Original Investigation Reports

Transthyretin amyloid cardiomyopathy: clinical features and staging, indications for treatment and mortality

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ABSTRACT

Transthyretin amyloid cardiomyopathy is still an underdiagnosed disease, but it is progressive and fatal without treatment.

Methods: retrospective observational study to describe clinical characteristics, indications for disease-modifying treatment and mortality.

Results: between SEP-2019 and AUG-2024, 32 patients were diagnosed, 24 (75%) men, median age 81.5 years. Eighteen were wild type (56.2%) confirmed by genetic test and 2 of them (11.1%) had the Val30Met variant; in 12/32 (37.5%) the test was not performed. Seven patients (21.8%) were in NYHA class I, 16 (50%) in class II and 9 (28.1%) in class III; there were no patients in class IV. According to the National Amyloidosis Centre of the United Kingdom (NAC) 21 patients (75%) were in stage I, 4 (14%) in II and only 3 (10.7%) in III; 4 cases were not staged. Atrial fibrillation was observed at 16 (50%) and moderate or severe aortic stenosis in 8 (25%). Disease-modifying treatment (tafamidis) was indicated in 17 cases (53.1%) and was effectively received by 8 patients (25%). Nine patients died (28.1%), 7 due to cardiac causes without disease-modifying treatment and 2 due to non-cardiac causes with disease-modifying treatment.

Conclusions: most patients were in NYHA class I and II and NAC stage I and II, and atrial fibrillation and aortic stenosis were very frequent. Disease-modifying treatment was indicated in more than 50% of the cases, but only 25% received it; of the 9 patients who died, 7 were without disease-modifying treatment.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM), considered up to a few years a rare disease, is currently an increasingly diagnosed pathology due to more knowledge and diagnostic methods, mostly noninvasive, which allow its detection. However, still in many cases it is diagnosed in advanced stages, in which the specific treatment is less efficient.[1,2] Transthyretin (TTR) is a tetrameric protein synthesized by the liver, which transports thyroxin and the retinol binding protein; in pathological conditions, the tetramer breaks down into folded dimers and monomers, and these become unstable forming poorly folded amyloidogenic monomers, which form accumulations of small oligomers, later amorphous aggregates and finally insoluble hydrophobic amyloid fibrils of 8-10 Angstroms of diameter, which progressively deposit in the tissues (osteoarticular system, heart, gastrointestinal tract, peripheral and/or autonomic nervous system, skin, subcutaneous tissue, salivary glands, etc.).[3] There are two clinical forms in ATTR-CM: one called wild type, which is the most frequent one, and whose cause is not well known to this date, although in most cases it is related to an advanced age; and another one, less frequent, which is hereditary, also called variant or mutant, caused by a genetic alteration where an amino acid is replaced by another, and this makes the TTR molecule unstable. ATTR-CM consists of amyloid deposition in the myocardial interstitium, causing a toxic restrictive infiltrative cardiomyopathy, with preserved left ventricular ejection fraction (PEF) in most cases. The disease is progressive and deadly depending on the time of diagnosis, but in most cases death occurs in 3.5 to 4 years with no specific treatment.[4,5] The cardiac manifestations could be preceded several years before by extracardiac alterations: tendinous, digestive, neuropathic, urologic, etc., so ATTR-CM should be taken into account in the presence of interventricular septal (IVS) thickness ≥12 mm, accompanied by at least

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one of the so-called red flags.[6] On the other hand, before the suspicion of ATTR-CM, a very aggressive form should always be ruled out, light-chain (AL) amyloidosis, which is lethal in almost 50% of cases within the first 6 months, and whose treatment is completely different.[5] Up to now there are at least 42 precursor proteins of pathological amyloid fibrils known, but 95-98% of cases are by TTR or AL, which in general simplifies diagnosis; but the other, rarer forms should not be forgotten, whose prognosis and treatment are different.[7,8]

The goal of this work is to describe a series of cases of ATTR-CM, diagnosed in a referral center, its clinical characteristics at the time of diagnosis, and indications of disease-modifying treatment and mortality.

