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Problems in the Diagnostics and Treatment of Transtiretinum Amyloidosis with Heart Disease in the Elderly: Clinical Experience

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Abstract—The article presents a modern understanding of the treatment of cardiac amyloidosis and provides data on the frequency of occurrence, classification, and variants of clinical manifestations of transthyretin amyloidosis. This pathology is a slowly progressive disease, the symptoms of which usually appear in elderly and senile age. This diagnosis may become more common in the future as the population ages and diagnostic methods improve. A description of the clinical case of transtritin amyloidosis of the heart in a 77-year-old patient, which occurred with a primary lesion of the heart and symptoms of chronic heart failure, is given as an illustration that shows the difficulties in the lifetime diagnosis of transthyretin amyloidosis.

Keywords: transthyretin amyloidosis, heart failure, *ATTR*, cardiomyopathy, "wild-type" amyloidosis

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INTRODUCTION

Amyloidosis is a group of diseases characterized by the deposition of amyloid fibrillar glycoprotein in the tissues and organs. Amyloidosis is a systemic disease in which several target organs can be affected—the kidneys, heart, liver, lungs, nervous system, etc. There are currently four main forms of systemic amyloidosis: AL (primary), AA (secondary), ATTR (transthyretin), and $A\beta_2M$ (dialysis). Symptoms of amyloidosis do not have specific clinical manifestations. They depend on the localization of amyloid deposits and can occur under the guise of various diseases. Modern amyloidosis diagnostics requires the histological identification of amyloid and an immunohistochemical determination of its type [6, 22, 24].

Clinical signs of heart lesion are found in more than 50% of patients with AL amyloidosis, only in 10% of patients with AA amyloidosis, and in less than 5% with other forms [11].

ATTR amyloidosis is caused by the deposition of an amyloid consisting of transthyretin protein (TTR). Normal transthyretin, which is synthesized in the liver, is a protein carrier of thyroid hormones and vitamin A (retinol) in healthy people. There are three main types of transthyretin amyloidosis: familial amyloid polyneuropathy (FAP), a hereditary form that can be combined with cardiomyopathy; familial amyloid cardiomyopathy (FAC), a hereditary form that can be combined with FAP; senile systemic amyloidosis, or ATTRwt a "wild-type" amyloidosis that is not inherited (SSA). Familial types of amyloidosis (ATTRm: FAP and FAC) are associated with various mutations in the gene responsible for the continuous synthesis of the abnormal amyloidogenic transthyretin molecule. To date, more than 100 mutation variants of familial transthyretin amyloidosis have been described [21, 22].

Familial amyloid polyneuropathy is more often manifested in middle age. Its main signs are associated with the development of peripheral and autonomic neuropathy manifested by muscle weakness, increased pain sensitivity in the extremities, impaired bowel and bladder, and changes in blood pressure, which is manifested by orthostatic hypotension. Symptoms caused by heart failure due to restrictive cardiomyopathy also develop often. Clinical signs can appear both before the age of 20 years and in old age. The age-related debut of the disease, the rate of progression, and the involvement of various systems and organs directly depend on the type of mutation [10].

Symptoms of familial amyloid cardiomyopathy usually occur after 60 years. The onset of cardiovascular manifestations is often preceded by carpal tunnel syndrome. Signs of amyloid transthyretin heart disease are symptoms of heart failure. According to the literature, this condition is most often detected in African Americans [8].

Until recently, it was believed that amyloid deposits consisting of normal (nonmutant) "wild-type" transthyretin (TTRwt) did not lead to significant organ damage. In recent years, thanks to the use of new imaging methods, it has become apparent that TTRwt is quite common and can be accompanied by significant organ lesion. In 2014, at the XIV International Symposium on Amyloidosis, it was decided to call this

type of lesion "wild-type" ATTR amyloidosis, or ATTRwt. This pathology is a slowly progressing disease, the symptoms of which usually appear after the age of 60, are more common in men [5].

Amyloid deposits, which consist of the "wild-type" TTR, are localized mainly in the heart. They cause restrictive cardiomyopathy, which is manifested by symptoms of heart failure: it is often in the form of diastolic dysfunction of various severity at the first stage of the disease, eventually progressing to biventricular systolic dysfunction. Almost 50% of patients with TTRwt have symptoms of carpal tunnel syndrome—tingling and pain in the wrists. Tunnel syndrome of the hand often occurs 3–5 years before the onset of signs of heart disease [20].

