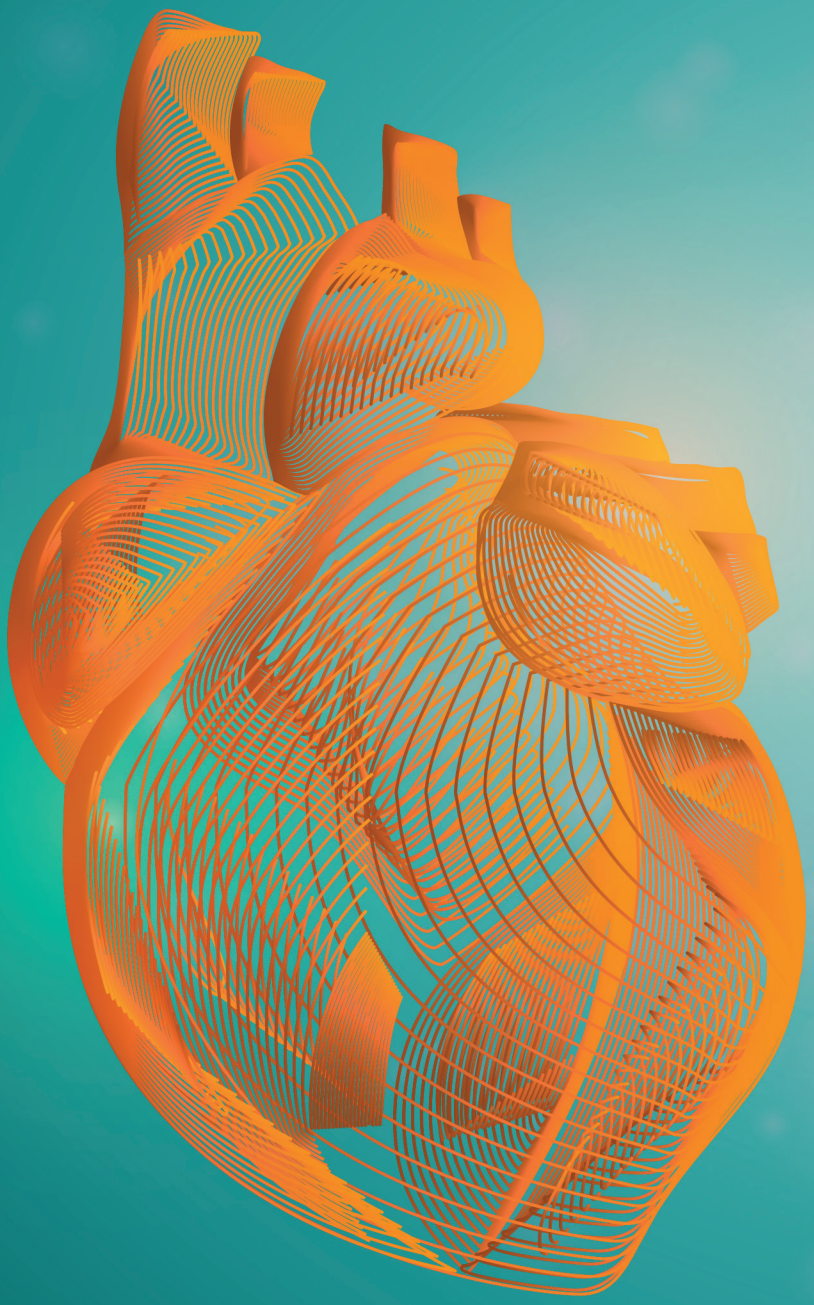
TRANSTHYRETIN AMYLOID CARDIOMYOPATHY

FROM PATIENT'S PERSPECTIVE



Instytut Praw Pacjenta i Edukacji Zdrowotnej

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INTRODUCTION TO THE REPORT

ARKADIUSZ NOWAK, PHD, PRESIDENT OF THE INSTITUTE OF PATIENTS' RIGHTS AND HEALTH EDUCATION

We present you the report „Transthyretin Amyloid Cardiomyopathy From Patient's Perspective" report. The Institute of Patients' Rights and Health Education invited clinicians, patient representatives and healthcare system experts to discuss the current and optimal diagnostic and therapeutic pathway for patients with cardiac amyloidosis. As part of the project, scientific workshops were held, followed by the preparation of this report. We hope that the album entitled „The Faces of ATTR – Stories of Amyloidosis Patients" and the report entitled „Transthyretin amyloidosis cardiomyopathy from patient's perspective" will be a solid basis for building knowledge and awareness about the rare disease – transthyretin amyloidosis cardiomyopathy.

BARTŁOMIEJ CHMIELOWIEC, PATIENT RIGHTS OMBUDSMAN

Dear Sirs,

I am giving you a short comment on "Transthyretin Amyloid Cardiomyopathy From Patient's Perspective" report. I am deeply convinced that creating a space where the voices of experts and people dealing with rare diseases meet is extremely important.

Cardiovascular diseases are one of the most important health problems, not only in Poland but also in the world. However, the affected patients are a diverse group with different needs. Therefore, any initiative that focuses on the experiences and problems of specific groups of patients, including those suffering from rare diseases such as transthyretin amyloid cardiomyopathy, is of great importance.

Patients with rare diseases often go a long way before receiving diagnosis due to the difficult, multi-step diagnostic process. Raising awareness and health education on rare diseases, aimed at both patients and doctors, is of great importance in this context. It is also important that during and after the diagnosis, patients have access not only to treatment consistent with current medical knowledge and comprehensive care, but also to reliable information about their disease. The opportunity to learn from the experiences of other patients is also irreplaceable.

The "Transthyretin Amyloid Cardiomyopathy From Patient's Perspective" report is, thus, an important step to build awareness about this disease and will certainly also be a valuable source of information for affected patients and their relatives.

TRANSTHYRETIN AMYLOID CARDIO-MYOPATHY – CLINICAL PERSPECTIVE

JACEK GRZYBOWSKI MD, PHD
ASSOCIATE PROFESSOR,
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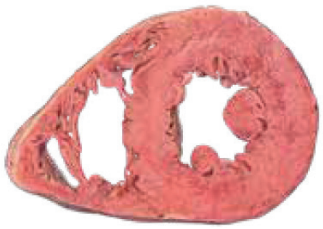
Transthyretin amyloid cardiomyopathy (ATTR-CM) is an ultra-rare infiltration cardiomyopathy, caused by depositing in the extracellular space of the heart muscle amyloid fibers formed by the defective conversion of transthyretin (TTR). There are two main types of amyloidosis ATTR. In the first of them, the precursor of amyloid is the correct TTR protein, which is present in older age. For this reason, this form was formerly called "senile amyloidosis" and is now called wild-type ATTR amyloidosis. The second type of ATTR is hereditary, associated with amyloidogenic mutations in the transthyretin gene. It is endemic, among others, in Portugal. It is very rare in Poland and has so far been diagnosed in only a dozen or so patients.