MATERIALS AND METHODS

This is an observational retrospective study, where the registry of patients of the institution, with diagnosis of amyloidosis, was investigated from September 18, 2019, to August 2, 2024. During 2020, there were very few studies due to the limitations of the COVID-19 pandemic. For the diagnosis of ATTR-CM, patients were included with symptoms or signs of heart disease, with an interventricular septum thickness ≥12 mm associated to ≥1 of the criteria called red flags, with bone scintigraphy with pyrophosphate labelled with technetium-99m (PYP-Tc99m) or with hydroxymethylene-diphosphonate (HMDP) labelled with technetium-99m *(Table 1)*. Myocardial uptake of the radiotracer was evaluated in planar images with the Perugini grading scale: grade 0 normal bone uptake and absence of cardiac uptake; grade 1 mild cardiac uptake and inferior to bone uptake; grade 2 moderate cardiac uptake accompanied by attenuated bone uptake; grade 3 strong cardiac uptake with mild or absent bone uptake.[9] The images were taken 1 hour and 3 hours after the radiotracer injection. In all cases, it was completed with myocardial SPECT to rule out false positives by blood uptake, and also, other false positives were ruled out (recent myocardial infarction, chest trauma, cardiotoxicity by hydroxychloroquine, etc.); only patients with grades 2 and 3 were included, and lab tests were carried out to rule out monoclonal protein pathology (free light chains in serum, protein immunofixation electrophoresis in serum and 24 h urine). The staging of the disease was made according to the National Amyloidosis Centre (NAC) system.[10] The measurement of glomerular filtration was made with serum creatinine using the 2021 CKD EPI equation. In all patients who gave their consent and in those in whom it was possible for logistical and financial reasons, testing was carried out to identify genetic variants. It was considered that patients were with disaease-modifying treatment when they had continuous therapy with tafamidis 61 mg/day. Data are presented as summation (percentage), mean (standard deviation) or median (quartiles) when it corresponds. The study was approved by the Institutional Committee of Ethics for Health Research (CIEIS) of the institution.

TABLE 1.
Search criteria for cardiac amyloidosis

Main criterion	Red flags
LV wall thickness >12 mm + >1 of the following:	. Heart failure in > 65 years . Aortic stenosis in > 65 years . Hypotension or normal BP if previously hypertensive . Sensitive compromise, autonomic dysfunction . peripheral polyneuropathy . Proteinuria . Skin bruising . Bilateral carpal tunnel syndrome . Biceps tendon tear . Cardiac MRI with subendocardial/ transmural late gadolinium enhancement or increased extracellular volume . Reduced LV global longitudinal strain with apical preservation . Decreased QRS voltage in relation to LV mass . Pseudo Q waves in ECG . AV conduction disorders . Possible family history

(Based on: García-Pavía P et al. Eur Heart J 2021;42:1554–1568.)
AV: atrioventricular; **ECG**: electrocardiogram; **LV:** left ventricle.

RESULTS

There were 66 patients identified in the Amyloidosis registry, of whom 30 were negative in the evaluation, 2 had a teleconsultation with confirmed diagnosis of familial amyloid polyneuropathy by TTR with the Val30Met variant, 2 presented AL and 32 had ATTR-CM confirmed; there were 24 men (75%) and the median of age was 81.5 years *(Figure 1)*. In 18 patients (56.2%), genetic testing was carried out, and in 2 (6.2%) the p.VaL50Met c.148G>A was detected, also known as Val30Met; in 12 patients (37.5%), testing was

