1 summarizes imaging findings suggestive of cardiac amyloidosis.

Monitoring of cardiac amyloidosis progression post-orthotopic liver transplantation

Post-OLT cardiac amyloidosis should be monitored based on clinical evaluation (including New York Heart Association [NYHA] class and cardiovascular hospitalizations), ECG, six-minute walk test (6MWT), NT-proBNP and troponin levels, and quality of life by the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score every six months, and echocardiogram and 24-hour Holter every year, in stable patients.[22,25,26]

Cardiac magnetic resonance may also be useful for quantifying amyloid burden and monitoring response to therapy.[27,28] Furthermore, a change in cardiac tracer uptake on bone scintigraphy also appears to be a marker of treatment-specific response or disease progression in ATTRv amyloidosis patients.[29]

The following signs have been proposed as criteria of cardiac disease progression: increase in NT-proBNP $\geq$30% and $\geq$300 ng/l; decrease in distance walked on the 6MWT; appearance of a restrictive transmitral filling pattern; and appearance or increase of pericardial effusion.[30] More recently, a European expert consensus defined cardiac disease progression as the presence of at least one criterion of cardiac disease progression in each of three domains: a clinical and functional domain; a laboratory domain; and an imaging and ECG domain. The clinical and functional domain includes an increase in NYHA class, worsening indicated by any hospitalization related to HF decompensation, a decrease of 5–10 points in KCCQ score or of 10% on the

