What's new in the treatment of amyloidosis? Part 2: Cardiomyopathy due to transthyretin amyloidosis*

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ABSTRACT

Transthyretin deposition amyloidosis is a rare disease caused by the deposition of fibrils of this protein in various tissues, although the most common manifestations are cardiac and neurological. It can be acquired (formerly known as "senile amyloidosis") or hereditary due to mutations in the gene encoding for transthyretin (TTR).

In 2020, the Amyloidosis Study Group created clinical practice guidelines for treating transthyretin amyloidotic cardiomyopathy. Since then, published clinical trials have strengthened the available knowledge, and new lines of research have emerged. This review updates the mentioned guidelines by exploring the state of the art. In the case of transthyretin (TTR) amyloidosis cardiomyopathy, therapeutic strategies are predominantly aimed at reducing the production and aggregation of TTR apart from providing supportive treatment for organ damage. Tafamidis, a TTR stabilizer that prevents its aggregation and deposition, is increasingly supported by evidence for its use in improving the survival of patients with this condition. Gene therapies such as messenger RNA silencers or in vivo gene editing to inhibit the expression of the gene encoding for TTR and generate long-term therapeutic effects are under investigation. Multiple monoclonal antibodies have been part of ongoing clinical trials since 2020.

Key words: amyloidosis, transthyretin, infiltrative cardiomyopathy, treatment, update guidelines

¿Qué hay de nuevo en el tratamiento de la amiloidosis? Parte 2: Cardiomiopatía por amiloidosis por transtiretina*

RESUMEN

La amiloidosis AL es una enfermedad debida al depósito, en órganos y tejidos, de fibrillas formadas por La amiloidosis por depósito de transtiretina es una enfermedad poco frecuente y se debe al depósito de fibrillas de dicha proteína en diversos tejidos, aunque la afectación más frecuente es la cardíaca y

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la neurológica. Puede ser adquirida (antiguamente llamada “amiloidosis senil”) o hereditaria debido a mutaciones en el gen que codifica para la transtiretina.
En 2020, el Grupo de Estudio de Amiloidosis confeccionó guías de práctica clínica para el tratamiento de la cardiomiopatía amiloidea por transtiretina. Desde entonces se han publicado múltiples trabajos que expanden el conocimiento disponible, y existen nuevas líneas de investigación. En esta revisión se actualizan las guías mencionadas explorando el estado del arte.
En el caso de la cardiomiopatía por amiloidosis por transtiretina (TTR), las estrategias terapéuticas están orientadas predominantemente a disminuir la producción y agregación de TTR, además del tratamiento de sostén del daño orgánico. El tafamidis, un estabilizador de la TTR que impide su agregación y depósito, presenta cada vez más evidencia a favor de su uso para mejorar la sobrevida de pacientes con esta patología. Están en estudio terapias génicas como silenciadores de ARN mensajero o la edición génica ***in vivo*** para inhibir la expresión del gen que codifica para la TTR y generar efectos terapéuticos a largo plazo. Desde 2020 hay múltiples anticuerpos monoclonales que forman parte de ensayos clínicos en curso.

Palabras clave: amiloidosis, transtiretina, cardiomiopatía infiltrativa, tratamiento, guías de actualización.

INTRODUCTION

Amyloidosis is considered a rare disease and, as such, has always represented a diagnostic and therapeutic challenge. However, in recent years, there have been significant advances in diagnosing and treatment of the different types of amyloidosis.

The Amyloidosis Study Group (GEA, according to its acronym in Spanish) comprises a multidisciplinary network of medical and non-medical professionals from the Hospital Italiano de Buenos Aires. In 2010, it created the Institutional Amyloidosis Registry, which served as a link for daily interdisciplinary work that includes weekly meetings, clinical sessions, courses, specialized medical consultations, conference presentations, symposium organization, and article publications, all aimed at improving the care of all people with amyloidosis. In 2020, the GEA developed various clinical practice guidelines for treating amyloidosis to provide the medical community with fundamental guidelines based on the best available evidence and considering the applicability of the different recommendations.

Since the year of its creation to date, numerous high-quality clinical trials have shed light on the efficacy of new treatments, and new lines of research have experienced exponential development. This narrative review aims to explore the state of the art in topics on treating transthyretin amyloidosis and, particularly, cardiomyopathy. To this end, the available information is expanded based on the recommendations previously published by the GEA[1].

