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Treatment of amyloidosis: present and future

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Cardiac amyloidosis (CA) is an infiltrative heart disease resulting from the deposition of amyloid fibrils in the interstitial spaces of the myocardium. The two main forms of CA are represented by light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) in the two forms familial or variant or wild-type or senile. Although considered a rare disease, CA is an underdiagnosed disease. Delay in diagnosis has a negative impact on the prognosis, delaying the initiation of specific therapy. The treatment of both forms of CA is based on: (i) prevention and slowing of the generation and deposition of amyloid fibrils and (ii) supportive care of complications. The main success of recent years has been the development of effective therapies that have been possible thanks to the understanding of the pathophysiology of amyloidosis. For the AL form, new therapeutic combinations between a proteasome inhibitor and a monoclonal antibody have been developed. For ATTR forms, the main strategies are transthyretin (TTR) production 'silencers' and TTR tetramer stabilizers. Supportive care of patients with CA involves various clinical aspects including treatment of heart failure, arrhythmias, conduction disturbances, thrombo-embolism, and the concomitant presence of aortic stenosis.

Introduction

Amyloidosis is a rare and debilitating disease caused by the misfolding of proteins that aggregate amyloid fibrils and are deposited in various organs. Cardiac amyloidosis (CA) is an infiltrative heart disease resulting from the deposition of amyloid fibrils in the interstitial spaces of the myocardium. The two main forms of CA are light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). Amyloid fibrils in the AL form consist of misfolded immunoglobulins produced by clonal proliferation of B-cells or plasma cell dyscrasias originating from the bone marrow. The misfolded fibrils of the ATTR are formed by dissociation either of the wild-type protein (ATTR-wt) or of that produced by the mutation of the transthyretin gene in the familial forms (ATTRv). Both forms of CA can be difficult to recognize and diagnose also due to the presence of non-specific symptoms or overlap with other cardiomyopathies.

Although it is considered a rare disease, data from recent years suggest that CA is an underdiagnosed disease. In fact, the improvement of imaging techniques has made it possible to recognize that some patients previously identified as suffering from hypertensive heart disease, hypertrophic cardiomyopathy, or heart failure with preserved systolic function were in fact affected by CA.[1]

In the US study DISCOVER, the presence of ATTR was demonstrated in nearly 13% of patients hospitalized for heart failure with preserved systolic function, in ~16% of patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR), and in up to 40% of patients at high risk such as that of Afro Caribbean origin with heart failure and increased wall thicknesses of the left ventricle.[2]

Delay in diagnosis has a negative impact on the prognosis, delaying the initiation of specific therapy. Particularly in the AL form, burdened by a worse prognosis, it has been shown that survival was better in those diagnosed within 6 months of the onset of symptoms than in patients who received a late diagnosis and who had an increased risk of death during the period of study (62% 5-year mortality).[3]

The treatment of AL, ATTR-wt, and ATTRv amyloidosis are very different. Therefore, it is crucial to identify the type of amyloidosis and to characterize the fibrils before starting treatment and to assure the patient of the correct care.

The treatment of both forms of CA is based on: (i) prevention and slowing of the generation and deposition of amyloid fibrils and (ii) supportive care of complications.

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Light chain amyloidosis

Treatment of cardiac AL amyloidosis should be guided by a multidisciplinary team involving oncohaematology and cardiology specialists and if possible should be followed by specialized amyloidosis centres.

Patients with AL amyloidosis have a haematologic malignancy with multi-organ involvement. The therapeutic approach and prognosis depend on the degree of cardiac involvement; patients with symptomatic heart failure frequently die within 6 months. However, the average survival has almost doubled in recent years mainly due to advances in chemotherapy. The therapy is based on autologous stem cell transplantation and chemo/immunotherapy against plasma cell dyscrasia. Autologous stem cell transplantation has important restrictions both in terms of age but also and above all of cardiac function and is contraindicated in patients with significant cardiac involvement. Chemotherapy can also be done before autologous stem cell transplantation.

Current guidelines recommend the combination of cyclophosphamide, bortezomib, dexamethasone (CyBorD), and daratumumab as the first-line therapy in patients newly diagnosed with AL.