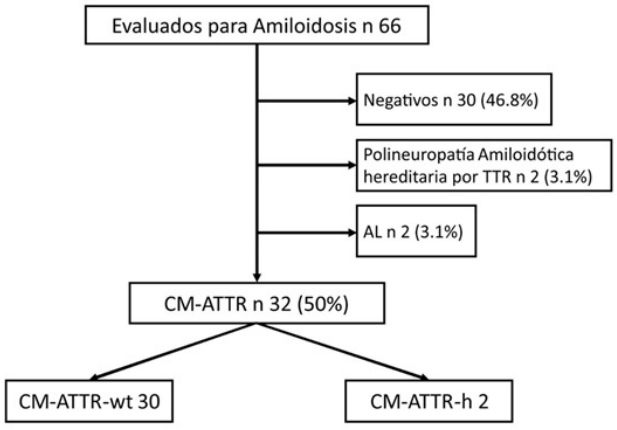


FIGURE 1.
Flowchart of patients with transthyretin amyloidosis
AL: light-chain amyloidosis; **ATTR-CM:** transthyretin amyloid cardiomyopathy; **h:** hereditary; **wt:** wild type; **TTR:** transthyretin.

TABLE 2.
Characteristics of 32 patients with ATTR-CM
ATTR-CM: transthyretin amyloid cardiomyopathy; **h:** hereditary; **wt:** wild type; **ICD:** implantable cardioverter defibrillator; **LVEF:** left ventricular ejection fraction; **PEF:** preserved LVEF; **mrEF:** mildly reduced LVEF; **rEF:** reduced LVEF; **hs-cTnT:** high-sensitivity cardiac troponin T; **PPM:** permanent pacemaker; **NAC UK:** National Amyloidosis Centre United Kingdom; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **NYHA:** New York Heart Association; **GLS:** global longitudinal strain; **VT:** ventricular tachycardia; * also known as Val30Met; ** in some cases there was more than one manifestation in the same patient.

Variables	
Male gender n (%)	24 (75)
Age	mean 79.8 + 7.9 – median 81.5 (74-86)
wt ATTR-CM (confirmed by negative genetic test) n (%)	18/32 (56.2)
ATTR-CM (without genetic test) n (%)	12/32 (37.5)
h ATTR-CM (p.Val50Met c.148G>A)* n (%)	2/18 (11.1)
Perugini score 3 n (%)	27 (84.3)
Perugini score 2 n (%)	5 (15.6)
NYHA class n (%)	
I	7 (21.8)
II	16 (50)
III	9 (28.1)
IV	0
Other extracardiac manifestationsn (%)**	
Gastrointestinal disorders	11 (34.3)
Carpal tunnel syndrome	8 (25)
Peripheral neuropathy	9 (28.1)
Spinal stenosis	5 (15.6)
Orthostatic hypotension	4 (12.5)
Supraspinatus tendon tear	3 (9.3)
Biceps brachii tendon tear	1 (3.1)
Dupuytren contracture	1 (3.1)
Abnormal ECG n (%)	32 (100)
Atrial fibrillation n (%)	16 (50)
Sustained VT n (%)	2 (6.2)
PPM n (%)	5 (15.6)
ICD n (%)	2 (6.2)
LVEF %	mean 53.8 + 9.4 – median 56.5 (50.5-60)
PEF n (%)	24 (75)
mrEF n (%)	2 (6.2)
rEF n (%)	6 (18.7)
E/e´ n=22	mean 19.3 + 8.6 – median 16.5 (15.7-28.7)
GLS n=24 (%)	mean -11.2 + 3.9 – median -9.5 (7.5-14)
Biatrial dilatation n (%)	26 (81.2)
Pericardial effusion n (%)	5 (15.6)
Cardiac tamponade	1 (3.1)
Aortic and mitral sclerosis n (%)	27 (84)
Moderate/severe aortic stenosis n (%)	8 (25)
Severe aortic stenosis n (%)	6 (18.7)
Moderate aortic stenosis n (%)	2 (6.2)
6 min walk test n (%)	15 (46.8)
Cardiac MRI n (%)	16 (50)
NT-proBNP n=26 (pg/mL)	mean 2695 + 2933 – median 1995.5 (749.5-3500.2)
hs-cTnT n=26 (ng/L)	mean 51.5 + 41.6 – median 42.5 (19.2-85.2)
Glomerular filtration (mL/min/1.73 m2)	mean 55.0 + 8.0 – median 53.5 (48.2-63.2)
NAC UK stage n=28	
I n (%)	21 (75)
II n (%)	4 (14.2)
III n (%)	3 (10.7)
Living	23 (71.8)
Deceased	9 (28.1)
Cardiac cause	7
Non-cardiac cause	2