Transthyretin is a protein produced in the liver whose main physiological role is the transport of thyroxine and retinol. The causes of amyloid formation from transthyretin are not fully understood. We know that amyloid deposition in the heart likely takes many years before cardiomyopathy develops and symptoms of heart damage appear. For this reason, it is so important to diagnose the disease quickly and initiate causal therapy early, before irreversible damage to the heart occurs.

Amyloid may also accumulate in other organs, but the most common clinical presentation of transthyretin amyloidosis is cardiomyopathy with a clinical picture of heart failure. Patients are often referred

Normal heart



A heart with amyloidosis ATTR

Illustrative mapping

to the Cardiomyopathy Department misdiagnosed with sarcomere hypertrophic cardiomyopathy. Transthyretin amyloidosis most often develops under the mask of a restrictive hypertrophic cardiomyopathy, and in its advanced phase a heart failure with a preserved ejection fraction occurs (so-called diastolic heart failure). And it is in these two populations of patients that it should be primarily sought.

Amyloidosis is a disease that has been known since the middle of the 19th century. At the time, however, these were post-mortem diagnoses and we were unable to differentiate between the types of amyloidosis. It was considered an idiopathic disease of unknown cause, not diagnosed in life nor possible to be treated. As medical knowledge advances, we have been learning about the causes of diseases, which is crucial for finding effective treatment methods. New diagnostic methods have been developed, too.

Transthyretin amyloidosis cardiomyopathy is one of two types of amyloidosis. To identify it, we must first exclude amyloidosis from immunoglobulin light chains. Although it is a completely different disease, originating from bone marrow plasma cells, related to multiple myeloma, its cardiological presentation and what we see in cardiac imaging is essentially identical in both types of amyloidosis. Only a more detailed diagnostics allows us to make the correct diagnosis, and this is crucial, because light-chain amyloidosis is increasingly successfully treated by hematologists.

An early diagnosis of ATTR-CM is extremely important because the prognosis worsens rapidly with further amyloid deposition, subsequent progressive organ dysfunction, and there is a significant decrease of the quality of life. The advanced stage of ATTR-CM in untreated patients is associated with serious cardiac complications and a poorer median survival. At diagnosis, the median survival of untreated patients with ATTR-CM and symptomatic heart failure is approximately 2 to 3.5 years. Early, accurate diagnosis of ATTR-CM can benefit patient care and achieve better treatment outcomes.

The diagnostic algorithm for transthyretin amyloidosis has changed from invasive to non-invasive. Historically, amyloidosis was diagnosed by adipose tissue biopsy, and this method is still used in the diagnosis of hematological amyloidosis,

from immunoglobulin light chains. In transthyretin amyloidosis, the sensitivity of adipose tissue biopsy is only a dozen or so percent. Therefore, I would encourage doctors to start with easily accessible non-invasive diagnostics, i.e. echocardiography and, if possible, magnetic resonance imaging of the heart, instead of performing a biopsy. A breakthrough in the diagnostics of transthyretin amyloidosis was the introduction of isotope diagnostics. The test that allows to diagnose this type of amyloidosis with very high accuracy is bone scintigraphy using technetium-labeled diphosphonate (99mTc-DPD). This test has been used in oncology for many years. Only recently has it been confirmed that the only disease where this isotope specifically accumulates in the heart – instead of in the bones – is transthyretin amyloidosis. This test is currently available in Poland in very few nuclear medicine laboratories, because this marker is not registered for heart examination. In every case we suspect amyloidosis, we must differentiate it from light-chain amyloidosis. Currently, we have at our disposal an easily available laboratory diagnostic test that requires only blood and urine samples, in which we look for the presence of monoclonal proteins and assess the level of free light chains. A negative test result in combination with a positive scintigraphy result is sufficient to make a diagnosis of transthyretin amyloidosis.

CHART.

Simplified algorithm for non-invasive diagnosis of ATTR-CM, according to Garcia-Pavia et al.[1]

Symptoms of Amyloidosis („red flags")			
Echocardiography			
Scintigraphic examination with 99m Tc-PYP / DPD /			
HMDP Assessment of monoclonal protein presence in blood and urine			
Scintigraphy – grade 2-3 and free light chains – none	Scintigraphy – grade 1, or scintigraphy – grade 2-3 with free light chains presence	Scintigraphy – grade 0 and free light chains – none	Scintigraphy – grade 0 and free light chains – present
ATTR	Specialist assessment	ATTR and AL unlikely	AL
Genetic test hATTR vs ATTRwt	Histopathological assessment MRI	MRI in questionable cases	Histopathological assessment MRI

Source. Holzman, Kostkiewicz. Terapia, Rok XXIX, Wydanie Specjalne, Listopad 2021

1 Garcia-Pavia P., Rapezzi C., Adler Y. et al..: Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. European Heart Journal 2021, 42: 1554–1568.

The main problem in the diagnosis of heart amyloidosis is still low awareness of this disease. First of all, we should start disseminating information about it among physicians, especially cardiologists. Another important factor is diagnostic vigilance, i.e. the knowledge of alarm sympthoms suggesting the development of the disease (red flags). These two conditions are crucial.

The suspicion of ATTR-CM and the need for further research are related to the following clinical symptoms, especially if multiple:

- preserved ejection fraction (HFpEF) heart failure in patients usually over 60 years of age,
- intolerance to standard treatments for heart failure such as angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and beta blockers,
- incompatibility between the voltage of the QRS complexes on the electrocardiogram (ECG) and the thickness of the left ventricular (LV) wall,
- echocardiography showing left ventricular wall thickening, with concomitant signs of restriction,
- diagnosis of orthopedic conditions, including carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon ruptures, or hip and knee arthroplasty,
- nervous system disorders, including polyneuropathy and disorders of the autonomic nervous system, including gastrointestinal discomfort or unexplained weight loss.[2]

Currently, initial diagnostics include relatively simple, commonly available non-invasive diagnostic methods, i.e. electrocardiography, echocardiography, and finally more and more widely available cardiac biomarkers (NT-proBNP and troponin T). Disseminating knowledge about amyloidosis among physicians is a prerequisite for earlier diagnosis of this disease. A few years ago, the results of a study conducted in the US were published, which showed that only 10% od patients suffering from amyloidosis was diagnosed by the first medical specialist. In turn, at least a quarter of patients were examined by at least five doctors of various specialties before obtaining the diagnosis of amyloidosis. An early diagnosis is very important because it is a progressive disease; amyloid builds up continuously in the heart muscle, and when the heart is heavily afected by amyloid, the symptoms of heart failure begin to progress very quickly. There is no treatment option available in the late stage of the disease. Recently, new drugs are emerging and there are prospects for causal treatment, so an early diagnosis is all the more important. In the last few years, we have diagnosed 39 patients with transthyretin amyloidosis in the Department of Cardiomyopathy of the National Institute of Cardiology in Warsaw – Anin. So far, the number of new diagnoses has been slowly increasing. We estimate that there may currently be around fifty patients eligible for treatment in Poland. If the awareness of the disease and its characteristics among physicians improves, the number of diagnoses will start to increase.