There is currently a hypodiagnosis of "wild-type" ATTR amyloidosis. This diagnosis may become more common in the future as the population ages and diagnostic methods improve [17].

CURRENT UNDERSTANDING OF THE TREATMENT OF TRANSTHYRETIN AMYLOIDOSIS WITH HEART LESION

The treatment of transthyretin amyloidosis with heart disease currently has two directions: the termination or slowing of the amyloid deposition and chronic heart failure treatment according to current recommendations. There are currently three main principles of influencing the infiltrative process in organs at ATTR: suppression of the synthesis of amyloid protein TTR, TTR stabilization (effect on TTR amyloidogenicity), and the degradation and extraction of TTR, i.e., inhibition of the formation of amyloid fibrils and the stimulation of amyloid resorption [19].

Suppression of the synthesis of amyloid protein TTR is possible with liver transplantation or the suppression of gene expression (gene therapy). Liver transplantation is recommended for patients with a hereditary form of ATTR, mainly for patients with FAP. The purpose of this surgical treatment is to prevent the formation of further amyloid deposits. A liver that synthesizes an abnormal (mutated) amyloidogenic TTR is removed and replaced by a donor one that will synthesize normal "wild-type" TTR. Thus, liver transplantation is not a treatment for senile systemic amyloidosis (ATTRwt). The greatest success in transplantation is achieved in the early stages of the disease (before the occurrence of severe damage to the nerves or heart) in young patients and in patients with the TTR Val30Met mutation [2].

Genetic treatments that "turn off" the synthesis of amyloid protein are currently in the early stages of development and clinical trials and include small (short) interfering RNAs and antisense oligonucleotides [4]. Such a drug is ALN-TTRsc, which belongs to the class of small interfering RNAs. The interaction of short interfering RNAs with messenger RNA of the selected (target) gene leads to its degradation, preventing the translation of mRNA on ribosomes into the pathological protein encoded by it. At the stage of preliminary tests in patients with transthyretin amyloidosis of the heart, both with ATTRwt and with hereditary forms of the disease, this drug did not show high efficiency [7]. Another drug, ISIS-TTRRx, belongs to the class of antisense oligonucleotides. Antisense oligonucleotides contribute to the removal of mutation coding regions from mature mRNA by the removal of noncoding sequences from the mRNA precursor and the connection of coding regions to each other. ISIS-TTRRx is currently undergoing clinical trials in patients with familial amyloid polyneuropathy and with ATTRwt [1, 9].

The next treatment approach, which has been developed in recent years, is aimed at the *stabilization of the tetrameric structure of TTR* (*reduction of amyloidogenic properties of the protein*). Thus, some new drugs (Diflunisal and Tafamidis) for the treatment of ATTR are in various research stages but are not yet available for use. Upon entering into the blood, these drugs are tightly bound to TTR. Such a complex makes TTR less amyloidogenic [14]. Diflunizal belongs to the class of nonsteroidal anti-inflammatory drugs developed over 40 years ago. Clinical studies are ongoing to evaluate the effect of Diflunisal on the progression of neuropathy and cardiomyopathy in patients with FAP and FAC [19]. Tafamidis is a specific oral drug developed for FAP that has shown its high efficacy in this hereditary pathology. According to a randomized, double-blind, placebo-controlled study, Tafamidis use in patients with transthyretin amyloid cardiomyopathy is associated with a reduction in mortality from all causes and hospitalizations associated with cardiovascular diseases, as well as an improved quality of life compared to placebo [12, 23].

Lastly, two additional agents have more recently demonstrated therapeutic potential. In vitro studies showed that the *AG10* molecule demonstrated a higher stabilization efficiency of "wild-type" TTRs than Diflunizal and Tafamidis [15]. Tolkapon, an antiparkinsonian drug, also demonstrated a stabilizing effect of the tetrameric structure of TTR as compared to Diflusal and Tafamidis in both in vitro and in vivo studies [18].

The formation of amyloid fibrils can be inhibited with Doxycycline, the tetracycline series antibiotic, which, in combination with tauroursodoxycholic acid, leads to amyloid destruction in tissues (amyloid-degrading agent). Preliminary data confirm a beneficial effect with an acceptable toxicity profile [13].