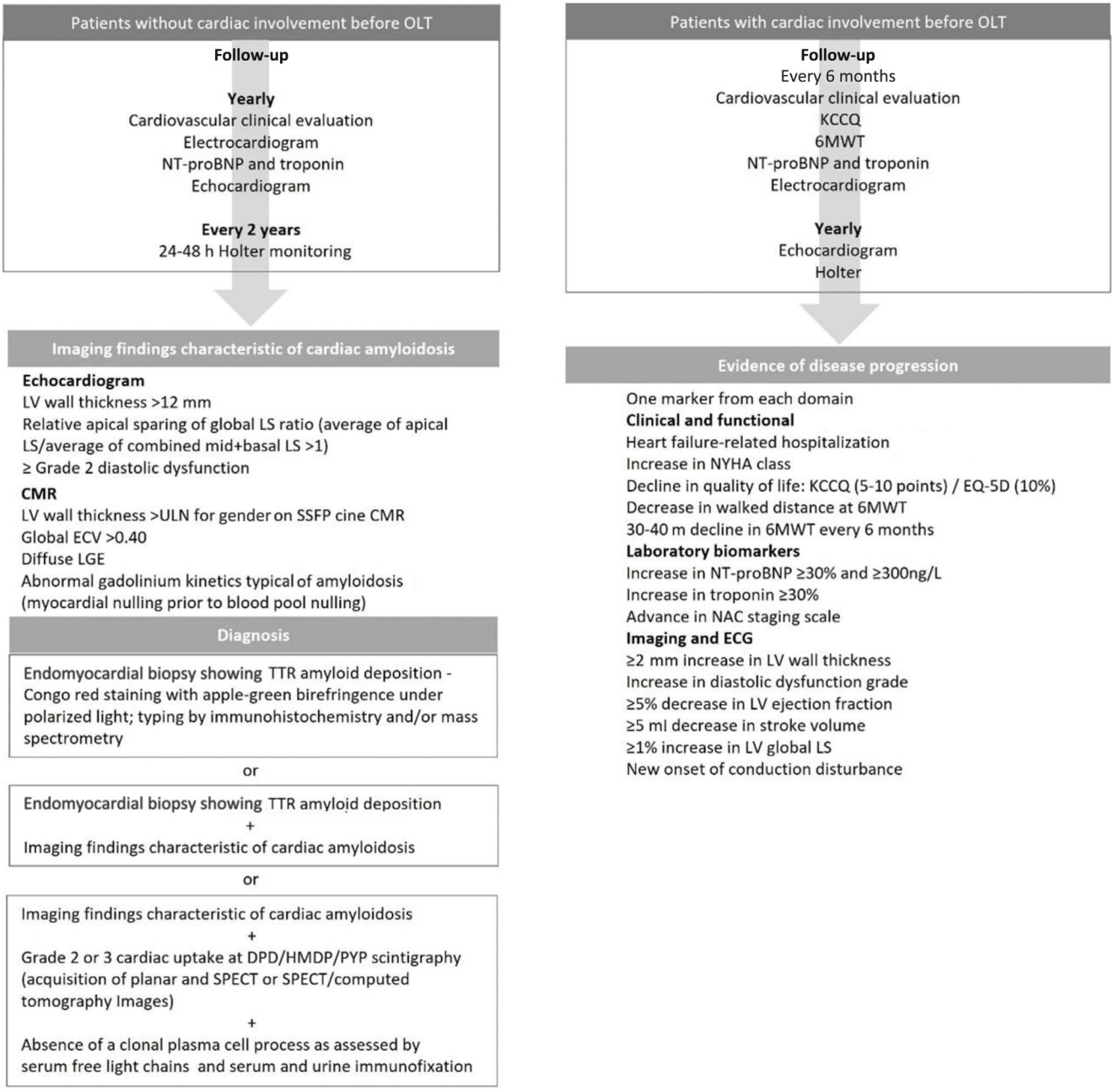

Figure 1 Diagnosis and monitoring of cardiac amyloidosis in patients with hereditary transthyretin amyloidosis after orthotopic liver transplantation. CMR: cardiac magnetic resonance; DPD: ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ECV: extracellular volume; EQ-5D: five-dimension EuroQol instrument; HF: heart failure; HMDP: ^{99m}technetium-hydroxymethylene diphosphonate; KCCQ: Kansas City Cardiomyopathy Questionnaire; LS: longitudinal strain; LV: left ventricular; 6MWT: six-minute walk test; NAC: UK National Amyloidosis Centre score; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; OLT: orthotopic liver transplantation; PYP: ^{99m}technetium pyrophosphate; SPECT: single-photon emission computed tomography; SSFP: steady-state free precession; TTR: transthyretin; ULN: upper limit of normal.

five-dimension EuroQol instrument (EQ-5D), and a decrease in 6MWT distance of 30–40 m every six months. The laboratory domain, besides an increase in NT-proBNP of ≥30% and ≥300 pg/ml, also includes a ≥30% increase in troponin level and an advance in the UK National Amyloidosis Centre (NAC) staging score. The imaging and ECG domain includes echocardiographic parameters (≥2 mm increase in left ventricular [LV] wall thickness, increase in diastolic dysfunction grade, ≥5% decrease in LV ejection fraction, ≥5 ml decrease in stroke volume, and ≥1% increase in LV global longitudinal strain) and new-onset conduction abnormalities[25] (Figure 1).

Table 1 Imaging findings suggestive of cardiac amyloidosis.

Echocardiography and magnetic resonance	
LV hypertrophy	
Right ventricular hypertrophy	
Biatrial enlargement	
Atrioventricular valve thickening	
Interatrial septal thickening	
Pericardial effusion	
Specific to echocardiography	*Specific to magnetic resonance*
LV wall thickness >12 mm	LV wall thickness >ULN for gender on SSFP cine
Sparkling appearance of the myocardium	Diffuse subendocardial or transmural LGE
Grade 2 or 3 diastolic dysfunction	Abnormal gadolinium kinetics (myocardial nulling prior to blood pool nulling)
Decreased mitral annular systolic velocity (s′)	Increased native T1 mapping
Relative apical sparing of global LS ratio (average of apical LS/average of combined mid+basal LS >1)	Increased ECV (particularly >0.40)

ECV: extracellular volume; LGE: late gadolinium enhancement; LS: longitudinal strain; LV: left ventricular; SSFP: steady-state free precession; ULN: upper limit of normal.