not made due to the family doctor decision, costs, logistics or due to the patient's decision. In *Table 2,* the main findings at the time of diagnosis are described. Approximately one every five patients were in class I of NYHA, half in class II and less than a third in class III; there were no patients in class IV. The most frequent extracardiac manifestations were digestive ones, in 1 in every 3 (particularly constipation that alternated with diarrhea episodes, not justified by any other pathology), followed by peripheral neuropathy (28.1%), carpal tunnel syndrome in 1 in every 4. Other pathologies with less prevalence were spinal stenosis, orthostatic hypotension, supraspinatus tendon tear, and less frequently bilateral biceps brachii tendon tear and Dupuytren contracture *(Table 2).* Among the cardiac manifestations, the most frequent were heart failure (78% in class II and III of NYHA), followed by atrial fibrillation (AF, 50%) and complete heart block (CHB) with permanent pacemaker (PPM) implant. In two patients, sustained ventricular tachycardia (SVT) was detected at the time of the diagnosis, so implantable cardioverter defibrillator (ICD) was implanted; one of them was in NYHA class I and it was his first manifestation of ATTR-CM. In all patients (100%), surface ECG was abnormal. For all the group, the median of LV ejection fraction (LVEF) was 56% (50.5-60), with PEF in 25 (75%) patients, but almost one in five (6 patients, 18.7%) had reduced LVEF (<40%) and 2 (6.2%) had mildly reduced LVEF (40% to 49%). From the 6 patients with reduced LVEF, four died within the period of the study. The median of diastolic function showed E/e´ ratio of 16.5 (15.7-28.7) and global longitudinal strain (GLS) a median of -9.5 (7.5-14); that is to say, severe left ventricular contractile function impairment in spite of preserved LVEF *(Table 2).* Biatrial dilatation and mitral and aortic valve sclerosis were very frequent (>80% of cases), and moderate or severe aortic stenosis was detected in 1 in every 4 patients (in a 58-year-old patient with bicuspid aortic valve and one with double aortic and mitral valve lesion by rheumatic fever in his youth). Eight patients (25%) had severe CAD associated. Five patients presented pericardial effusion (15.6%) and one of them had cardiac tamponade. Cardiac scintigraphy showed score grade 3 in 84% of cases, and the rest were grade 2. In 16/32 patients (50%), cardiac MRI was conducted with gadolinium, and in all cases the typical findings described for this pathology were found; in the rest of the cases it was not made as patients refused

due to claustrophobia, or due to metal devices not compatible with the study (PPM, mechanical heart valves, ICD), or due to the decision of the family doctor. NT-proBNP and hs-cTnT were measured in 26 patients and both biomarkers showed significant elevations, although with a very wide range for NT-proBNP (172 pg/mL to 14,400 pg/mL); the median of glomerular filtration showed mild to moderate deterioration of renal function (stage 3a). In 28/32 patients, staging of the disease was made according to the NAC; in those that this was not made it was because of absence of NT-proBNP measurement. Twenty-one patients (75%) were in stage I, 4 (14%) in stage II and just 3 (10.7%) in stage III. The baseline walk test was made in 15/32 patients (46.8%) and all walked more than 100 m; in the rest, it was not obtained for different reasons: refusal by patients, difficulty to walk due to arthrosis, not coming to the appointment, etc.