Antibodies to serum amyloid protein, which stimulate amyloid resorption, show promising results for *ATTRwt*, but clear indicators and toxicity profiles are still subject to clinical trials [16].

Thus, with population aging, ATTRwt and ATTRm are likely to become the most common types of cardiac amyloidosis. The timely identification of

transthyretin amyloidosis and the choice of optimal tactics for its treatment will make it possible in the near future to delay a disease outcome unfavorable for the patient; however, the drug treatment for this pathology is currently more in the developmental stage.

A clinical case of senile transthyretin amyloidosis that occurred with the involvement of the heart and CHF events is described.

CLINICAL CASE

Patient G., 77 years old, was sent from a polyclinic to our cardiology department for the selection of drug therapy in connection with decompensation of CHF. On admission, he complained of severe weakness, shortness of breath with minimal physical activity, and edema of the lower extremities. In addition, the patient was disturbed by persistent yellowness of the skin, accompanied by persistent itching.

Anamnesis of the Disease

Over the past 2 years, he noted transient ochrodermia; according to ultrasound scan, hepatomegaly was revealed. The condition was regarded as chronic steatohepatitis with minimal activity and cholestasis syndrome (obstructive jaundice was excluded). In the future, shortness of breath appeared with moderate physical exertion, rare episodes of burning pains behind the sternum. After consultation with a cardiologist, he was diagnosed with effort angina pectoris III FC, and received medication with β-blockers and nitrates. However, the condition did not improve; burning pains behind the sternum persisted with moderate physical exertion. Frequent heart failures became worrisome (paroxysms of atrial fibrillation were verified); the shortness of breath intensified; edema of the lower extremities appeared, joined by severe weakness, lethargy, and memory impairment; persistent ochrodermia with persistent itching began to be noted. In connection with these complaints, he was hospitalized in a cardiology hospital, where coronary angiography was performed. The angiography data revealed moderate diffuse changes in the anterior interventricular artery and stenosis in the middle third to 75% in the right coronary artery. Angioplasty and stenting of the right coronary artery were performed, and a simple stent with a good angiographic result was implanted.

The anginal pain did not recur, but the phenomena of biventricular heart failure and liver failure with cholestasis persisted. The patient was examined in a planned manner at a surgical hospital, where a significant increase in bilirubin (up to 91.6 μmol/L) was detected against the background of a normal level of transaminases. Upon multispiral CT of the abdominal organs, peritoneal carcinomatosis was suspected, and the following was found: hyperplasia of the lymph nodes of the abdominal cavity and retroperitoneal space with a maximum size of 1.0 × 1.2 cm, a diffuse decrease in density indicators of the liver, signs of atrophic changes in pancreatic tissue, a change in the ischium on the right, the most characteristic of tumor lesions, and fluid in both pleural cavities and the pericardial cavity. Fibrogastroduodenoscopy and fibrocolonoscopy were performed, polyposis of the stomach and colon was detected, the biopsy was refused in connection with warfarin therapy. A polypositional skeleton scintigraphy was also performed, and a pathological accumulation of a radiopharmaceutical was revealed in the projection of the ischium on the right. A cytological study of ascitic fluid was performed, but pathological cells were not identified. The patient was seen at the Petrov NMRC of Oncology, where it was suggested that there is no evidence of an oncological process; the condition was regarded as deterioration in the course of heart failure. Hospitalization in the cardiology department was recommended. It should be noted that the patient's history included rectal adenocarcinoma; resection (*T2N0M0*) was performed 7 years prior.

Objective Data

General state of moderate severity, clear consciousness, hypersthenic physique, height—182 cm, body weight—85 kg, BMI—25.7 kg/m^2. The skin and sclera are icteric. Edema of the lower extremities to the inguinal folds was determined. Peripheral lymph nodes were not enlarged. Heart rate—80 beats/min, blood pressure—95/60 mm Hg. By percussion: the left border of relative cardiac dullness along the midclavicular line, heart sounds are muffled, the first tone at the apex is weakened, noises are not auscultated. Respiratory rate—18/min, with percussion, blunting of percussion sound below the VIII rib on both sides, hard breathing. Tongue coated in white, wet. The abdomen on palpation is soft, painless. The liver is enlarged, protrudes from under the lower edge of the costal arch by 3 cm, the edge of the liver is elastic, even, compacted, the spleen is not palpable.