Targeted disease-specific therapy for transthyretin amyloidosis

In Europe, based on current evidence, two formulations of tafamidis have been approved for ATTR amyloidosis: tafamidis 20 mg (tafamidis meglumine) for the treatment of adult patients with polyneuropathy in stage 1 related to ATTRv amyloidosis, and tafamidis 61 mg (equivalent to oral tafamidis meglumine 80 mg) for the treatment of cardiomyopathy related to ATTR amyloidosis, either variant or wild-type.

Patisiran is approved for the treatment of adult patients with ATTRv amyloidosis and stage 1 or 2 polyneuropathy (with or without cardiomyopathy). Vutrisiran is approved for the treatment of adult patients with ATTRv amyloidosis and stage 1 or 2 polyneuropathy.

Inotersen is approved for the treatment of adult patients with ATTRv amyloidosis and stage 1 or 2 polyneuropathy.

Evidence on targeted disease-specific therapy for transthyretin amyloidosis cardiomyopathy

Tafamidis

Tafamidis is an oral TTR stabilizer that selectively binds to the thyroxin-binding sites of TTR, stabilizing the TTR tetramer and slowing the dissociation of TTR into monomers and thereby fibril formation and tissue deposition.[31] Tafamidis has been shown to slow the progression of peripheral neurological impairment in transthyretin amyloid polyneuropathy.[32,33]

ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) was a phase 3 double-blind randomized clinical trial including 441 patients, 106 with ATTRv and 335 with ATTRwt (76.0%), that compared tafamidis 20 or 80 mg with placebo, for 30 months. This study demonstrated a significant reduction in the primary endpoint, a hierarchical analysis of all-cause mortality followed by frequency of cardiovascular-related hospitalizations, in patients treated with tafamidis. Furthermore, tafamidis also showed benefit in secondary endpoints: it also reduced decline in 6MWT and KCCQ-OS score and was associated with a smaller increase in NT-proBNP.[7]

In this trial, the benefit in quality of life was seen earlier (six vs. 12 months) with the 80 mg dose of tafamidis than with the 20 mg dose.[7] Furthermore, long-term extension data of the ATTR-ACT trial showed a significantly greater survival benefit and a significantly lower increase in NT-proBNP with tafamidis 80 vs. 20 mg, thus supporting the use of the 80 mg dose in cardiac ATTR amyloidosis.[34]

In the ATTR-ACT trial, greater benefit of tafamidis was noted in earlier stages of the disease (NYHA functional class I and II),[7] emphasizing the importance of early diagnosis and treatment. Long-term extension data of the ATTR-ACT trial also showed that patients under tafamidis since the beginning of the trial had better survival than those who were under placebo and then switched to tafamidis, further supporting the prognostic benefit of early treatment.[35] It is also noteworthy that this survival benefit with continuous tafamidis treatment compared with delayed treatment (placebo then tafamidis) was also observed over a median follow-up of around five years in patients who were in NYHA class III at baseline.[36]

Notably, patients who had undergone liver transplantation were excluded from the ATTR-ACT trial.[7]

Although experience with tafamidis in post-OLT patients with ATTRv amyloidosis is limited, an isolated case report on a V50M patient documented stabilization of neurological manifestations and improvement of nutritional status with the use of tafamidis after liver transplantation, without safety issues.[37]

Acoramidis

Acoramidis, another oral TTR stabilizer, binds to TTR, mimicking the specific disease-protective action of the T119M variant in stabilizing TTR.