• Review of recommendations for the treatment of transthyretin amyloid cardiomyopathy

Diflunisal

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that acts to stabilize the transthyretin (TTR) tetramer, preventing the formation of amyloid fibrils. It is administered orally in two daily doses. Its potential adverse effects occur at the gastrointestinal level (bleeding), alteration of renal function, fluid retention, bleeding, and hypertension.

Recommendation 7

In patients with wild-type transthyretin amyloidosis (ATTRwt), with functional class ≤ 3 cardiomyopathy according to the New York Heart Association (NYHA) classification and in the presence of other treatments with approved efficacy, the use of oral diflunisal 250 mg twice daily is not suggested to prevent cardiomyopathy progression, but the evidence is very uncertain.

Evidence Quality: Very Low
Strength: Weak in Favor

“In patients with ATTRwt amyloidosis with functional class ≤ 3 cardiomyopathy (NYHA) and in the presence of other treatments with approved efficacy, **we suggest the use of oral diflunisal 250 mg twice daily to prevent cardiomyopathy progression, but the evidence is uncertain.**”[2]

Previously, there was very low-quality evidence, with weak strength in favor of taking diflunisal, with a less favorable profile of desirable effects/adverse effects (minor desirable effects with moderate undesirable effects). That’s why using this drug was not suggested in previous guidelines.

Currently, new studies from 2022 support the use of diflunisal at a dose of 500 mg/day, orally, in two daily doses, and suggest its use in patients with amyloid heart disease.

In a new study published in June 2022 from the Boston University Amyloidosis Center, 104 patients with ATTRwt amyloidosis with cardiac involvement were retrospectively evaluated, of whom 35 received diflunisal for at least one year between 2006 and 2019. Patients in the diflunisal-treated group were younger (73.8 vs. 76.8 years, p = 0.034), had lower levels of brain natriuretic peptide [(BNP) (335 +/- 67 vs. 520 +/- 296 pg/mL, p = 0.006)],

similar troponin levels (0.1 +/- 0.1 vs. 0.2 +/- 0.3 ng/mL, p = 0.09), and better estimated glomerular filtration rate [(eGFR) (67 +/- 17 vs. 53 +/- 18 mL/min/1.73m2, p = 0.0002)] at baseline. The median follow-up was 3.2 years, and the administration of diflunisal was associated with better survival in an unadjusted analysis [(Hazard ratio, HR, 0.13, 95% confidence interval (CI) 0.05 - 0.36, p < 0.001)], a result that persisted after adjusting for ejection fraction (EF), age, baseline BNP, eGFR, troponin value, septal thickness (HR 0.18, 95% CI: 0.06 - 0.51, p = 0.0006).

Furthermore, its efficacy as a TTR tetramer stabilizer has been recently proved in a study published in November 2022 in the Amyloid Journal, in which plasma concentration of diflunisal and the consequent stabilization of TTR were measured in two groups of previous clinical trials (a placebo-controlled clinical trial and a Japanese open-label trial of patients with hereditary polyneuropathy), demonstrating in both cases that an oral dose of 500 mg/day of diflunisal reached plasma levels necessary to achieve a 95% reduction in plasma TTR protein dissociation, which is sufficient to inhibit aggregation. This is consistent with the clinical efficacy demonstrated by diflunisal at these doses[3]. "In terms of required resources, diflunisal is administered orally and has a lower cost when compared to other potentially usable therapies in ATTR amyloid cardiomyopathy. However, it is not yet available in Argentina."[2]

Tafamidis

Tafamidis is a drug that stabilizes TTR, binding to its tetrameric conformation by preventing its breakdown into unstable amyloidogenic monomers. The route of administration is oral, once daily. It does not present serious adverse events.

Recommendations 8 and 9

In patients with variant transthyretin amyloidosis (ATTRv) or with ATTRwt amyloidosis with functional class ≤ 3 (NYHA), treatment with tafamidis 80 mg (tafamidis meglumine 80 mg/tafamidis free acid 61 mg) orally, once daily, is suggested, as it is likely to reduce overall mortality, cardiovascular mortality, cardiovascular hospitalizations, and progression of cardiomyopathy.

Evidence Quality: Moderate

Strength: Weak in favor[2]

Nowadays, although the evidence in favor continues to be moderate, the recommendation is stronger. The European Society of Cardiology (ESC) has assigned a class 1B recommendation to the use of tafamidis (tafamidis meglumine 80 mg/tafamidis free acid 61 mg) in patients with ATTRv amyloid cardiomyopathy or ATTRwt amyloid cardiomyopathy with NYHA functional class I or II to reduce symptoms, hospitalizations, and mortality[5].