During the period studied, 9 patients died (28%), 7 due to cardiac cause and 2 by non-cardiac causes; from those who died, seven had no disease-modifying treatment (tafamidis) and the two remaining ones had it, and both died due to non-cardiac causes: one due to persistent hyponatremia with neurological deterioration (with no brain structural disease in two consecutive CTs), and another one due to sepsis secondary to traumatic skin lesion *(Table 2).*

In regard to disease-modifying treatment, 8 patients (25%) received tafamidis 61 mg continuously, in 5 cases (15.6%), the medication was indicated but there were obstacles to provide them, and in 2 patients (6.4%) the treatment was indicated but they refused it for personal reasons. At the time of this publication, 2 patients (6.4%) are doing the paperwork to obtain the medication from the medical insurance; in other words, in 17/32 cases (53.1%) the indication was considered appropriate. In 5 patients (16%), it was not indicated by cognitive deterioration observed when evaluated by neurologists or the family doctors, or due to an advanced age with frailty, in whom no significant improvement was expected in the next 18 months. Four patients (12.5%) presented severe comorbidities like cancer (Merkel cell carcinoma, stomach cancer) or severe anemia due to chronic non-amyloid gastrointestinal disease (2 patients: one due to upper gastrointestinal bleeding and another due to lower gastrointestinal bleeding); in 3 cases (9.6%), it was not indicated due to the family doctor's decision making the referral to the center, and in an equal number to the Group of Amyloidosis of the institution considering that there would be no benefit from the indication *(Table 3).*

TABLE 3.
Reasons for disease-modifying treatment indication

Characteristics	n (%)
In treatment n (%)	8 (25)
Barriers for the administration of the treatment n (%)	5 (15.6)
Indicated but the patient refuses the treatment n (%)	2 (6.4)
Medication requested and paperwork is advancing with the medical insurance n (%)	2 (6.2)
Not indicated due to cognitive deterioration/ advanced age n (%)	5 (16.1)
Not indicated due to severe comorbidity n (%)	3 (9.3)
Not indicated by family doctor n (%)	3 (9.6)
Not indicated by Amyloidosis Group n (%)	3 (9.6)

DISCUSSION

The main findings in this study were: 1) nearly two thirds of the patients (72%) were in class I and II of NYHA and 79% in stages I and II of NAC; 2) in nearly all cases, there was at least one extracardiac manifestation that preceded the diagnosis of ATTR-CM; 3) in most, LVEF was preserved, but in 1 in every 5, LVEF was mildly reduced or reduced, and in the latter, 4 out of 6 died; 4) AFib was the most frequent arrhythmia, detected in 50% of cases; 5) moderate or severe aortic valve stenosis was diagnosed in 1 in every 4 patients; 6) in more than half of cases, disease-modifying treatment was considered appropriate; 7) from the 9 deceased patients, 7 were without disease-modifying treatment and died due to cardiac causes.

Currently, the incidence and prevalence of ATTR-CM is unknown, but we can state that it is no longer a rare disease; however, it is still underdiagnosed, in part because LVEF is preserved and it is mistakenly diagnosed as other etiologies (HTN, hypertrophic cardiomyopathy, hypertrophy caused by aortic stenosis, etc.).[11,12,13,14] Due to TTR deposition being systemic, extracardiac manifestations are frequent and may precede the heart disease by 5-15 years; particularly gastrointestinal disorders of uncertain origin, non-diabetic peripheral neuropathy with fine fibers compromise, bilateral carpal tunnel syndrome or tendon tears; this is important for timely diagnosis and for the specific treatment to be more efficient.[15,16] Heart failure was the main manifestation in this series; García-Paiva et al. showed that prevalence in patients with heart failure and preserved LVEF was 16.8% and 95% of cases were in class II and III of NYHA (48.4% and 46.8%, respectively).[17] In this series, 78% were in this condition. It is remarkable that from the nine deceased patients, four had reduced LVEF, which would be an indicator of severity and progress of the disease. The ATTR-ACT study (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) showed that in patients in class I through III of NYHA, treated with tafamidis for 30 months, mortality was reduced by 30% and hospital admissions due to cardiovascular causes by 32% in comparison with placebo, although the highest benefit was observed in classes I and II.[18] Patients in class III had more hospital admissions in comparison with those in class II; but in a post-hoc analysis, a significant improvement was observed in quality of life in patients in class III.[19] Furthermore, in the long-term extension trial of the ATTR-ACT (58.5 months of follow-up), where since 30 months all patients received tafamidis, including those who had initially received placebo, mortality reduced by