Bortezomib is a proteasome inhibitor. Proteasomes are involved in reducing proteotoxicity and regulating proteins that control cell progression and apoptosis. Amyloid-generating plasma cells are particularly sensitive to proteasome inhibition because they rely on the proteasome to reduce the toxic effects of light chains and prevent apoptosis.

Daratumumab is a monoclonal antibody (mAb) that binds to CD38, the transmembrane glycoprotein expressed on the surface of plasma cells, causing apoptosis. It is the only agent specifically approved for the treatment of AL amyloidosis when administered with CyBorD. The efficacy of CyBorD-daratumumab is very high, with 78% of patients achieving significant haematologic response (defined as complete response or very good partial response). The median survival in a small group of patients treated with CyBorD ($n = 15$) was 655 days compared with 178 days for those patients treated with other melphalan-dexamethasone-based treatment ($n = 10$).[4]

However, these therapies have numerous side effects including cardiotoxicity which lead to the need to reduce the dose or suspend the treatment and the use of other less effective but more tolerated therapeutic strategies.

Isatuximab, an anti-CD38 mAb similar to daratumumab, is being studied for the treatment of the plasma cell dyscrasia underlying AL.

Three monoclonal antibodies birtamimab, CAEL-101, and AT-03 are currently being studied which aim at the removal of amyloid fibrils from the affected organs, the results of these studies will be able to offer direct proof of the hypothesis that by removing the fibril deposits of light chains from the organs there is an improvement in their function.

Transthyretin amyloidosis

Transthyretin (TTR) is a protein involved in the transport of thyroxine (T4) and retinol-binding protein. Transthyretin is mainly synthesized by the liver and is rich in beta filaments which tend to aggregate into insoluble amyloid fibrils. In the variant or familial form (ATTRv), a single base substitution results in missense mutations which account for the majority of genetic alterations. There are more than 120 mutations that manifest the various presenting phenotypes from those with predominantly neurological impairment with autonomic dysfunction to those with mixed cardiac and neurological forms, and those with predominantly cardiac impairment. The variant most commonly associated with cardiomyopathy is V122I which is present in 34% of African Americans.

Transthyretin amyloidosis wild-type or senile is a sporadic disorder that generally affects elderly men in 80% of cases. Transthyretin amyloidosis amyloidosis should be sought in patients with heart failure, syncope or bradyarrhythmia, conduction disturbances, increased ventricular wall thicknesses and symptoms of dysautonomy, history of carpal tunnel, and biceps tendon rupture.

Transthyretin amyloidosis-induced CA has a more favourable prognosis than AL, with a median survival of 75 months (vs. 11 months). On the other hand, ATTR cardiomyopathy is a progressive disorder with limited therapeutic options until a few years ago. In the last few years, we have been seeing many various trials of specific amyloid drugs that are obtaining promising results. However, one aspect is clear: an early diagnosis is essential to promptly start treatment of cardiac and systemic neurological manifestations since the therapy is more effective in the initial stages of the disease. Current guidelines for the treatment of ATTR amyloidosis include: (i) specific therapies that modify the synthesis, production, and aggregation of amyloid fibrils; (ii) symptomatic therapy for the treatment of neurological and cardiovascular complications; (iii) support; and (iv) genetic counselling for familial forms.

Specific therapy of amyloidosis

There are currently two types of therapeutic strategies that have proven effective for the treatment of ATTR-induced CA: (i) the 'silencing' of TTR synthesis and expression and (ii) the stabilization of TTR proteins with the aim of limiting their degradation. In addition, there are some early stage agents such as 'extractors/degraders', antisense therapies, and inhibitors of TTR aggregation.

Liver transplantation

The liver produces 95% of the TTR measured in serum. Therefore, liver transplantation has historically (since 1990) been proposed as the first-line therapy for the elimination of the main source of amyloidogenic TTR in patients in the familial form (ATTRv), while it is not indicated in the ATTR-wt form. Liver transplantation in young patients in the early stages of the disease has been associated with a high 20-year survival rate. Liver transplantation appears to be more effective in some mutations and less in others such as V122I (the one associated with cardiomyopathy). Combined liver and heart transplantation is also possible in young ATTRv patients with cardiomyopathy, and literature data on a small series of patients suggest that this combination has a better prognosis than heart transplantation alone.

