What's New in the Treatment of Amyloidosis? Part 3: Familial Amyloidotic Polyneuropathy

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ABSTRACT

Transthyretin amyloidosis is a rare disease caused by the deposition of fibrils of this protein in various tissues, with cardiac and neurological involvement being the most common. It can be acquired (formerly known as 'senile amyloidosis') or hereditary due to mutations in the gene encoding transthyretin (TTR), although this is less common. A common manifestation of mutated TTR (hereafter referred to as ATTRv) is familial amyloid polyneuropathy.

At the Hospital Italiano de Buenos Aires, since 2010, there has been a transdisciplinary group of professionals united by the interest in optimizing the care of people with amyloidosis. This group is formed by professionals from different specialties, with a national reference, focusing on care, education, and research. In 2020, this team, known as the Amyloidosis Study Group (GEA), developed clinical practice guidelines for treating familial amyloid polyneuropathy.

Since then, numerous clinical trials have been published that strengthen the available knowledge and new lines of research are being developed, enhancing and encouraging study in this area. This review provides an update of the existing guidelines regarding transthyretin familial amyloid polyneuropathy and explores the state of the art.

In the treatment of familial amyloid polyneuropathy, the use of patisiran (a small interfering RNA or siRNA aimed at interfering with the hepatic synthesis of transthyretin) is well known. It is currently also approved for patients with a previous liver transplant and symptomatic progression. In addition to this medication, vutrisiran is currently recommended, from the same pharmacological family, but with an easier dosing regimen and an acceptable side effect profile.

In vivo gene editing is also in vogue as a new line of research, being part of multiple ongoing clinical trials.

Key words: transthyretin, amyloidosis, treatment, familial amyloid polyneuropathy.

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¿Qué hay de nuevo en el tratamiento de la amiloidosis? Parte 3: Polineuropatía amiloidótica familiar

RESUMEN

La amiloidosis por depósito de transtiretina es una enfermedad infrecuente y se debe al depósito de fibrillas de dicha proteína en diversos tejidos, aunque la afectación más frecuente es la cardíaca y la neurológica. Puede ser adquirida (antiguamente llamada "amiloidosis senil") o, menos frecuentemente, hereditaria debido a mutaciones en el gen que codifica para la transtiretina (TTR). Una manifestación habitual de la TTR mutada (de ahora en adelante ATTRv) es la polineuropatía amiloidótica familiar.

En el Hospital Italiano de Buenos Aires, desde el año 2010 existe un grupo transdisciplinario de profesionales nucleados por el interés en optimizar la atención de personas con amiloidosis, formado por profesionales de distintas especialidades y de referencia a nivel nacional, con foco en la asistencia, la docencia y la investigación. En el año 2020, este grupo, denominado Grupo de Estudio de Amiloidosis (GEA), confeccionó guías de práctica clínica para el tratamiento de la polineuuropatía amiloidótica familiar. Desde entonces se han publicado múltiples ensayos clínicos que aportan contundencia al conocimiento disponible hasta el momento, mientras están en desarrollo nuevas líneas de investigación que robustecen y estimulan el estudio en el área.

En esta revisión se realiza una actualización de las guías existentes en lo que respecta al tratamiento de la polineuropatía amiloidótica familiar por transtiretina y se explora el estado del arte.

En el tratamiento de la polineuropatía amiloidótica familiar es conocido el uso del patisirán (un siRNA o *small interfering* RNA dirigido a interferir con la síntesis hepatocitaria de transtiretina). Actualmente está aprobado también para pacientes con trasplante hepático previo y progresión sintomática.

Además de este medicamento, hoy se recomienda el vutrisirán, de la misma familia farmacológica pero con una posología de más fácil manejo y un perfil aceptable de efectos adversos.

La edición génica *in vivo* también está en boga como nueva línea de investigación, siendo parte de múltiples ensayos clínicos actuales en curso.

Palabras clave: transtiretina, amiloidosis, tratamiento, polineuropatía amiloidótica familiar.

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 treating the different types of amyloidosis.

At the Hospital Italiano de Buenos Aires, since 2010, there has been a transdisciplinary group of professionals brought together by the interest in optimizing the care of people with amyloidosis, made up of professionals from different specialties and of national reference, with a focus on assistance, teaching, and research. In 2020, this Amyloidosis Study Group (GEA) developed clinical practice guidelines for treating familial amyloidotic polyneuropathy to provide the medical community with fundamental guidelines based on the best available evidence and bearing in mind the applicability of the different recommendations.

Since the year of its creation, numerous high-quality clinical trials have emerged, shedding light on the efficacy of new treatments, and new lines of research have experienced exponential growth. This narrative review aims to explore the state of the art in topics related to the management of familial amyloid polyneuropathy. To this end, the available information is expanded based on the recommendations previously published by GEA.

Review of recommendations for the treatment of hereditary amyloidotic polyneuropathy.