Laboratory Indicators

General blood test: erythrocytes—5.74 × 10^{12}/L, hemoglobin—118 g/L, MCV—68.3 fL, leucocytes—8.2 × 10^9/L, lymphocytes—14%, monocytes—13%, neutrophils—73%, eosinophils—0.2%, basophils—0.2%, platelets—146 × 10^9/L, ESR—5 mm/h, reticulocytes—16‰. Anisocytosis, microcytosis, hypochromia, poikilocytosis.

Clinical urine test: color—yellow, transparent, acid, density—1.010 g/L, protein—0.138 g/L, leucocytes—0–1 per field of view, erythrocytes—0–1 per field of view, squamous epithelium—0–1 per field of view. Daily protein loss—1.5 g.

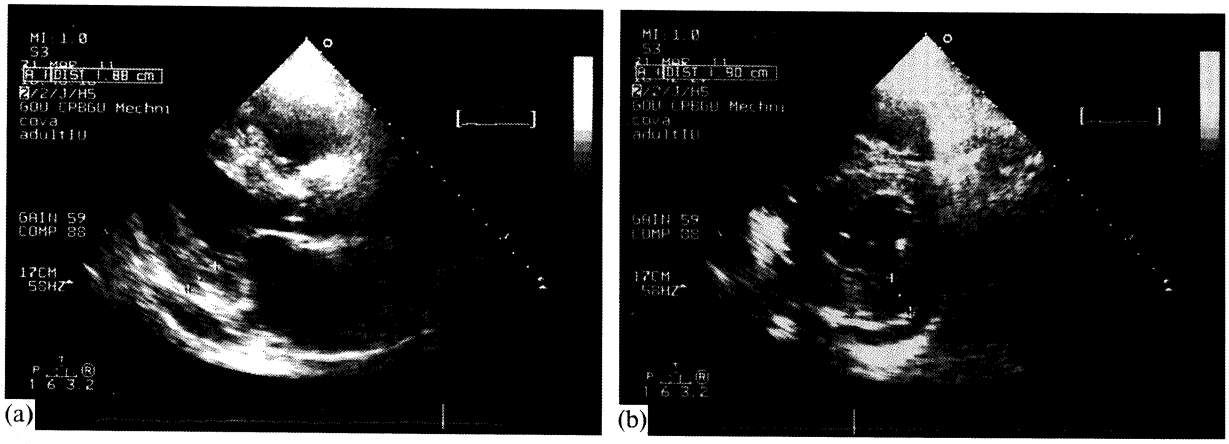

Fig. 1. Echocardiographic image of the heart. Parasternal position, long axis (a), short axis (b). Increased myocardial echogenicity (the phenomenon of "brilliant myocardium").

Biochemical blood test: glucose—5.3 mmol/L, total protein—81 g/L, albumin—42%, total creatinine phosphokinase—89 U/L, urea—20.6 mmol/L, creatinine—166 μmol/L, uric acid—447 μmol/L, total bilirubin—69 μmol/L, direct bilirubin—26.73 μmol/L, indirect bilirubin—42.27 μmol/L, γ-glutamyl transpeptidase (GGTP)—89 U/L, α-amylase—45 U/L, alkaline phosphatase—46 U/L, total cholesterol—2.2 mmol/L, LDL cholesterol—0.88 mmol/L, HDL cholesterol—1.17 mmol/L, AST—23 U/L, ALT—13 U/L, iron in serum—5.58 μmol/L, iron-binding capacity—73.3 μmol/L. GFR according to the *MDRD* formula—38 mL/min 1.73 m^2.

Instrumental Examinations

ECG: low voltage, atrial fibrillation, normosystolic form with a ventricular rate of 80/min. Fibrous changes in the anterior septum, high lateral parts of the left ventricle. Blockade of the posterior branch of the left leg of the bundle of His. Signs of systolic load on the left ventricle.