Transthyretin expression silencer

TTR expression can be pharmacologically reduced using agents that 'silence' or block TTR protein synthesis. Antisense oligonucleotides (ASO), such as inotersen (Tegsedi Alkcea Therapeutics), are complementary to the target mRNA and are able to block the production of TTR. Inotersen, administered subcutaneously at a dosage of 300 mg once a week, has been shown to be effective in stabilizing cardiac symptoms in patients with ATTRv cardiomyopathy.[5] Treatment with inotersen significantly improves neurological symptoms, in rare cases causing severe thrombocytopenia and glomerulonephritis which are life-threatening adverse events. In the USA, the drug is prescribed by specialized centres and subjected to regular monitoring programmes. In Italy, the drug has been approved for the treatment of adult patients with hereditary TTR storage amyloidosis (ATTRv) with Stage 1 or 2 polyneuropathy.

Small-interfering RNA (siRNA) drugs, such as patisiran (Onpatro, Alnylam Pharmaceuticals), are a class of small non-coding double-stranded RNA molecules that recognize and degrade target mRNA, in this case TTR mRNA. Patisiran uses lipid nanoparticles that facilitate its hepatic uptake. In the APOLLO study, 225 patients with familial ATTR with polyneuropathy (ATTR-PN) and New York Heart Association (NYHA) Class I–II were assigned to receive patisiran (0.3 mg/kg every 3 weeks) or placebo in a 2:1 ratio and followed for one 18-month follow-up.[6] At follow-up, arrest of progression or regression of polyneuropathy was achieved in the patisiran group. Furthermore, in a predefined group of 126 patients with CA, patisiran reduced left ventricular wall thickness, global longitudinal strain, and obtained a reduction in NTproBNP values.[7] A *post hoc* analysis of the APOLLO study demonstrated a 46% reduction in hospitalization and all-cause mortality in patients randomized to patisiran compared with those on placebo. In a small study of 16 patients studied with cardiac magnetic resonance, patisiran was associated with a reduction in extracellular volume.[8] Patisiran was also investigated in a population of 300 patients with CA due to ATTR (NYHA functional Class I–III, excluding NYHA Class IV) randomized to receive patisiran or placebo and evaluated at 12 months in the APOLLO B study (NCT03997383). Preliminary data were presented at the XVIII International Symposium on Amyloidosis (Heidelberg in Germany, September 2022) and showed that patisiran significantly improved functional capacity, as measured by the walking test 6 minutes walking time and quality of life (QoL) at 12 months, of patients affected by ATTR CA with a good tolerability and safety profile. However, no significant benefit of secondary endpoints including all-cause mortality was demonstrated.

Treatment with patisiran is currently only approved to treat ATTR-PN. Patisiran should also be administered by expert centres. Patients receiving patisiran therapy should premedicate with cortisone and antihistamines to limit infusion-related allergic reactions. Both patisiran and inotersen by dramatically reducing serum levels of TTR, which is a transporter of vitamin A, require additional administration of vitamin A during treatment.

Second-generation small-interfering RNA agents

Vutrisiran (Amvuttra, Alnylam Pharmaceuticals) is a second-generation siRNA that has a high affinity for hepatocytes due to conjugation with *N*-acetyl galactosamine (Gal NAC). Vutrisiran is administered at a dosage of 25 mg subcutaneously every 3 months and does not require premeditation due to the absence of lipid nanoparticles. In the Phase I study in healthy volunteers, vutrisiran caused an 83% reduction in TTR levels at 6 weeks that was sustained up to 90 days. In the HELIOS-A study,[9] vutrisiran has shown, compared with placebo, to reduce NTproBNP values, to improve some echocardiographic parameters and to improve tracer uptake on bone scintigraphy in patients with ATTRv with polyneuropathy.[9] A Phase III study is ongoing in ~600 NYHA functional Class I-III patients with ATTR CA randomized 1:1 to vutrisiran and placebo (HELIOS-B, NCT04153149). A subset of patients will be allowed to take the TTR stabilizer tafamidis in combination. The duration of the study will be 30–36 months with the composite end point of mortality and recurrence of cardiovascular events. Vutrisiran is currently approved for the treatment of ATTR-PN.