Recommendation 2

In patients with ATTRv amyloidosis and stage I and II neuropathy, treatment with patisiran 0.3 mg/kg intravenous once every three weeks is suggested, given that it is likely to stabilize or slow the progression of neuropathy measured with mNIS +7 and the worsening of quality of life measured with QOL-DN.

Quality of evidence: moderate.

Strength of recommendation: conditional in favor[1].

In 2022, the FDA (Food and Drug Administration of the United States) approved the use of patisiran for patients with progressive neuropathy after liver transplantation at a dose of 0.3 mg/kg intravenously (1 application every three weeks).

According to a prospective, multicenter, open-label phase 3 study,[2] treatment with patisiran in patients with progressive polyneuropathy in ATTRv after liver transplantation is safe and has shown a benefit in improvement of neuropathy, quality of life, and autonomic symptoms.

This study followed 24 patients with ATTRv and progressive polyneuropathy post-liver transplantation for

12 months; it showed a reduction in serum TTR levels, the primary objective outcome, with a median TTR reduction percentage between month 6 and month 12 of 91.0% (95% CI: 86.1-92.3; $p = 4.5 \times 10^{-8}$). The median TTR reduction from baseline was over 80% at all measured time points.

Regarding the study's secondary objective outcomes, at month 12, there was an improvement in neuropathy, quality of life, and dysautonomia symptoms, evidenced by a decrease from baseline in the NIS score with a mean of 3.7 [2.7], a mean reduction in the Norfolk QOL-DN score from baseline of −6.5 [4.9], and a mean decrease in the COMPASS-31 score of −5.0 [2.6] from baseline.

At month 12, disability measures and nutritional scores remained stable.

• New Recommendation for the Treatment of Hereditary Amyloid Polyneuropathy

Vutrisiran

In 2022, the FDA approved vutrisiran at a dose of 25 mg subcutaneously every three months (AMVUTTRA) for the treatment of hereditary ATTR amyloidosis polyneuropathy.

Vutrisiran is a drug from the siRNA (small interfering RNA) group that interferes with the synthesis of both TTRv and TTRwt in the liver.

In the HELIOS-A3 study (Phase III, global, open-label), vutrisiran therapy was compared against an external placebo cohort (APOLLO study), and patients were followed for 18 months. Treatment with vutrisiran led to a statistically significant improvement in the neuropathy score (mNIS+7) compared to placebo (primary objective outcome) at months 9 and 18. Regarding secondary objective outcomes, vutrisiran treatment significantly improved the Norfolk Quality of Life scale compared to placebo at months 9 and 18. Other secondary objective outcomes, such as walking speed, nutritional status, and disability, were statistically significant when comparing vutrisiran treatment to the placebo group.

Vutrisiran was well tolerated, with frequent but only mild or moderate adverse effects. TTR reduction using this dose proved to be non-inferior to treatment with patisiran.

Since it is administered subcutaneously every three months without requiring premedication, it is estimated that the cost for the patient and the healthcare system will be lower with vutrisiran.

The drug is not registered in Argentina and is only available as an exceptional medication. It underwent a review in October 2022 by the National Commission for the Evaluation of Health Technologies and Clinical Excellence (CONETEC)[4].

• New Therapies for Hereditary Amyloid Polyneuropathy

**Eplontersen:* Is is an antisense drug, successor to inotersen, with GalNAc conjugation. It was evaluated in the NEURO-TTRansform study, whose results were published at the end of 2023. This phase 3 study compared plasma levels of serum transthyretin and symptoms/disability associated with ATTR polyneuropathy in 144 patients who received the drug versus a "historical" placebo group used in the Neuro-TTR (a similar study with inotersen from 2017) of 60 patients. In this study, the mean reduction in serum transthyretin in treated patients was 81.7% versus 11.2% in the placebo group (difference in CI 70.4%: 75.2-65.7%, p<0.001), and quality of life scores were statistically significantly better in treated patients, with no severe adverse effects reported.

**Gene Editing:* 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).

Since it is a monogenic disease, TTR amyloidosis is an interesting target for this strategy. The normal function of non-mutated TTR is limited, so knocking down the gene that encodes it would have minimal adverse effects. NTLA-2001 is a new in vivo gene-editing therapy based on CRISPR-Cas9, administered via intravenous infusion. Its goal is to edit the TTR gene in hepatocytes, leading to a reduction 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 sustained reductions in serum TTR protein by 95% or more, a potentially greater reduction in TTR than the one with currently available therapies.

For the time being, it was evaluated in 6 patients with polyneuropathy, all of whom had a New York Heart Association (NYHA) functional class of I6. Administration of this drug was associated in each case with sustained reductions in serum TTR protein concentration with a dose-dependent effect (at day 28, 52% reduction in dose group 0.1 mg/kg and 87% in dose group 0.3 mg/kg) and mild adverse events.

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