Recently, the ATTRibute-CM trial, a phase 3 double-blind randomized clinical trial using acoramidis, reinforced the

evidence of the efficacy of TTR stabilizers in improving outcomes in patients with ATTR cardiomyopathy. This trial included 632 patients with cardiac ATTR amyloidosis (ATTRv and ATTRwt). At 12 months, the primary endpoint of 6MWT distance was not met, but a significant benefit was seen in quality of life as assessed by the KCCQ and NT-proBNP levels. At 30 months, the four-step primary hierarchical analysis included death from any cause, cardiovascular-related hospitalization, change from baseline in NT-proBNP level, and change from baseline in 6MWT distance. The trial showed a significant benefit of acoramidis in the primary outcome at 30 months compared to placebo, as well as in cardiovascular hospitalizations, 6MWT distance, quality of life and NT-proBNP levels. Notably, the effect of acoramidis on mortality did not achieve statistical significance, probably due to the need for a larger sample and longer follow-up.[9]

Patisiran

Patisiran is a small interfering RNA (siRNA), which is administered intravenously every three weeks and delivered to the liver within lipid nanoparticles. In hepatocytes, it targets a genetically conserved sequence of the 3′ region of the messenger RNA of TTR, leading to the RNA-induced silencing complex-mediated degradation of the messenger RNA of TTR and thereby to the suppression of TTR synthesis, both variant and wild.

In the APOLLO phase 3 double-blind randomized clinical trial, patisiran showed a statistically significant benefit compared to placebo on the modified Neuropathy Impairment Score Plus 7 at 18 months in 225 ATTRv amyloidosis patients with polyneuropathy.[38] This trial reported data from a prespecified analysis of the subpopulation of 126 patients with cardiac amyloidosis, showing that patisiran compared to placebo appeared to be associated with lower mortality and hospitalization rate, higher speed in the 10-m walk test, lower NT-proBNP, lower LV wall thickness, and better cardiac output and global longitudinal strain.[39] However, this trial did not include patients who had undergone liver transplantation.

APOLLO-B was a phase 3 double-blind randomized clinical trial that included 360 patients with ATTR cardiac amyloidosis (ATTRwt or ATTRv), randomized to patisiran or placebo. The primary endpoint was 6MWT distance at 12 months. Patisiran showed a statistically significant benefit compared to placebo in 6MWT distance, quality of life as assessed by the KCCQ, and NT-proBNP levels, although the secondary composite outcome of all-cause mortality, cardiovascular events and 6MWT distance at 12 months was not met.[8] However, this trial also excluded post-OLT patients.

A phase 3b global open-label trial assessed the efficacy and safety of patisiran in patients with ATTRv and polyneuropathy progression after OLT. The primary endpoint was reduction in serum TTR (mainly wild-type) at six and 12 months. Secondary efficacy endpoints included change from baseline to six and 12 months in neuropathy impairment, quality of life, autonomic symptoms and nutritional status. Patients were enrolled at ten centers in seven European countries, including Portugal. Individuals in NYHA class >II were excluded. Twenty-three patients received patisiran. Fifteen (65.2%) patients had the V50M genotype. A significant reduction in serum TTR levels was observed with patisiran. There was also an improvement in neuropathy, quality of life and autonomic symptoms; disability and nutritional status appeared to be stable compared to baseline. According to the authors, 10 patients (43.5%) had some degree of cardiac involvement, but data on cardiac evolution were not reported. Most patients had normal liver function tests. The only case of transplant rejection, consistent with inadequate immunosuppression, remained on patisiran and completed the study. Patisiran was well tolerated, without significant safety issues.[40]

Vutrisiran

Vutrisiran is a double-stranded siRNA that specifically targets the messenger RNA of TTR. It is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes, in which it induces RISC-mediated degradation of the messenger RNA of TTR, thereby inhibiting TTR production.