44% in those in classes I and II of NYHA (0.56 [0.38-0.82]; P=0.003), and in 35% for class III (0.65 [0.41-1.01]; P=0.06). The survival curve tended to change from a descending direction to a more horizontal one in patients who had initially received placebo and later started with the active drug, similarly to the curve of those receiving the drug from the onset of the study.[20] Anyway, the higher benefit in mortality reduction, hospital admissions, quality of life and 6-minute walk tests was observed in those receiving the drug from the onset of the study, indicating that the earliest and longest the treatment, the greater the benefit.[20] In a study in the real world by Nies et al. on 366 patients, 55% were in class I and II of NYHA, while in this small series it was 72%; this clinical condition is important because it would indicate an early stage of the disease, with more potential benefit with the treatment.[21]

Equally, 75% of patients were in stage I of NAC, which also matches a not so advanced age of the disease, a greater survival and greater potential of response to the treatment.[11] Another indicator of ATTR-CM evolution is renal function; the UK National Amyloidosis Centre group showed a >20% reduction in glomerular filtration in one year significantly increases mortality both in the wild type of ATTR-CM and in the hereditary one, and for any of the NAC staging groups.[22]

Typically, ATTR-CM is described as restrictive and with preserved LVEF, although in reality there is contractility impairment that could be detected with GLS measurement, reflecting longitudinal deformity or myocyte contractile function, which was found deteriorated in all patients in whom it was measured, in spite of an apparently normal LVEF.[5,12,16] In ATTR-CM there is also a group of patients that present LVEF <50%. In this series, 25% of cases had reduced or mildly reduced LVEF, so with this condition, the presence of ATTR-CM cannot be ruled out. In this subgroup, probably a low LVEF is due to prolonged evolution of the disease by two mechanisms: 1) a continuous deposition of amyloid fibers in the myocardial interstitium; 2) poorly folded oligomers and monomers of a smaller size (<100 kDa), containing hydrophobic amino acids, bind with the cell membrane causing direct damage to cardiomyocytes and/or nerve fibers, and this is more pronounced in the hereditary forms than in wild-type ones.[23,24] Another factor is that ATTR-CM can coexist with other cardiac pathologies which, in the long run, also affect the LV structure and function, as hypertension, CAD or congenital or rheumatic valve disease, as observed in two cases.

Pericardial effusion was mild in most patients, but there was a severe one with cardiac tamponade, a finding similar to other series.[25] All patients had abnormal ECG, and although they are not described in detail, the whole range of ATTR-CM findings was observed (QRS microvoltage, pseudoinfarctions, discrepancy between LV thickness in echocardiogram or MRI and QRS voltage, AV blocks with PPM implant, branch blocks, etc.). The most frequent arrhythmia was AF, worsening ATTR-CM prognosis; Bandera et al. showed in a histological test on explanted atria, that they present extensive amyloid infiltration with loss of normal architecture, amyloid infiltration in atrial arteries and veins, capillary disruption and subendocardial fibrosis; furthermore, in echocardiogram with speckle tracking on 906 patients with ATTR-CM, they detected increase in atrial rigidity, significant deterioration of the three functional phases of the atria: reservoir, conduit and booster-pump, all of which was related to a poor prognosis. Also, they found that in 22% of patients in sinus rhythm, mechanical contraction of the atria was absent, and this "atrial electromechanical dissociation", as they called it, had a prognosis similar to those with AF.[26] In this center, we have started to measure atrial strain in these patients, as they may require oral anticoagulation even being in sinus rhythm. Ventricular arrhythmias are frequent and non-sustained ventricular tachycardia (NSVT) has been described in up to 74% of patients and SVT or ventricular fibrillation (VF) in 19%; in this series, it was remarkable that a patient debuted with SVT as first manifestation, and another presented NSVT during the diagnostic evaluation.[27] In both, ICD was implanted, and later received appropriate discharges during follow-up. Currently, it is considered that there is not enough evidence for ICD implant as primary prevention in ATTR-CM or AL outside the indications recommended by the Guidelines or Consensuses, and the decision to do it should be individualized.[5] The prevalence of aortic stenosis in ATTR-CM is variable due to the different populations studied (Asian or European), and evaluation methods (imaging and endomyocardial biopsy (EMB)), but there is an agreement that it would be around 6% in patients receiving surgical valve replacement and 16% in transcatheter aortic valve implantation (TAVI); it has been proven by EMB that amyloid deposition may occur in the myocardium and the valve, but also in isolation in the valve with no septal myocardium compromise.[28,29] In this series, the prevalence of moderate or severe aortic stenosis was 25%. Although aortic stenosis and wild-type ATTR-CM is more prevalent since age 65, in a 58-year-old patient, before surgical valve replacement by bicuspid valve in another center, there were signs highly suggestive of amyloidosis in cardiac MRI with gadolinium, which was confirmed 5 years later with PYP-Tc99m. Therefore, in patients with moderate to severe aortic stenosis, if there are red flags or suggestive signs, they should be evaluated for amyloidosis because their prognosis worsens with this association; also in severe stenosis, patients should be evaluated by a Heart Team and TAVI should be considered, as reports have shown better results with pharmacological treatment rather than surgery, because amyloidosis significantly increases morbidity and mortality and surgical risk.[30]