• New lines of research in the treatment of transthyretin amyloidotic cardiomyopathy

Acoramidis (AG10)

Acoramidis, or AG10, is a drug that shares the mechanism of action with tafamidis, as it is a selective stabilizer of TTR. Its dosage is 800 mg, twice a day, orally. It does not present serious adverse events.

There is currently a randomized, double-blind, controlled study (ATTRibute-CM) that is evaluating the efficacy and safety of acoramidis vs. placebo in different outcomes such as the 12-month walk test and mortality, hospitalizations related to cardiovascular disease due to TTR and walking for 30 months. Preliminary 12-month results are currently known in which the primary outcome was not reached (NCT03860935).

Vutrisiran

So far, this gene-silencing drug, which blocks the transcription of TTR mRNA, thereby reducing the production of the TTR protein at the hepatic level, has been approved for treating hereditary TTR polyneuropathy. HELIOS-B is a phase 3, placebo-controlled, double-blind study evaluating the efficacy and safety of vutrisiran in patients with TTR cardiomyopathy. The estimated completion date for this study is 2025. Patients are randomized in a 1:1 ratio to receive 25 mg of vutrisiran or placebo, administered as a subcutaneous injection once every three months for up to 36 months. The primary endpoint will be to evaluate the efficacy of vutrisiran in the composite outcome of reducing all-cause mortality and cardiovascular hospitalizations at 30 months (NCT04153149).

NTLA-2001

An alternative to mRNA silencers is the in vivo gene editing strategy using the CRISPR-Cas9 system (clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease). NTLA-2001 is a novel in vivo gene editing therapy based on CRISPR-Cas9, administered by intravenous infusion, aimed at editing the TTR gene in hepatocytes, resulting in a decrease in the production of both wild-type and mutant TTR after a single administration. In mouse and non-human primate models, single doses resulted in durable reductions in serum TTR protein of 95% or more, a potentially much steeper decline in TTR than currently available therapies.

So far, this therapy has been tested in 6 patients with polyneuropathy, all of whom had a NYHA functional class of I[6]. Administration of this drug was, in each case, associated with sustained reductions in serum TTR protein concentration with a dose-dependent effect (at day 28, 52% reduction in the 0.1 mg/kg dose group and 87% in the 0.3 mg/kg dose group) and mild adverse events.

NI006

NI006 is an investigational human monoclonal antibody targeting TTR amyloid. It is being evaluated in a phase 1 trial in patients with variant or wild-type TTR cardiomyopathy. The first patient was enrolled at the end of 2020[7].

NNC6019-0001

NNC6019-0001 is a humanized monoclonal antibody currently being evaluated in a randomized, double-blind, placebo-controlled study. Patient enrollment in this study began in 2022 and includes patients with ATTRv or ATTRwt amyloidosis with NYHA functional classes II or III. The dosage of NNC6019-0001 is 30 mg/kg or 100 mg/kg, administered intravenously. Follow-up is planned every four weeks for a total of 52 weeks. The primary endpoints are changes in the 6-minute walk test and BNP from baseline. The secondary endpoints include cardiac measurements (echocardiogram with strain, extracellular volume in cardiac MRI, troponin levels), hospitalizations for cardiovascular events, and emergency visits for heart failure.

· Review of Good Clinical Practices

The following are four good clinical practice behaviors developed during the creation of the guide and currently reviewed.

Good Practice 1: The therapy for patients with ATTR cardiomyopathy should focus on supportive treatment, mainly managing arrhythmias and heart failure, and the specific treatment of ATTR[2].

Good Practice 2: In supportive treatment, do not use angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) as they promote hypotension and worsen preload, subsequently deteriorating renal function and cardiac output. Furthermore, whenever possible, we should avoid beta-blockers, as these drugs have poor tolerance in these patients. The negative chronotropic effect of these drugs inhibits the most effective mechanism for improving cardiac output in these patients, which is obtained by increasing the heart rate. Amiodarone can be indicated as an antiarrhythmic.

Calcium channel blockers and digoxin are also not chosen as first-line treatments in these patients, as they could have an amyloid protein binding effect with a higher risk of adverse effects due to digoxin intoxication.

Good practice 3: In supportive treatment, early anticoagulation is recommended in fibrillating patients, and diuretics (preferably loop diuretics like furosemide in combination with potassium-sparing agents, if necessary, to avoid hypokalemia that could impact arrhythmogenic risk). It is vital to monitor conduction abnormalities and consider heart transplantation in patients with advanced heart failure.

Good practice 4: Evaluate treatment efficacy: aim for stability/clinical improvement, biochemical or echocardiographic progress, and patient values[2].

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