HELIOS-A was a phase 3 global open-label study that included 164 ATTRv patients with polyneuropathy. Patients were randomized 3:1 to subcutaneous administration of vutrisiran every three months (n=122) or intravenous administration of patisiran every three weeks (n=42) for 18 months. Vutrisiran compared to an external placebo group (from the APOLLO trial) showed a statistically significant benefit in the modified Neuropathy Impairment Score Plus 7 and quality of life.[41] In the cardiac subgroup, vutrisiran (n=40) compared to the external placebo (n=36) showed a significant benefit in NT-proBNP levels and LV stroke volume and cardiac output.[42]

HELIOS-B was a phase 3 multicenter double-blind randomized placebo-controlled trial that enrolled 655 patients with ATTR-CM, randomly assigned in a 1:1 ratio to receive vutrisiran (25 mg) or placebo. In the overall population, 88% of patients had ATTRwt amyloidosis. Sixty per cent of patients in the vutrisiran group and in the placebo group were not taking tafamidis at baseline, constituting the monotherapy population. Among this population, 22% in the vutrisiran group and 21% in the placebo group began tafamidis after randomization. Treatment with vutrisiran reduced the risk of death from any cause and recurrent cardiovascular events (hospitalizations for cardiovascular causes or urgent visits for heart failure) compared to placebo, in both the overall and monotherapy populations. Vultrisiran also reduced decline in functional capacity and in quality of life.[43] However, this study did not mention patients who had undergone liver transplantation.

Inotersen

Inotersen is a second-generation 2′-O-methoxyethyl-modified antisense oligonucleotide that selectively binds to a region in the 3′-UTR of the messenger RNA of TTR, which leads to RNase H1-mediated degradation and consequent inhibition of TTR production.

NEURO-TTR was a phase 3 double-blind randomized clinical trial that included 172 ATTRv patients with polyneuropathy. Weekly subcutaneous administration of inotersen compared to placebo resulted in a statistically significant

benefit in the modified Neuropathy Impairment Score Plus 7 and quality of life at 66 weeks.[44] In the subset of 108 patients with cardiac amyloidosis, exploratory echocardiographic parameters, including LV wall thickness, mass, ejection fraction, global longitudinal strain and E/E′ lateral ratio, were not significantly affected by inotersen.[45] The main serious adverse events associated with inotersen were glomerulonephritis and thrombocytopenia. This trial also excluded patients who had undergone liver transplantation.

A single-center open-label study enrolled 33 patients with ATTR cardiac amyloidosis (ATTRwt or ATTRv) in NYHA class I–III to receive inotersen. At two-year follow-up, mean LV mass had decreased by 8.4%, measured by cardiac magnetic resonance, and LV ejection fraction remained stable in most patients. Exercise tolerance, measured by 6MWT, increased mainly in ATTRv patients, whereas in ATTRwt patients it remained relatively stable.[46]

A retrospective review of nine patients with ATTRv amyloidosis (one with the V50M variant) with disease progression after OLT, medicated with inotersen, showed that the neuropathy impairment score remained stable or improved in all patients. However, the medication was suspended in five patients due to thrombocytopenia (n=3) and reversible liver rejection (n=2).[47] Two of the nine patients had undergone liver and heart transplantation, but no data on cardiac evolution are available in the article.[47]

Eplontersen

Eplontersen is another antisense oligonucleotide, which shares the same nucleotide sequence as inotersen. However, eplontersen uses ligand-conjugated (LICA) technology for delivery to hepatocytes and a triantennary N-acetylgalactosamine moiety (GalNAc3) that increases its potency, enabling a lower dose and frequency of administration compared to inotersen.

NEURO-TTRansform was an open-label single-group phase 3 trial that included 168 patients with stage 1 or 2 ATTRv polyneuropathy. In this trial, patients received a subcutaneous administration of eplontersen every four weeks (n=144) or inotersen every week (n=24). Eplontersen was compared to the historical placebo of the NEURO-TTR trial, and showed a significant benefit in the modified Neuropathy Impairment Score Plus 7 and quality of life at 66 weeks.[44] In the cardiac subgroup, eplontersen (n=49) compared to placebo (n=30) showed significant improvements in LV ejection fraction and stroke volume at 65 weeks.[45] However, this study also excluded patients who had undergone liver transplantation.