2 Cardiomyopathy in the course of transthyretin amyloidosis (ATTR-CM). ATTR-CM imaging diagnostics by means of scintigraphy. PP-VYN--POL-0064, Pfizer Rare Diseases.

For now, however, in Poland it is not so much a rare disease, but rather an ultra-rare disease.

Patients with amyloidosis often respond poorly to a standard symptomatic treatment — cardiac drugs used to treat hypertension and heart failure — angiotensin converting inhibitors and betablockers. This can be helpful in the diagnosis itself — in older people who are treated with these drugs, at some point the blood pressure drops, there is an intolerance to the treatment used, which is a signal that we may be dealing with amyloidosis. Due to the progressive dysfunction of the autonomic nervous system in the advanced amyloidosis, these drugs greatly exacerbate hypotony and faintness in this mechanism. Sometimes betablockers are needed to control the heart rhythm, but they need to be used them with caution. On the other hand, loop diuretics are the basic symptomatic drugs in the treatment of heart failure in patients suffering from transthyretin amyloidosis

The causal treatment with tafamidis gives hope for patients with cardiac amyloidosis. Tafamidis was approved for the treatment of transthyretin amyloid cardiomyopathy by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020. The drug stabilizes transthyretin tetramers, that is, it prevents the formation of amyloid fibers, acting selectively. It has no anti-inflammatory effect. Tafamidis slows the progression of the disease by stopping the production of amyloid that no longer builds up in the organs, especially the heart. It inhibits the progression of transthyretin amyloidosis, but it doesn't eliminate the amyloid deposits that are already present in the heart. Therefore, it is extremely important that it be applied as early as possible to the patients. It should be remembered that before the introduction of this therapy, the average survival time of patients from the moment of diagnosis of the disease ranged from 2 to 6 years, depending on the severity of the disease at the time of diagnosis. In Poland, tafamidis is not reimbursed yet, it is used as part of charity therapy, financed by the manufacturer, mainly in two specialized centers: in the Department of Cardiomyopathy of the National Institute of Cardiology in Warsaw – Anin and in the Hospital of John Paul II in Krakow. In total, about 40 patients are treated in Poland, including 26 patients in the Department of Cardiomyopathy. The Early Access Programme showed that the youngest enrolled patient was 47 years old and the oldest – 79 years old. In those patients who receive tafamidis in the moderately severe stage of their disease, our initial experience is good and disease progression has been halted. Although our observations are brief, the results are very promising. In the advanced phase of clinical trials, there are currently drugs using a different mechanism of action: they inhibit the expression of the gene responsible for transthyretin production.

In cardiac amyloidosis, a comprehensive care for patients and their families is very important from the beginning of the diagnosis process, through treatment, to rehabilitation. A model example of a clinical centre providing comprehensive care for several thousand patients in Great Britain is the National Amyloidosis Centre (NAC) in Royal Free Hospital and University College London (UCL).

The National Amyloidosis Centre is a fully integrated research and clinical facility that has been

at the forefront of research and treatment for all aspects of amyloidosis for more than 30 years, and has been providing nationwide, highly specialized clinical care since 1999 on behalf of the UK National Health Service (NHS). The activities of the Centre include molecular, genetic, biochemical, physiological, clinical, experimental and pathological research on new drugs, as well as optimization of therapy and rehabilitation. In many of these fields, there are extensive collaborations with scientists, clinicians, and industry. The primary research mission of the National Amyloidosis Centre is to elucidate the basic pathobiological mechanisms in order to improve the diagnostics and treatment of amyloidosis. Multidisciplinary clinical care is provided by specialists in the field of rheumatology, immunology, nephrology, neurology and cardiology.[3] In Poland, in accordance with the recommendations of the Rare Diseases Plan, specialist reference clinical centres providing multidisciplinary and comprehensive care for patients with cardiac amyloidosis should be established. The National Institute of Cardiology in Warsaw – Anin and the Heart and Vascular Diseases Clinic of the Hospital of John Paul II in Krakow.

3 Philip N Hawkins, FMedSci, Marianna Fontana, MD PhD, Julian D Gillmore, MD PhD, The UK National Amyloidosis Centre: The National Amyloidosis Centre at the Royal Free Hospital and University College London is the world's largest amyloidosis centre with almost 1500 patient referrals annually, European Heart Journal, Volume 40, Issue 21, 1 June 2019, Pages 1661–1664, https://doi.org/10.1093/eurheartj/ehz346

TRANSTHYRETIN AMYLOID CARDIO-MYOPATHY – CLINICAL PERSPECTIVE

PROF. PIOTR PODOLEC MD, PHD
HEAD OF THE DEPARTMENT OF HEART AND VESSEL DISEASES OF THE INSTITUTE OF CARDIOLOGY, JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE IN THE JOHN PAUL II SPECIALIST HOSPITAL IN KRAKÓWPLENIPOTENTIARY OF THE DIRECTOR OF THE HOSPITAL FOR RARE DISEASES

Currently, more than 8,000 disease units that meet the criteria for rare disease have been described. Apart from the rare incidence (1/2000), these diseases are characterised by a lack of diagnostic algorithms and therapy and a significant threat to life.

Amyloidosis meets these criteria: it is a multi-organ disease, untreated leads to permanent invalidity and premature death, requires the cooperation of a multi-specialist team of doctors and the support of social workers.

The most important information on pathophysiology, clinical picture, contemporary diagnostic and therapeutic options was presented in the newsletter "Transthyretin cardiac amyloidosis from the patient's perspective" by an excellent expert on this condition, prof. Jacek Grzybowski from the National Institute of Cardiology.

In order to improve the situation of patients, it is undoubtedly necessary to improve the awareness of phycisians: not only cardiologists, neurologists, rheumatologists, but above all primary care physicians and family doctors, and to implement the National Rare Diseases Plan as soon as possible. Like other countries, it is necessary to set up regional centres for rare diseases, where, in addition to research and comprehensive patient care, registers and international consultations would also be carried out.