Echocardiography: left atrium, anteroposterior size—43 mm, medial-lateral size—52 mm, long axis—74 mm; atrial septum not changed; LV: interventricular septum (IVS)—18–21 mm, posterior wall (PW)—18 mm, final diastolic size—46 mm, final diastolic volume—69 mL, final systolic volume—35 mL, LVEF—50% according to Simpson; right ventricle in the parasternal position—30 mm; right atrium—52–70 mm; inferior vena cava—22 mm. Conclusion: atrial cavities are dilated, pronounced concentric LV myocardial hypertrophy, global LV myocardial contractility at the lower border of the norm—diffuse hypokinesia. IVS has a heterogeneous structure and increased echogenicity of the myocardium (the phenomenon of "brilliant myocardium," Fig. 1). Zones of violations of local contractility were not detected. The aorta is not expanded, fibrosis of the half-moons, with elements of calcification; the aortic flow is normal. Mitral regurgitation of the I degree. Tricuspid regurgitation of the I degree. The estimated systolic pressure in the pulmonary artery is 34 mm Hg. The divergence of the pericardial leaves behind the PW is 1.1 cm; behind the lateral—up to 1.8 mm, behind the right sections—3–4 mm.

Ultrasound scan of the kidneys: right kidney—the usual position, dimensions 105 × 50 mm, the parenchyma is 15 mm thick, homogeneous, echogenicity is within normal limits, no calculi. Left kidney—the usual position, dimensions 105 × 53 mm, the parenchyma is 15 mm thick, homogeneous, echogenicity is within normal limits, no calculi. The pyelocaliceal system is not expanded.

Ultrasound scan of the abdominal organs: moderate diffuse changes in the liver: the right lobe—145 mm, the left lobe—86 mm, the structure of the parenchyma is homogeneous, fine-grained, echogenicity is increased, bile ducts are not dilated, portal vein—12 mm. Moderate diffuse changes in the pancreas: head size—26 mm, body—15 mm. Contours are even and clear, echogenicity is diffusely increased. Focal formations are not found. The gall bladder is deformed, and a polyp with a diameter of 5 mm is determined. The spleen is not enlarged. Free fluid is not detected in the abdominal cavity.

X-ray analysis of the chest organs: no focal-infiltrative changes were revealed on the survey radiographs. Diffuse pneumosclerosis. The roots of the lungs with a fibrous component. The sinuses are free. The diaphragm location is normal. The shadow of the heart is expanded due to LV.

Fibrogastroduodenoscopy: polyps of the stomach body the against the background of atrophic gastritis with erosion in the antrum. Atrophic duodenitis. *Helicobacter pylori* test positive (+++). A biopsy revealed a hyperplastic polyp and chronic atrophic gastritis of moderate activity with hyperplasia of the integumentary epithelium.

Additional Examination Methods and Differential Diagnosis

Thus, for a 77-year-old patient with a history of coronary artery disease (angioplasty and stenting of the right coronary artery) and a constant form of atrial fibrillation with biventricular heart failure and rectal resection for adenocarcinoma in the anamnesis, the focus was on the following examination data: pronounced ictericity of the skin and sclera, swollen cervical veins, enlargement of the liver and edema of the lower extremities, the presence of hepatic cell failure with cholestasis, increased levels of urea and creatinine, as well as ECG and echocardiography data (low voltage). The latter showed atrial enlargement with small ventricular cavities, preserved LV systolic function, thickening of the LV myocardium walls (the patient had no history of arterial hypertension) and the phenomenon of "brilliant myocardium." In this regard, differential diagnosis was primarily performed between systemic amyloidosis with lesions of the heart, liver, and kidneys, as well as in connection with a rectal tumor in the anamnesis and previous examination data indicating foci of destruction in the sciatic bone and suspected peritoneal carcinomatosis—an oncological process.

Fibrocolonoscopy with biopsy of polyps was performed to exclude malignant process in the colon. A rectal mucosa biopsy with Congo red staining, a blood test for κ and λ chains, an immunological blood serum test for immunoglobulins, a urine test for Bens-Jones protein, and sternal puncture were performed to verify systemic amyloidosis.

Fibrocolonoscopy: condition after resection of the sigmoid colon, anastomosis 10 cm from the anus, passable, the mucous membrane in the anastomosis zone without neoplasia, a polyp of a cylindrical shape in the region of the hepatic angle, up to 1 cm in diameter. Mucosal biopsy (staining for amyloidosis). *Biopsy result*: negative (amyloid Congo red staining).

Urine test for Bens-Jones protein: negative.

Blood test for light chains: free κ-chains of Ig in serum: 40.01 μg/mL (normal 8.5–35); free λ-chains of Ig in serum: 10.05 μg/mL (normal 0.5–4.5).