The CARDIO-TTRansform phase 3 double-blind randomized clinical trial (NCT04136171), testing eplontersen in patients with ATTR cardiomyopathy (ATTRv and ATTRwt), is currently ongoing, but also excluded post-liver transplantation patients.

Other therapies

Several monoclonal antibodies are currently being tested in phase 1, 2 or 3 trials.[48]

NI006 has been tested in a phase 1 trial that included 40 patients with wild-type or variant ATTR cardiomyopathy and chronic heart failure, who were randomized in a 2:1 ratio for NI006 or placebo. NI006 appeared to reduce NT-proBNP and troponin levels, cardiac tracer uptake on scintigraphy and extracellular volume on cardiac magnetic resonance at 12 months.[49]

CRISPR-Cas9-mediated gene editing has also shown to be safe and decrease serum TTR levels at 28 days in a phase 1 open-label trial of NTLA-2001 with six ATTRv patients with polyneuropathy.[50] NTLA-2001 was also tested in a phase 1 open-label trial including 12 patients with ATTR cardiomyopathy (ATTRwt or ATTRv), in which it was shown to be safe and to significantly reduce serum TTR levels at 28 days.[51]

Targeted disease-specific therapy for patients with hereditary transthyretin amyloidosis and post-orthotopic liver transplantation cardiac amyloidosis

In view of the results of the above-mentioned phase 3 trials for ATTR cardiomyopathy, which included patients with ATTRv and ATTRwt, and taking into consideration that the progression of cardiac disease after OLT is secondary to deposition of wild-type fibrils, it may be postulated that well-tested targeted disease-specific therapy is potentially beneficial in this subset of patients.

Considering the poor prognosis conferred by cardiac disease progression and the favorable safety profile of these therapies, this Task Force recommends that targeted disease-specific therapy with documented benefit in ATTR cardiomyopathy should be considered in ATTRv amyloidosis patients with evidence of symptomatic cardiac involvement or progression after OLT, as its pathophysiology is similar to wild-type TTR cardiac amyloidosis, for which there is robust evidence of reductions in mortality and heart failure hospitalizations, and benefit in functional capacity and quality of life.[7,9,52]

Targeted disease-specific therapy should be considered in patients with an established diagnosis of post-OLT cardiac amyloidosis and at least one of the following criteria:

- Clinical evidence of heart failure (with or without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic
- NYHA functional class II or III
- NT-proBNP level $\geq$500 pg/ml
- Progressive cardiac conduction abnormalities or pacemaker implantation due to cardiac conduction abnormalities

Patients with the following characteristics are not candidates for this therapeutic approach:

- NYHA functional class IV
- Functional capacity <100 m on 6MWT (except if considered secondary to neuropathy and not cardiomyopathy)
- Estimated life expectancy less than one year
- Advanced dementia
- Pregnancy and breastfeeding
- Lack of therapeutic compliance