In this institution, the cases of amyloidosis by TTR or AL are discussed in a multidisciplinary group (Amyloidosis Group), where the following intervene: clinical cardiologists, internists, intensivists, imaging specialists, hematologists, neurologists, nephrologists, pulmonologists,

hemodynamics specialists, cardiovascular surgeons and other specialists when it corresponds (ophthalmologists, gastroenterologists, etc.). In the indication of disease-modifying medication, the recommendation of the Group is taken into account, as well as patients' wishes, and the opinion by the family doctor. In this series, 53% of cases had an indication of disease-modifying medication, although just 25% received it effectively; in those that had it indicated and did not receive it, it was due to the decision by the patient or the family doctor, and in 15.6% it was not provided due to access issues. In the remaining 47%, there were different medical reasons to not indicate it, as advanced age or biological conditions in which no benefit is expected in the next 18 months (a period over which, a reduction in mortality was observed with tafamidis in the ATTR-ACT trial), progressive cognitive deterioration, current cancer or another severe condition that may influence poor outcomes in spite of the specific treatment for amyloidosis. In this series, 25% of patients received disease-modifying treatment, similar to the Ioannou et al. study, where 23% of 2001 patients received this treatment, in contrast with 77% of 293 patients that received tafamidis in the real world study by Nies et al., so every case should be carefully evaluated individually and by a team, considering the likely benefits, safety and costs.[5,21,22]

LIMITATIONS

As this is a retrospective, single-center study, some variables were not complete for the 32 patients. The hereditary ATTR-CM research was limited by the decision of the patients or due to logistical reasons, and although we tried to investigate all of them, this was not possible in 37.5% of them, so in spite of the prevalence of the variant form in this group being relatively low, it could be considered unknown. The 6-minute walk test, a marker of the disease progress, was only carried out in nearly 50% of cases. However, the description of clinical, management and mortality variables represent a cohort from the real world.

CONCLUSIONS

In this series of patients with ATTR-CM, 11% of patients with genetic test had the variant or hereditary form, nearly 3 in every 4 patients were in functional class I-II of NYHA and 9 in every 10 in stages I and II of NAC, suggesting that they were diagnosed in relatively early stages of the disease. Fifty percent presented AF and one in every four patients had moderate or severe aortic stenosis. Nine patients (28%) died during the period of study, and from them, seven who had no disease-modifying treatment, did it due to cardiovascular cause; the two remaining ones who had modifying treatment died by non-cardiac causes. In 53% of cases, the disease-modifying treatment was considered indicated, but only 25% received it effectively; in the rest, there were medical reasons to not consider the indication appropriate. The management of patients with ATTR-CM is challenging due to the complexity proper of the pathology and due to the coexisting diseases, so a multidisciplinary team is required for diagnosis, follow-up, treatment indication and rational use of resources and costs.

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