Since 2011, the Centre for Rare Cardiovascular Diseases has been operating in the John Paul II Specialist Hospital in Kraków within the structures of

the Department of Heart and Vessel Diseases and the Specialist Clinic. Thanks to the Małopolska Regional Operational Programme (2007-2013) funds, a network of cooperation with Polish and European centres (16 units) was established, including experts and permanent international consultations, and with a dedicated website and editing of Journal of Rare Cardiovascular Diseasess (JRCD). During the ESC Congress in Amsterdam a proposal to classify rare cardiovascular diseases was presented. Currently, at the Centre we run treatment programmes for arterial and venous pulmonary hypertension, familial hypercholesterolemia, Fabry's disease, congenital heart defects in juveniles and adults and amyloidosis. Over 2,500 patients with rare diseases, including more than 20 patients with ATTR amyloidosis treated with tafamidis, remain under the supervision of the Department of Heart and Vessel Diseases in the John Paul II Specialist Hospital in Kraków.

Unfortunately, the lack of adequate infrastructure and financing of modern diagnostic methods and research do not allow for shortening the waiting lists and offering comprehensive care for patients with rare diseases. It also applies to amyloidosis. Although the Centre managed to implement modern diagnostics for patients with suspected amyloidosis, including the possibility of performing isotope tests, biopsies, magnetic resonance and laboratory tests, unfortunately we still do not have an efficient treatment programme and treatment reimbursement system.

Tafamidis, after clinical trials, has been approved by the U.S. and European supervisory institutions (EMEA and FDA) and is reimbursed in many countries.

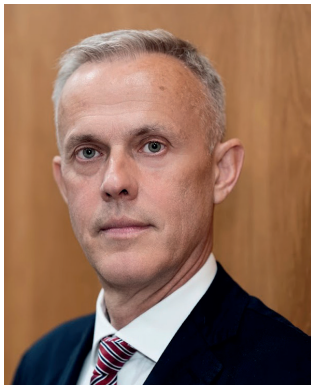
The results of the *Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy* study published in 2022 by Elliott P. (Circ Heart Fail. 2022 Jan;15(1):e008193 doi: 10.1161/CIRCHEARTFAILURE.120.008193), over 50-month follow-up indicates a significant reduction in mortality among patients treated with tafamidis (hazard ratio 0,59 [95% CI, 0,44-0,79]; P<0,001). Mortality was also reduced in the subgroups of hereditary transthyretin amyloidosis (0.57 [0.33-0.99]; P = 0.05) and wild-type transthyretin amyloidosis (0.61 [0.43-0.87]; P = 0.006).

In the recommendations of the European Society of Cardiology of 2021, tafamidis is recommended in two indications in class I: in patients with hereditary transthyretin amyloidosis confirmed in genetic studies and symptoms in NYHA class I or II to reduce symptoms, cardiovascular hospitalisation and mortality, and in patients with wild-type transthyretin-type amyloidosis and symptoms in NYHA class I or II to reduce symptoms, cardiovascular hospitalisation and mortality.

This is also confirmed by the clinical experience of our facility, where so far 21 patients have been treated with tafamidis who have shown improved survival and reduced re-hospitalisation associated with exacerbation of heart failure. No serious side effects were reported during treatment and the capsule formulation provides easy dosing.

It is advisable to urgently implement a drug programme and reimburse tafamidis treatment in this so far incurable disease with extremely unfavorable prognosis. The implementation of comprehensive care and ATTR amyloidosis patient registry is essential for extending and improving the quality of life of amyloidosis patients.

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY – SYSTEM PERSPECTIVE

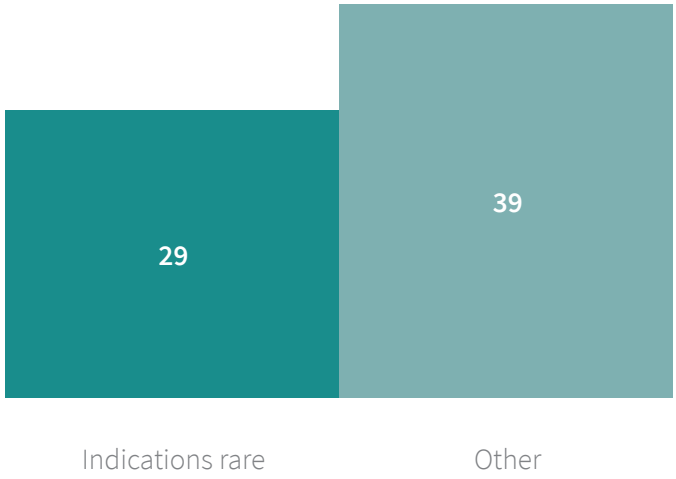


JAKUB GIERCZYŃSKI MD, PHD, MBA

The optimisation of health care in rare diseases is based on two pillars — a comprehensive model of care and access to health technologies, both drug and non-drug. The decisions of the Minister of Health in the last few years have significantly improved the reimbursement access of patients with rare diseases to new drugs. In 2018-2022, the Ministry of Health refunded new drug therapies in rare non-oncological diseases: Fabry, Duchenne, Cushing and Wilson disease, spinal muscle atrophy, acromegaly, hemophilia A and B in children, cystic fibrosis, pulmonary arterial hypertension, primary hyperoxalgia type 1, night haemoglobinuria, acute liver porphyria, phenylketonuria, congenital angioedema, nephropathic cystinosis, polycystic degeneration of the kidneys, Lambert-Eaton myathenic syndrome, aplastic anemia and primary immune thrombocytopenia. Patients with blood cancers and rare solid tumours also received reimbursed access to new drugs in the treatment of: chronic lymphocytic and myeloid leukemia, acute lymphoblastic and myeloid leukemia, myeloma, plasmocytic myeloma, malignant lymphoma, myelofibrosis and mastocytosis, as well as artichoke cell carcinoma, hepatic cell carcinoma, thyroid cancer and Merkel cell cancer. According to the data of the Ministry of Health, in 2021, out of 68 new indications reimbursed, as many as 29 were related to rare diseases.

CHART.