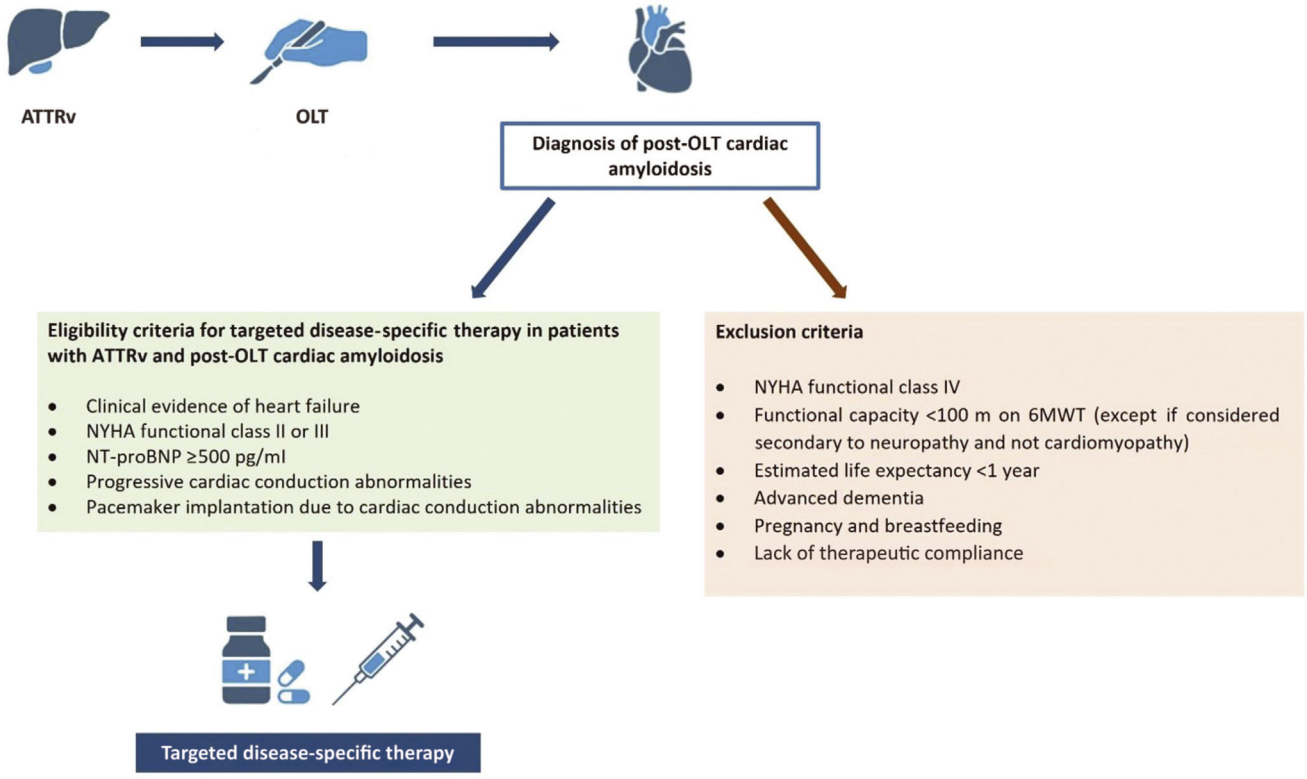

Figure 2 Targeted disease-specific therapy for patients with hereditary transthyretin amyloidosis and post-orthotopic liver transplantation cardiac amyloidosis. ATTRv: hereditary transthyretin amyloidosis; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; OLT: orthotopic liver transplantation; TTR: transthyretin.