Transthyretin stabilizer drugs

Another approach to the treatment of TTR amyloidosis is to stabilize the tetrameric TTR protein complex, thereby preventing its dissociation into amyloidogenic TTR monomers and oligomers. Since both thyroxine sites must be occupied to stabilize the tetramer of TTR, high concentrations of TTR stabilizers are required to prevent it from dissociating.

Diflunisal

Diflunisal is a non-steroidal anti-inflammatory drug that stabilizes the tetramer of TTR. At the recommended dosage for amyloidosis (250 mg/day), lower than that used as an anti-inflammatory, it is well tolerated in practice. It has been shown to be effective in a small study of patients with ATTR-PN. It also appears to have a beneficial therapeutic effect in slowing the progression of ATTR-induced CA with stable heart failure. The most frequent side effects are fluid retention, worsening of heart failure, renal failure, and gastrointestinal bleeding, so it should be used with caution and close monitoring in patients with amyloidosis and cardiac and renal impairment.[10]

Tafamidis (Vindaquel, Pfizer) is an orally bioavailable agent that acts by binding with high affinity and selectivity to thyroxine sites on both wild-type and variant TTR preventing dissociation, unlike diflunisal it lacks non-steroidal anti-inflammatory activity.

The drug was studied in the ATTR-ACT trial[11] which randomized 441 subjects affected by cardiac TTR amyloidosis (wild-type and familial) to 80 or 20 mg of tafamidis or placebo for 30 months. The trial demonstrated that treatment with tafamidis, especially at a dose of 80 mg/day, compared with placebo, was associated with stabilization of TTR in almost all patients, with a significant reduction in all-cause mortality (29.5 vs. 42.9%), to a 32% reduction in hospitalizations for cardiovascular causes in patients

with NYHA Class I and II. A minor reduction in functional capacity as measured by 6MWT was also observed, indicating that tafamidis stabilized the disease, slowing its progression and reducing the decline in QoL indices. However, in a prespecified subgroup of NYHA Class III patients (those in Class IV were excluded from the study), representing those patients with more advanced disease, there was an increase in hospitalizations compared with placebo, as if there was an inverse relationship between efficacy and NYHA class. In a recent report presented at the European Society of Cardiology Heart Failure Congress (26–29 May 2022 in Barcelona, Spain), improved 5-year follow-up survival was reported among NYHA Class III patients treated with tafamidis compared with those treated with placebo. Interesting is the recent analysis of data from the 'long-term extension' study of patients from the ATTR-ACT study which demonstrated that the reduction in mortality can be prolonged in the long term up to a follow-up of 58 months and that the survival was better in the group treated with early tafamidis than in the group with later start of treatment, confirming the importance of early therapy.[12]

In 2019, tafamidis at a dosage of 61 mg in free acid (equivalent to the 80 mg dosage used in the study) became the first therapy for ATTR amyloidosis to be approved by the FDA and later by EMA and AIFA for the treatment of patients with both wild-type and familial ATTR CA.

Acoramidis

Acoramidis (AG10/ALXN2060, Eldos Therapeutics) is a promising new TTR stabilizer under investigation for the treatment of ATTR amyloidosis and appears to be highly effective for the variant form with polyneuropathy, slowing disease progression. Acoramidis binds to TTR more selectively than tafamidis or diflunisal, increases serum TTR tetrameter levels, and appears to be well tolerated. The Eldos AG10 study (ATTRIBUTE-CM-NCT03860935) is a Phase III study that planned to enrol 510 patients with ATTR and cardiomyopathy in a 2:1 ratio to receive either 800 mg acoramidis or placebo twice daily for 30 months. The primary endpoints will be the change in walk distance at 12 months and all-cause mortality and cardiovascular hospitalization rate at 30 months.