Immunological examination of blood serum: CEC—70 units (normal 50–80 units); IgA—5.82 g/L (normal 0.7–4 g/L); IgM—2.186 g/L (normal 0.4–2.3 g/L); IgG—15.38 g/L (normal 7–16 g/L). Increased IgA concentration. *Myelogram*: bone marrow punctate is moderately rich in cellular elements; hematopoietic tissue predominates over adipose tissue. Granulocytic lineage is deployed; the ratio of ripening and mature elements is correct. Moderate lymphocytes, located diffusely. The number of plasma cells within normal limits (0.5%). Erythroid lineage is sufficient, normoblastic. The megakaryocytic lineage is represented by elements of various maturation stages and degrees of activity.

DISCUSSION

Thus, based on the results of fibrocolonoscopy and fibrogastroduodenoscopy with biopsy, no data on gastrointestinal malignancies were revealed, amyloid staining was negative, and the results of light chain and myelogram content did not indicate AL amyloidosis and myeloma. However, the presence of severe "diastolic" CHF with thickening of the LV walls in a patient without a history of hypertension or myocardial infarction, the ECG and mainly echocardiography data, and the neurologist's conclusion about polyneuropathy of the hands and feet, systemic amyloidosis of a different nature—transthyretin—could not be excluded, despite the negative results of a biopsy of the mucous membrane rectum. The liver lesion with the phenomena of hepatic cell failure and cholestasis, as well as kidney lesions with signs of decreased functioning and moderate proteinuria, also did not contradict this diagnosis. However, myocardial biopsy was required to verify systemic amyloidosis with predominant heart lesion. Due to the severity of the patient's condition and the futility of the specific treatment in case of confirmation of the diagnosis, it was decided not to conduct the diagnosis for ethical reasons.

During hospitalization with drug therapy for heart failure and hepatoprotectors, the patient's condition improved: exercise tolerance increased, dyspnea decreased, edema disappeared (only foot pastosity remained), and the effects of encephalopathy, liver failure, cholestasis decreased. The patient was discharged in a relatively satisfactory condition for outpatient treatment with a basic diagnosis of systemic amyloidosis. Trepanobiopsy of the sciatic tubercle in the conditions of the Petrov National Medical Research Center (NMRC) of Oncology to exclude the malignant process of the bone was recommended. The patient was also recommended to perform heart MRI to verify signs of amyloidosis of the heart. We would like to note that the patient suffered from a constant form of atrial fibrillation, which often leads to a deterioration in imaging quality during MRI.

Since the final diagnosis of the patient was not verified, we traced his fate. The disease progressed; over the course of a year, the phenomena of cardiac, renal, and liver failure rapidly increased. In the terminal stage, the patient was hospitalized in a cardiology hospital, where he died due to an increase in multiple organ failure. The autopsy results found a systemic senile amyloidosis (transthyretin, histological examination was performed at the Federal State Budgetary Institution Almazov NMRC) with lesions of the heart (heart weight 667 g), lungs, kidneys, adrenal vessels, and colon. Genotyping was not performed. Micronodular liver cirrhosis, chronic inductive pancreatitis in the acute stage, and pancreatic necrosis were also diagnosed. Autopsy data showed that the liver lesion

was not associated with amyloidosis and was explained by micronodular cirrhosis due to venous stasis.

CONCLUSIONS

The presented clinical case shows the difficulties in the intravital diagnosis of transthyretin amyloidosis. According to the literature, the presence of amyloid heart lesion worsens the prognosis of patients as compared with lesions of other organs [17]. The average life expectancy after verification of the diagnosis is a little more than one year [3]. Unfortunately, there are no effective methods at present for the treatment of transthyretin amyloidosis in the stage of developed manifestations of heart failure, but the identification of this pathology in the early stages makes it possible to inhibit the process of amyloid formation.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participant involved in the study.