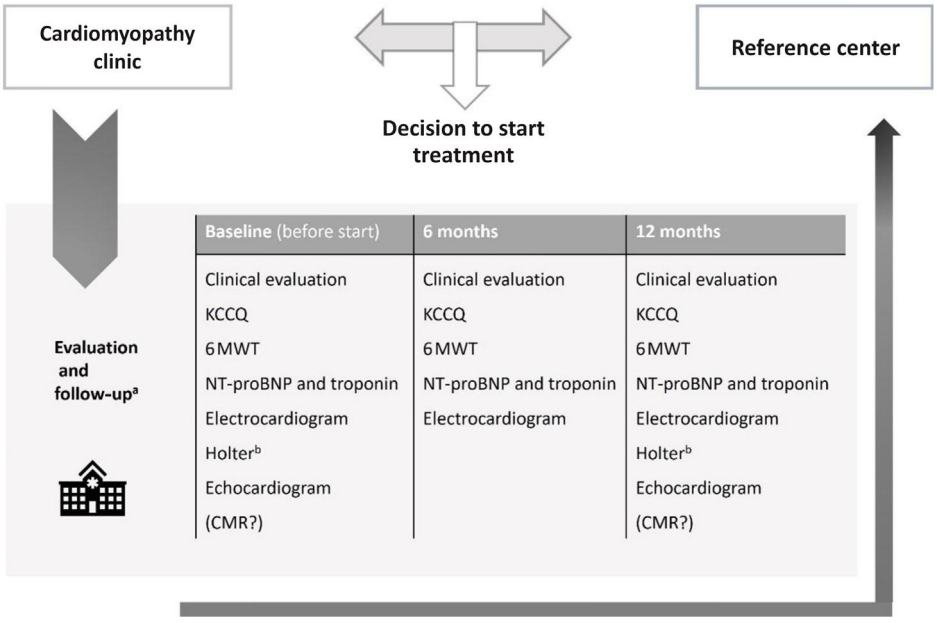

Figure 3 Evaluation and follow-up of patients with post-orthotopic liver transplantation cardiac amyloidosis undergoing targeted disease-specific therapy. Laboratory tests should include hemogram, biochemistry (including renal and hepatic function), troponin, and NT-proBNP. 6MWT: six-minute walk test; CMR: cardiac magnetic resonance; KCCQ: Kansas City Cardiomyopathy Questionnaire.
[a] The frequency of follow-up may be adjusted in accordance with clinical status.
[b] In patients without cardiac devices.

Networking between cardiomyopathy clinics and reference centers for amyloidosis

Periodic follow-up assessments should be performed by a multidisciplinary team to cover the wide range of manifestations of disease progression due to the continued deposition of wild-type TTR after OLT (Figure 2). At a minimum, this team should consist of a neurologist, a cardiologist and an ophthalmologist. Other specialists, including geneticists, gastroenterologists, nutritionists, physical therapists, nephrologists, and urologists, should be consulted as needed.[53–55]

Patients in whom post-OLT cardiac amyloidosis is suspected or diagnosed can be followed at the nearest center with a dedicated cardiomyopathy clinic, in close communication with the reference center. The decision to start targeted disease-specific therapy in post-OLT cardiac amyloidosis should be a shared decision process with the involvement of the patient, the cardiologist specialized in Cardiomyopathies who follows the patient at the nearest center and the remaining multidisciplinary team of the Reference Center. Dispensation of oral medication or administration of intravenous medication should take place at the nearest center with a dedicated cardiomyopathy clinic, in order to simplify and improve patient care.

Cardiac assessment and follow-up of patients with post-OLT cardiac amyloidosis receiving targeted disease-specific therapy should also be performed in the nearest center with a dedicated cardiomyopathy clinic, in close communication with the reference center. Likewise, the decision whether to discontinue therapy should also be shared between the patient, the cardiomyopathy specialist following the patient at the nearest center, and the multidisciplinary team at the reference center.

Figure 3 summarizes the evaluation and follow-up of patients with post-OLT cardiac amyloidosis in the first year of targeted disease-specific therapy.

After the first year of treatment, surveillance should also be adapted on an individual basis, according to the patient's clinical course, but a biannual evaluation, as the one presented in figure 2 for the 6 and 12 months, may be appropriate. Other complementary tests may be used, depending on local availability and clinical indications.

Conclusion

A significant number of patients with ATTRv amyloidosis due to the p.Val50Met variant develop post-OLT cardiac amyloidosis, which constitutes the main cause of death in these patients. Targeted disease-specific therapy should be considered in symptomatic patients with an established diagnosis of post-OLT cardiac amyloidosis. Follow-up should be performed by a multidisciplinary team consisting of a cardiologist specializing in cardiomyopathies and the reference center team.

Supplement information

This article is part of a supplement entitled 'Portuguese WGMPD Recommendations and consensus documents on Transthyretin Amyloidotic Cardiomyopathy' which is sponsored by Grupo de Estudo de Doenças do Miocárdio e do Pericárdio da Sociedade Portuguesa de Cardiologia - Portuguese Society of Cardiology Working Group on Myocardial and Pericardial Diseases.

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