New therapeutic approaches to reduce transthyretin

CRISP–Cas9 is a therapeutic approach that is based on the modification or repair of a specific point of the target DNA using a guide RNA. This process leads to: (i) the induction of a cellular repair process to correct the mutation and (ii) the deletion of the mutation or its repair (direct homologous repair) through the inoculated guide RNA. A Phase I study is ongoing investigating NTLA2001 for intravenous infusion in ATTRv patients with polyneuropathy (NC04601051). NTLA2001 uses nanoparticles to release guide RNA and messenger RNA coding for Ca59 protein production with the aim of achieving curative treatment for ATTR with a single administration. Animal data demonstrated that a single dose of NTLA2001 achieved 97% knockdown of TTR protein at 12 months in mice.[13]

Extraction/degradation of amyloid

There are currently two monoclonal antibodies under investigation for the elimination or removal of amyloid fibrils from tissue: NI006 (Neuroimmune; CPHPC) and NN6019-0001 (formerly known as PRX004). They will help us understand if the hypothesis of the removal and improvement of the function is confirmed.

The mAb anti-SAP (serum amyloid P) dezamizumab has not shown improvement in the amount of cardiac amyloid and is currently no longer under study even due to an unfavourable risk/benefit ratio.

Costs of therapy

Although emerging ATTR amyloidosis therapies have shown significant improvement in mortality and morbidity, the costs of these new treatments need to be considered. The annual cost of tafamidis is approximately $250 000/year, making it one of the most expensive cardiovascular therapy drugs on the market. A cost-effectiveness analysis showed that making tafamidis affordable would require a 92.6% reduction in list price.

Supportive care

Supportive care of patients with CA involves various clinical aspects including treatment of heart failure, arrhythmias, conduction disturbances, thrombo-embolism, and the concomitant presence of aortic stenosis. An in-depth analysis of these aspects goes beyond the scope of this review, but it is good to underline the difficulty of treating heart failure in these patients. It should be remembered that patients with amyloidosis are excluded from heart failure studies. Beta-blockers may be poorly tolerated or even contraindicated due to hypotension, rhythm disturbances, and inability to increase cardiac output; ACEi (angiotensin-converting enzyme) or ARBs (angiotensin receptor blockers) are poorly tolerated due to a tendency towards hypotension, although ~30% of patients in the ATTR-ACT study were on beta-blocker or ACEi/ARB therapy, supportive therapy is therefore based on diuretic therapy and mineralocorticoid receptor antagonists. As far as the prevention of thrombo-embolism is concerned, it should be remembered that patients with CA having atrial dysfunction have a high risk of atrial thrombus formation even if in sinus rhythm and anticoagulant therapy is often recommended regardless of the CHA2DS2-VASC score. Amiodarone is the preferred therapy for the treatment of atrial fibrillation, while data on ablation are scarce. Conduction disturbances are frequent in patients with CA and often these patients have an indication for pacemaker) implantation, the indication for cardiac resynchronization therapy implantation is debated but could be recommended in patients in whom a high pacing rate is expected. Implantable cardioverter defibrillator (ICD) implantation is indicated in secondary prevention, while there are no recommendations on ICD implantation in primary prevention. Finally, the association of aortic stenosis and CA is very frequent; this gives the pathology a worsening of the prognosis, improved by treatment with TAVR.[14]

Conclusions

The treatment of amyloidosis has undergone a major change in recent years. Even though we currently have only a few drugs to use for the treatment of CA, very promising new treatments will be available to the cardiologist in the near future. It is fundamental to understand the need to keep the diagnostic suspicion alive whenever the 'red flags' arise to allow for an early diagnosis. It will be the task of future research to individualize the therapy, propose any combinations of drugs to optimize the beneficial effects, identify the selection criteria for starting the treatment, and refine the prognostic evaluation criteria. Screening, monitoring, and treatment strategies for subclinical forms of CA-ATTR will also require further study. Finally, the supportive and specific therapy of patients with advanced heart failure for which mortality and morbidity is still high remains to be defined.

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Data availability

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