REFERENCES

1. Adams, D., Cauquil, C., Labeyrie, C., et al., TTR kinetic stabilizers and TTR gene silencing: a new era in therapy for familial amyloidotic polyneuropathies, *Exp. Opin. Pharmacother.*, 2016, vol. 17, no. 6, pp. 791–802.
2. Benson, M.D., Liver transplantation and transthyretin amyloidosis, *Muscle Nerve*, 2013, vol. 47, no. 2, pp. 157–162.
3. Brunjes, D.L., Castano, A., Clemons, A., et al., Transthyretin cardiac amyloidosis in older Americans, *J. Card. Failure*, 2016, vol. 22, no. 12, pp. 996–1003.
4. Coelho, T., Adams, D., Silva, A., et al., Safety and efficacy of RNAi therapy for transthyretin amyloidosis, *New Engl. J. Med.*, 2013, vol. 369, pp. 819–829.
5. Connors, L.H., Sam, F., Skinner, M., et al., Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study, *Circulation*, 2016, vol. 133, pp. 282–290.
6. Falk, R.H. and Durbey, S.W., Amyloid heart disease, *Prog. Cardiovasc. Dis.*, 2010, vol. 52, pp. 347–361.
7. Gillmore, J., Falk, R., Maurer, M., and Hanna, M., Interim results from pilot phase 2 trial of revusiran (ALN-TTRsc), *Proc. American Heart Association (AHA) 2014 Scientific Sessions*, Chicago, 2014, pp. 15–19.
8. Jacobson, D.R., Alexander, A.A., Tagoe, C., and Buxbaum, J.N., Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14333 African-Americans, *Amyloid*, 2015, vol. 22, pp. 171–174.
9. Kanasty, R., Dorkin, J.R., Vegas, A., and Anderson, D., Delivery materials for siRNA therapeutics, *Nat. Mater.*, 2013, vol. 12, pp. 967–977.
10. Koike, H., Tanaka, F., Hashimoto, R., et al., Natural history of transthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas, *J. Neurol. Neurosurg. Psychiatry*, 2012, vol. 83, pp. 152–158.
11. Kyle, R.A., Amyloidosis, *Circulation*, 1995, vol. 91, pp. 1269–1271.
12. Maurer, M.S., Schwartz, J.H., Gundapaneni, B., et al., Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy, *N. Engl. J. Med.*, 2018, vol. 379, no. 11, pp. 1007–1016.
13. Obici, L., Cortese, A., Lozza, A., et al., Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study, *Amyloid*, 2012, vol. 19, suppl. 1, pp. 34–36.
14. Obici, L. and Merlini, G., An overview of drugs currently under investigation for the treatment of transthyretin-related hereditary amyloidosis, *Exp. Opin. Invest. Drugs*, 2014, vol. 23, pp. 1239–1251.
15. Penchala, S.C., Connelly, S., Wang, Y., et al., AG10 inhibits amyloidogenesis and cellular toxicity of the familial amyloid cardiomyopathy-associated V122I transthyretin, *Proc. Natl. Acad. Sci. U.S.A.*, 2013, vol. 110, no. 24, pp. 9992–9997.
16. Phay, M., Blinder, V., Macy, S., et al., Transthyretin aggregate-specific antibodies recognize cryptic epitopes on patient-derived amyloid fibrils, *Rejuvenation Res.*, 2014, vol. 17, no. 2, pp. 97–104.
17. Rapezzi, C., Lorenzini, M., Longhi, S., et al., Cardiac amyloidosis: the great pretender, *Heart Fail Rev.*, 2015, vol. 20, pp. 117–124.
18. Sant'Anna, R., Gallego, P., Robinson, L.Z., et al., Repositioning tolcapone as a potent inhibitor of transthyretin amyloidogenesis and associated cellular toxicity, *Nat. Commun.*, 2016, vol. 7, p. e10787.
19. Sekijima, Y., Tojo, K., Morita, H., et al., Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis, *Amyloid*, 2015, vol. 22, no. 2, pp. 79–83.
20. Sekijima, Y., Uchiyama, S., Tojo, K., et al., High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in the elderly, *Hum. Pathol.*, 2011, vol. 42, pp. 1785–1791.
21. Sekijima, Y., Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments, *J. Neurol. Neurosurg. Psychiatry*, 2015, vol. 86, no. 9, pp. 1036–1043.
22. Sipe, J.D., Benson, M.D., Buxbaum, J.N., et al., Amyloid fibril proteins and clinical classification of the amyloidosis, *Amyloid*, 2014, vol. 21, pp. 221–224.
23. Waddington, C.M. and Benson, M.D., A review of tafamidis for the treatment of transthyretin-related amyloidosis, *Neurol. Ther.*, 2015, vol. 4, pp. 61–79.
24. Westermark, P., Benson, M.D., Buxbaum, J.N., et al., Amyloid: toward terminology clarification. Report from the Nomenclature Committee of the International Society of Amyloidosis, *Amyloid*, 2005, vol. 12, pp. 1–4.

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