Number of reimbursed new indications in 2021, divided into rare diseases and other diseases – data of the Minister of Health



From a healthcare system perspective, rare diseases affect a small percentage of the population. Treatment is carried out in highly specialized clinical centres, and drugs are reimbursed mainly under the drug programmes of the National Health Fund. In terms of optimizing the model of care for patients with rare diseases, solutions have been prepared and financing has been secured under the Rare Diseases Plan for 2021-2023 and the Medical Fund. The aim of the Healthy Future strategy is to provide citizens with equal and adequate access to high-quality health services, adequate to their health needs, through a friendly, modern and effective health care system.[4]

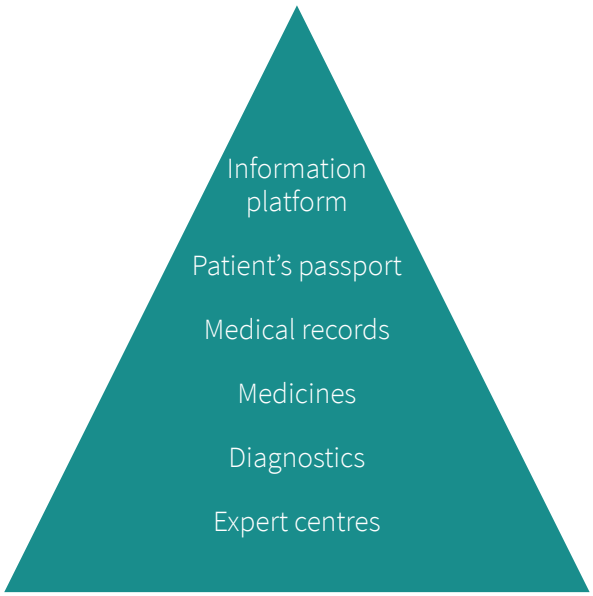
In 2021, the Rare Diseases Plan for the years 2021-2023 was adopted by the Council of Ministers. The plan envisages the creation of national reference centres, defined for a selected rare disease or group of diseases, that will play a key role in the integration of care, as well as collaborating centres of expertise. Access to diagnostics of rare diseases and drugs is to be improved. In addition, medical registers for specific rare diseases, an information platform and a passport of a patient with a rare disease are to be created.[5]

4 Healthy Future. Strategic framework for the development of the health care system for 2021-2027, with a perspective until 2030. https://www.gov.pl/web/zdrowie/zdrowa-przyszlosc-ramy-strategiczne-rozwoju-systemu-ochrony-zdrowia-na-lata-2021-2027-z--perspektywa--do-2030

5 Resolution No. 110 of the Council of Ministers of August 24, 2021 on the adoption of the document Rare Diseases Plan. https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WMP20210000883

CHART.

Six key areas of the Rare Diseases Plan 2021-2023



Approximately PLN 130 million has been allocated to the implementation of the Rare Diseases Plan. A representative of patients with rare diseases was also appointed to the Rare Diseases Council – Mr. Stanisław Maćkowiak, President of the National Forum for the Treatment of Rare Diseases – Orphan.

The model of care for patients with transthyretin amyloidosis cardiomyopathy (ATTR-CM) may soon be fully consistent with the assumptions of the adopted Rare Diseases Plan. Currently, there are 5 multidisciplinary expert centres in Poland – cardiology clinics, which in cooperation with nuclear medicine laboratories conduct comprehensive diagnostics. A registry is also kept.

TABLE.

Assumptions of the Rare Diseases Plan for 2021-2023, and the optimization of diagnostics and therapy of amyloidosis

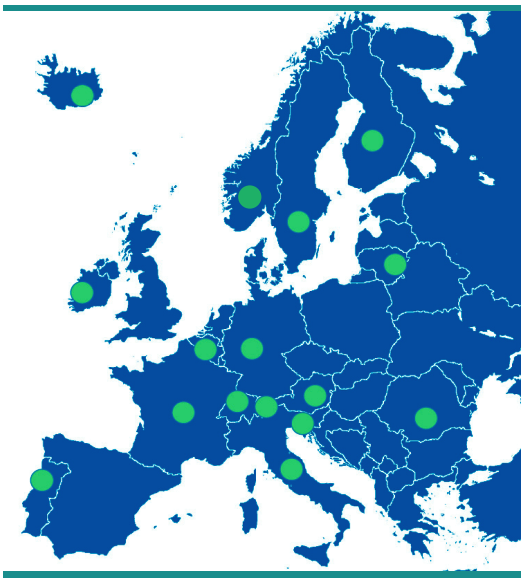
ASSUMPTIONS OF THE RARE DISEASES PLAN FOR 2021-2023	OPTIMIZATION OF DIAGNOSTICS AND THERAPY OF CARDIAC AMYLOIDOSIS IN POLAND FOR 2021-2023
Rare disease expert centres	5-6 expert clinical centres
Directions for improving the diagnostics of rare diseases, including the availability of modern diagnostic methods using genomic technologies	Full ATTR-CM diagnostics
Access to drugs in rare diseases	Tafamidis reimbursement required under the drug programme
Polish Registry of Rare Diseases	ATTR-CM patients registry
Passport of a patient with a rare disease	39 diagnosed patients
Information Platform „Rare Diseases"	Website: https://amyloidoza.edu.pl/login/

At the same time, patients with rare diseases have great hopes for the Medical Fund, to which PLN 4.2 billion is allocated annually, including PLN 720 million for drug reimbursement in rare and oncological diseases.[6] Under the Medical Fund, patients with rare diseases may receive reimbursement for therapies under the List of innovative drug technologies (TLI) and the List of high clinical value drugs (TLK). The lists of these technologies are prepared by the Agency for Health Technology Assessment and Tariffs and approved by the Minister of Health. It is worth appreciating that among the members of the Medical Fund Council, apart from clinicians and officials, representatives of two organizations of patients suffering from rare diseases were appointed – incl. Stanisław Maćkowiak, president of the National Forum for the Treatment of Rare Diseases – Orphan.

Currently, a key postulate of the community of phycisians and patients is the public reimbursement of tafamidis in Poland. Tafamidis was approved in the European Union for the indication of cardiac amyloidosis on February 19, 2020. The drug obtained orphan drug status. It is an oral therapy. Tafamidis is the only causal therapy option for patients suffering from cardiomyopathy associated with transthyretin amyloidosis (cardiac amyloidosis). The results of clinical trials show that the introduction of new pharmacotherapy leads to a reduction in the number of deaths and prolonged life of patients, a reduction in the number of hospitalizations and an increase in the quality of life of patients. Currently, tafamidis is reimbursed in 16 EU / EFTA countries, i.e .: Austria, Belgium, Finland, France, Ireland, Iceland, Lithuania, Luxembourg, Germany, ,Norway, Portugal, Romania, Slovenia, Switzerland, Sweden and Italy. Additionally in other countries reimbursement procedures aimed at increasing the availability of patients to therapy are being procedeed.

CHART.

Public reimbursement of tafamidis in European Union (EU) and European Free Trade Association (EFTA) countries, as of June 2022 – Pfizer data

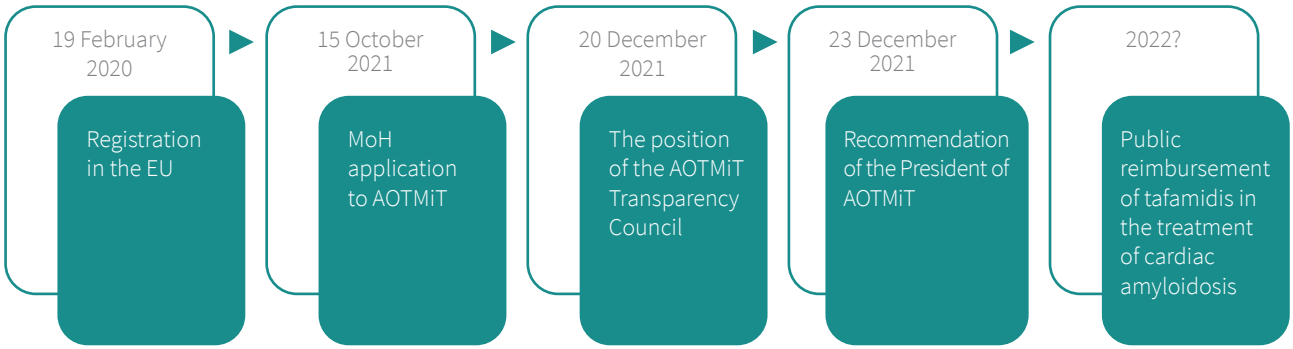


In Poland, the reimbursement procedure for tafamidis began on October 5, 2021. On December 20, 2021, the Transparency Council issued Position No. 143/2021, and on December 23, 2021. The President of the Agency for Health Technology Assessment and Tariff System (AOTMiT) issued Recommendation No. 141/2021 on reimbursement of the medicinal product tafamidis for use under the drug programme "Tafamidis treatment of cardiomyopathy in the course of transthyretin amyloidosis in adults (ICD-10 E85)".

6 Act of October 7, 2020 on the Medical Fund. https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20200001875

CHART.

Tafamidis in the treatment of hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) - the process from registration to public reimbursement in Poland



It should be emphasized that the negative position of the Transparency Council and the negative Recommendation of the President of AOTMiT were justified only by the excessively high cost of tafamidis therapy, and not by the lack of evidence of the effectiveness of this therapy in cardiac amyloidosis. In its Position, the AOTMiT Transparency Council stated that cardiomyopathy in the course of transthyretin amyloidosis (ATTR-CM) is a rare and even less recognized storage disease caused by the accumulation of amyloid fibers – transthyretin in the extracellular space. This results in a gradual deterioration of the diastolic function, and in more advanced stages – also of the systolic function of the left ventricle. It is resistant to the usual treatments for heart failure, resulting in the rapid death of the patient. The mean age of diagnosis is 74; the survival from diagnosis is approx. 4 years. The Council emphasized that, so far, tafamidis has been used mainly for the treatment of amyloid neuropathy. Its efficacy in the treatment of ATTR-CM has been demonstrated in a multicentre randomized trial – ATTR-ACT. Tafamidis in a dose of 80 mg was associated with a 30% reduction in the composite endpoint (causal mortality and cardiovascular hospitalization); this was a statistically significant effect. For the coming years, ATTR-CM will be recognized only in highly specialized centres. Reimbursement recommendations in other countries are divergent (positive: Canadian, New Zealand; negative: British, including NICE, Irish and Dutch).[7] In his recommendation, the President of the Agency for Health Technology Assessment and Tariff System (AOTMiT) stated that the use of tafamidis in a dose of 80 mg was associated with a statistically significant reduction

7 Transparency Council Position No. 143/2021 of December 20, 2021 on the evaluation of Vyndaqel (tafamidisum) under the drug programme „Tafamidis treatment of cardiomyopathy in the course of transthyretin amyloidosis in adults (ICD-10 E85)". AOTMiT, 2021. https://bipold.aotm.gov.pl/assets/files/zlecenia_mz/2021/146/SRP/U_56_332_20122021_s_143_Vyndaqel_tafamidisum_w_ref_prop_REOPTR.pdf

in total mortality (HR = 0.690) and the frequency of hospitalizations for cardiovascular reasons (RR = 0.70). At the same time, in the position it was stressed that the main argument against the financing of the medicinal product tafamidis under the proposed conditions is the results of an economic analysis, according to which the estimated value of ICUR is too high (excesive price of the drug).[8] In its verification analysis, the Agency for the Assessment of Medical Technology and Tarification stressed that the search resulted in 3 positive (HAS 2020, PHARMAC 2019 and CADTH 2020) and 4 negative recommendations (SMC 2021, Zorginstituut 2021, NICE 2021 and NCPE 2020) concerning the reimbursement of tafamidis for the treatment of cardiomyopathy in the course of ATTR. The Canadian CADTH issued a positive recommendation on condition of reducing the price of the drug, while PHARMAC recommends financing tafamidis therapy with an average priority. The positive recommendations mainly draw attention to the lack of financing of alternative pharmaceuticals modifying the progression of the disease, significant clinical benefits and a favorable ratio of effectiveness of the drug to side effects. The negative recommendations mainly draw attention to the lack of cost-efficiency and inconsistent results regarding the effectiveness of tafamidis in different types and stages of ATTR-CM.[9]

It should be emphasised that the proposed tafamidis therapy applies only to estimated 109 patients treated in the first year since the launch of the drug programme, 42 of which are new patients and 141 potentially treated patients in the second year of public reimbursement of tafamidis (51 of which are new patients).

8 Recommendation No. 141/2021 of 23 December 2021 of the President of the Agency for Health Technology Assessment and Tariffs on the reimbursement of the medicinal product tafamidis, soft capsules, 61 mg, 30 capsules (1 × 30), GTIN code: 05415062359426 for use in the drug programme „Tafamidis treatment of transthyretin amyloid cardiomyopathy in adults (ICD-10 E85)". AOTMiT, 2021 https://bipold.aotm.gov.pl/assets/files/zlecenia_mz/2021/146/REK/2021_12_23_BP_Rekomenda- cja_141-2021_Vyndaqel_BIP_REOPTR.pdf

9 Application for reimbursement and official selling price of tafamidis as part of the drug programme for the treatment of transthyretin amyloid cardiomyopathy in adults (ICD-10 E85). Verification analysis. No. OT.4231.49.2021. AOTMiT, 2021. https://bipold.aotm.gov.pl/assets/files/zlecenia_mz/2021/146/AWA/146_OT.4231.49.2021_Vyndaqel_BIP_REOPTR.pdf

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY – PATIENT'S PERSPECTIVE

ZBIGNIEW PAWŁOWSKI, PRESIDENT OF THE ASSOCIATION OF FAMILIES WITH AMYLOIDOSIS ATTR

The Association of Families with Amyloidosis ATTR has been carrying out educational activities for patients and families, as well as aimed at the general public in order to disseminate knowledge about the disease in Poland since 2017. We are a group of people who themselves or their family members suffer from rare Amyloidosis-TTR disease. It is a very rare family (hereditary), progressive, irreversible and fatal disease caused by a defect in the gene responsible for the coding of the TTR protein. Life expectancy in untreated patients suffering from this disease is on average 10 years after the onset of symptoms. Therefore, an early correct diagnosis and choice of treatment options are very important. Due to its rarity, the diagnostics of amyloidosis-TTR is a big challenge for phycisians. This is related to a very little knowledge about the disease, the lack of specialised centres and the undetermined treatment pathway of amyloidosis-TTR. The aim of the Association is to improve the diagnostics of rare diseases and improve the availability of orphan drugs for people suffering from rare genetic diseases. The Association pursues its objectives by launching information campaigns for universal and uninterrupted treatment and rehabilitation of patients with amyloidosis and other diseases with similar biological, mental and social consequences. We strive to promote issues related to amyloidosis and other diseases with similar biological, psychological and social effects in medical scientific research. We work for the benefit of all the patients and their families, with the aim of supporting them in preventing the negative effects of the disease. We support social initiatives and run a website: http://amyloidozattr.pl/

Cardiomyopathy in transthyretin amyloidosis (ATTR-CM) is an extremely rare, debilitating and multi-organ disease that affects adults, often still professionally active. Early detection of transthyretin amyloidosis in the form of cardiomyopathy is increasingly possible due to non-invasive diagnostic methods. This is an important step for patients, because the constant deposition of amyloid and the progressive age of patients affect a sharp deterioration in prognosis. Patients are diagnosed in the age group from 46 to 75 years old, and given the average, stopping the disease process translates into professional activity and its benefits for the society. Regardless of the variant, ATTR-CM is associated with a significant deterioration in the quality of life in the disease. In clinical trials, patients often report physical, social and functional impairment that worsens with the progression of the disease. The average survival time of patients since the diagnosis of the disease, without access to effective causal therapy, is between 2 and 6 years.

The causal therapy registered in the European Union for the treatment of cardiac amyloidosis is tafamidis. The therapy is already reimbursed in 15 countries of the European Union, including countries with similar Gross Domestic Product to Poland, such as Romania, Slovenia and Portugal. Patients with cardiac amyloidosis in Poland are waiting for a public refund of tafamidis, which is a fundamental and still unmet medical need of this group of patients. Tafamidis is a life-saving drug. The estimated population of patients with transthyretin amyloidosis in the form of cardiomyopathy is approx. 100-150 patients who will be diagnosed in the next 2-3 years. Currently, 33 patients in 5 clinical centres have been diagnosed and treated in Poland as part of the manufacturer's early access programme. Full diagnostics of transthyretin amyloidosis cardiomyopathy has been available in Poland since 2018. Both proper diagnostics and treatment of transthyretin amyloidosis cardiomyopathy should be carried out by specialised heart diseases centres in cooperation with nuclear medicine laboratories. However, in order to secure patients' access to diagnostics and treatment, a systemic solution is needed, such as public reimbursement under the drug programme.

A very socially important element is the burden of disease for both patients and their caregivers and families. ATTR symptoms negatively affect patients' independence, and their progressive nature is associated with difficulties in everyday life and the growing need for external care. A large proportion of patients are unable to perform typical homework. Many of them show an inability or decrease in labour productivity resulting from the symptoms of the disease, resulting in a worsening of the financial situation of this group. Caregivers and family of patients with ATTR experience depression, anxiety and fatigue. ATTR-CM, therefore, entails high indirect costs.

We fully agree with the goal of the Healthy Future strategy, which is to provide all Polish citizens with equal and adequate access to quality health services through a friendly, modern and efficient health system. The Rare Diseases Plan also provides access for patients with rare diseases— that is, us – to effective drug therapies and expert centres. Both of these documents support the legitimacy of public reimbursement of tafamidis in the treatment of cardiomyopathy in transthyretin amyloidosis as part of the drug programme in

Poland, and the effect of introducing therapy for patients will be an increase in life expectancy and a significant improvement in the quality of life in the disease.

I was diagnosed with cardiac amyloidosis at the age of 53, so theoretically, there were several years of active professional and social life ahead of me. To my question after receiving the diagnosis: "What's next? What should I do?" an eminent professor answered: "I do not know". I was the addressee of this short sentence, but other patients are, too. This sentence is simply taking away from us what is most important: hope. It will sound very harsh, but our life clock has sped up a lot, pointing to imminent, quick death. But diagnosing amyloidosis cardiomyopathy is only the first step. The most important element is the access to a life-saving drug. And this drug is there. And it works. Thanks to the early access programme, me and the other 32 patients get tafamidis. Another 18 patients are awaiting access to the drug. The effectiveness of tafamidis, in addition to the results of clinical trials, is confirmed by our results of regular studies. You have a vivid example in front of you that thanks to therapy I am a man who got what is the most important and what other patients are waiting for – I got hope! I can live, make plans for the future, I can have a good personal and professional life.

Me and other patients can and want to repay this huge debt of second life to our families, the health system and society working for others. We are determined and willing to help — hence our association. We work with others for others. We cooperate with excellent doctors, nurses, diagnosticians who take care of us with great dedication and care. First of all, we are visible to the system – and until recently we were not; now we can face the adversities together with the raised forehead. I am a qualified sports teacher. I have been active for many years, teaching children and young people how to overcome their weaknesses and fight until the end of the match. I am currently the headmaster of the school and, admittedly, from a different position, but I continue to inculcate and teach children that they are not allowed to give up halfway before the finish line. The match is over after the last whistle, so let's not throw this great effort of so many people away and make the access to the drug for so few happen.

Let's not allow the therapy of transthyretin amyloid cardiomyopathy to be a white spot in the group of rare diseases that have obtained public reimbursement of effective therapies in Poland. Let's all play to the end, until the last whistle, and then we all rejoice at the common victory – public reimbursement of tafamidis in the treatment of cardiac amyloidosis in Poland.

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY - PATIENT'S PERSPECTIVE

AGNIESZKA WOŁCZENKO, PRESIDENT OF THE NATIONAL ASSOCIATION OF PATIENTS WITH HEART AND VASCULAR DISEASES ECOSERCE

People with cardiovascular diseases have been the largest group of patients in Poland for many years. Most cardiovascular diseases take years to develop. Thanks to effective diagnostic and therapeutic solutions, patients can live with their condition longer and in a better quality of life. Many solutions have been known and used in the world for several years. Polish institutions also know these technologies well. In many cases, however, despite many years of experience, effectiveness and safety confirmed in scientific research and positive observations in everyday clinical practice, these solutions are not available to patients in Poland. We must do everything to ensure that effective drugs that save lives and significantly improve the patient's condition are reimbursed. In general, we know exactly how many patients need a specific solution. As a result, it is a budget that can always be estimated and planned. In the case of transthyretin cardiac amyloidosis, only a few dozen patients in Poland need a reimbursed life-saving therapy. This is a very small group of patients, but without this drug, there is no chance for a longer life for them. From the National Consultant in the field of Cardiology and experts of the Polish Cardiology Society, we know that programmes based on comprehensive care for a given group of patients really pass the exam. This means that patients have better treatment effects — their condition improves and stabilises, they don't, have to go back to the hospital so often,

they are more active at the professional, family and social level. Centres can better plan specialist visits and procedures, and this helps spend money more efficiently in case of a limited budget. We are waiting for these solutions. It is high time to take care of cardiac patients.

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY AS A RARE DISEASE – PATIENT'S PERSPECTIVE

STANISŁAW MAĆKOWIAK,
PRESIDENT FO THE NATIONAL FORUM FOR TREATMENT OF RARE DISEASES - ORPHAN

According to the National Orphan Forum Audit 2021: *The needs of patients with rare diseases in accessing health technologies and optimising care*, the needs of this group of patients are still very high. Patient organisations have pointed out various problems in accessing health technologies and the need to create models of care that are appropriate for the disease. 85 % of patient organisations indicated the need to improve access to genetic diagnostics. 76 % of patient organisations stressed the need to change the model of care for patients with rare diseases — especially the creation of reference centres, interdisciplinary care of different specialists and the inclusion of telemedicine solutions. 71 % of patient organisations expressed the need for organisational changes in the education of physicians, the provision of benefits to patients, support for the family and caregivers at school, education and increased access to information, and the creation of a patient registry. 66 % of patient organisations indicated the need to improve access to reimbursement of medicinal products. 32 % of patient organisations indicated improved access to medical devices as part of individual supply, taking into account the increase in funding and the setting of time limits for the use of devices. 21 % of patient organisations saw the need to increase or change the funding model in different care areas. 15 % of patient organisations pointed out.

the need to increase the volume of scientific research, clinical trials and their additional funding. Access to causal therapy in heart amyloidosis is the implementation of the priorities and provisions of the Rare Diseases Plan and the Medical Fund. Patients suffering from rare diseases should be prioritised and taken care of in the process of reimbursement of medicines and benefits. The need for reimbursement of tafamidis in cardiac transthyretin therapy is one of the drug technologies proposed by rare disease patient organizations both in the National Orphan Forum Audit 2021 as well as in the current 2022 Audit.

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY – THE ROLE OF HEALTH EDUCATION

IGOR GRZESIAK,
VICE PRESIDENT OF THE INSTITUTE OF PATIENTS' RIGHTS AND HEALTH EDUCATION

On October 26th, World Amyloidosis Day is celebrated. Meanwhile the life of every patient with this disease runs 365 days a year, hopefully for many, many years.

In 2021, the Institute of Patient Rights and Health Education has released an album entitled "The Faces of ATTR — Stories of Amyloidosis Patients".[10] It shows how people with this rare disease live, what challenges they face and how they deal with adversities. Transthyretin amyloidosis is a very rare and difficult to diagnose disease. Initially, it has no characteristic sympthoms. The awareness of the existence of this disease among phycisians is low, so many patients often wander from doctor to doctor for years in search of the correct diagnosis. In the case of cardiac amyloidosis, the patient's survival time without access to effective treatment is approx. 2-6 years after diagnosis. Therefore, educational activities among patients and physicians – above all cardiologists and GPs — are very important to speed up the diagnosis and start life-saving therapy.

Examples of outstanding educational initiatives in the field of amyloidosis include: the website of the Association of Families with Amyloidosis and the Polish Amyloidosis Network [Polska

10 Oblicza ATTR- historie pacjentów z amyloidozą [Eng. The Faces of ATTR — Stories of Amyloidosis Patients]. The Faces of ATTR — Stories of Amyloidosis Patients. 2021 http://ippez.pl/wp-content/ uploads/2021/03/album_chorobyRzadkie_02.pdf

Sieć Amyloidozy, PSA]. The Polish Amyloidosis Network is an educational and scientific project initiated by a group of specialists of various fields, including hematologists, cardiologists, pathologists, nephrologists, neurologists and radiologists interested in improving the situation of patients with amyloidosis in Poland. The reason for the establishment of PSA are problems with early and proper recognition of various types of amyloidosis in Poland, including the lack of specialised reference centres. It should be emphasised that a patient with amyloidosis diagnosed in an early stage may live for many years or even decades, while the prognosis in late-recognised amyloidosis is very unfavorable. Amyloidoza.edu.pl is a specialised website addressed to both physicians and patients suffering from this condition. In the website you can find: information on the latest clinical trials, digital stories from nationwide and international meetings, information, description and instructional videos on the diagnostics of amyloidosis, or a calendar with upcoming events, scientific conferences. The patient's life and its quality, are extremely important for the website's creators, so the mission of the scientific website amyloidoza.edu.pl is to strive to discover new therapeutic solutions, as well as to collect reliable knowledge about amyloidosis and to learn more about this disease in order to diagnose and treat amyloidosis more effectively. The guarantee of the authenticity of the information provided is a team of the best specialists in the field of amyloidosis.

CONCLUSIONS

Transthyretin amyloid cardiomyopathy is a rare disease that currently affects several dozen diagnosed patients in Poland.

Without access to effective therapy, patients live 2 to 6 years after diagnosis.

In 2020, the tafamidis drug was registered in the European Union, which significantly reduces the mortality of patients with transthyretin amyloid cardiomyopathy and improves their health and quality of life.

Public reimbursement of tafamidis as part of a drug programme implemented by several expert clinical centres will meet the medical needs of patients in Poland.

Access to effective treatment of transthyretin amyloid cardiomyopathy is secured by the provisions of the National Programme of Cardiovascular Diseases, the National Cardiology Network, the Healthy Future strategy, the Rare Diseases Plan and the guidelines of the Medical Fund.

RECOMMENDATIONS

The process of diagnostics and therapy of transthyretin amyloid cardiomyopathy should be optimized based on the experience gained so far in specialized clinical centres in Poland.

Public reimbursement of tafamidis is recommended in the drug programme „Tafamidis treatment of cardiomyopathy in the course of transthyretin amyloidosis in adults".

It is recommended to build awareness on transthyretin amyloid cardiomyopathy among cardiologists and primary care physicians, as well as through patient associations and the media of public awareness of this disease.

Instytut Praw Pacjenta i Edukacji Zdrowotnej

stowarzyszenie rodzin z amyloidozą TTR

Ogólnopolskie Stowarzyszenie Pacjentów ze Schorzeniami Serca i Naczyń EcoSerce

Orphan
Krajowe Forum na rzecz terapii chorób rzadkich