New Medications in the Treatment of Hereditary Transthyretin Amyloidosis

Scot Walker¹

Abstract

Hereditary transthyretin amyloidosis is an inherited disorder that results in the gradual progressive deposit of abnormal protein called amyloid in the body's organs and tissues. There are currently no approved drugs to treat transthyretin amyloidosis, and patients may require liver transplantation for survival. There are a few drugs in development to treat hereditary transthyretin amyloidosis either by stabilizing the abnormal protein or by decreasing production of transthyretin. Both methods are being developed to slow progression of the disease.

Keywords

formulary management / P & T, drug information, investigational drugs

Epidemiology

Transthyretin (TTR) is a protein found in serum and cerebrospinal fluid, where it transfers thyroxine and retinol. Hereditary transthyretin (hATTR) amyloidosis is an inherited disorder that results in the gradual progressive deposit of abnormal protein called amyloid in the body's organs and tissues. Most often, the proteins are deposited in the heart, peripheral nervous system, and central nervous system. As the disease progresses, patient's motor skills deteriorate, and walking becomes difficult. In advanced stages of the disease, patients develop neuropathies, gastrointestinal (GI) impairment, and weight loss that can be life-threatening.¹ It is estimated that approximately 50 000 people worldwide have hATTR amyloidosis.² The median survival for patients with a hATTR amyloidosis diagnosis depends on organ system involvement. When neurologic involvement is dominant, survival is estimated to be 5 to 15 years, but cardiac involvement indicates reduced survival of 2.5 to 4 years.¹ Researchers in Portugal estimated the lifetime costs for health care to be \$154 819 per untreated hATTR polyneuropathy patient.³ An analysis of liver transplantation costs estimated a cost of \$1 427 805 per patient for a liver transplantation. This would profoundly increase the lifetime cost in patients who receive a liver transplant.⁴

Current Treatment

There are currently very limited choices in the treatment of hATTR amyloidosis. There are no treatments for prevention or reversal of the disease. Symptomatic treatment is the first line of treatment.¹

Transthyretin proteins are produced in the liver. To inhibit or stop the creation of abnormal amyloids, patients may

receive a liver transplantation.⁵ This is sometimes combined with kidney or heart transplantation depending on organ damage.⁶ Limits in organ availability and the possibility of disease progression in other organs after liver transplantation limits the use of transplants.

Diffunisal complexes with thyroxine binding sites, which stabilizes circulating TTR tetramers.⁷ This leads to an inhibition of the TTR monomer used in amyloidogenesis. In a 2-year, 130 patient, phase III trial, diflunisal reduced the rate of neurological progression and improved the quality of life in patients with familial amyloid polyneuropathy.⁸ Due to the adverse effect profile of nonsteroidal anti-inflammatory drugs, there is an increased risk for GI, cardiac, and nephron toxicity.¹ In the phase III diflunisal trial, there was an increase in GI events, but not renal or cardiac events.⁸

New Treatment Options

Tafamidis is approved in Europe to slow disease progression. The Food and Drug Administration rejected the drug in 2012 due to a limited efficacy data. Tafamidis stabilizes TTR, which delays progression of hATTR. In an 18-month, 128 patient, phase III trial, tafamidis improved the Neuropathy Impairment Score compared with placebo in patients with TTR polyneuropathy.⁹ The drug was shown to slow disease progression for up to 5.5 years in a 71-patient extension of

¹Prescribe Right, LLC, Wildwood, MO, USA

Corresponding Author:

Scot Walker, Chief Executive Officer, Prescribe Right, LLC, 1602 Westglen Farms Dr, Wildwood, MO 63011, USA.
Email: scot.walker@prescriberight.com

Table 1. New Treatment Options.

Generic name	Sponsor	Drug class	Efficacy summary
Inotersen	Akcea Therapeutics	Antisense drug	Improved neuropathy impairment compared with placebo and baseline measurements.
Patisiran	Alnylam Pharmaceuticals	RNAi drug	Improved neuropathy impairment compared with placebo and baseline measurements.
Tafamidis	Pfizer, Inc	PPAR agonist	Reduced all-cause mortality and cardiovascular-related hospitalizations.

Note. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.¹¹ RNAi = RNA interference, peroxisome proliferator-activated receptor = PPAR.

the trial.¹⁰ Pfizer announced that in a 30-month, 441 patient, phase III trial, tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations compared with placebo.

While tafamidis stabilizes TTR proteins to slow disease progression, 2 drugs in development work by decreasing TTR levels (Table 1). Inotersen and patisiran decrease total TTR production (mutant and nonmutant), which leads to lower levels of all TTR. Efficacy is measured in these trials with the Modified Neuropathy Impairment Score + 7 neurological tests (mNIS+7) score, which measures neuropathy impairment.

Inotersen is a weekly subcutaneous injection. The drug binds to TTR messenger RNA leading to the RNA responsible for TTR production to degrade. This prevents both normal and mutant TTR from being formed. Patients receiving inotersen must be monitored for thrombocytopenia and changes in renal function. This would require careful titration and monitoring in patients with renal or cardiac disease. Ionis announced that in a 172 patient, phase III trial, treatment with inotersen resulted in a 20-point improvement in the mNIS+7 score after 15 months in patients with hereditary TTR amyloidosis. While patients had an improvement compared with placebo, treatment with inotersen showed a 5-point decrease in the mNIS+7 from baseline. Inotersen-treated patients also had an improved health quality of life compared with placebo patients. The improvement was maintained during a 12-month open label extension study.

Patisiran is a lipid-formulated RNA interference (RNAi) drug, which blocks creation of both normal and mutant TTR resulting in lower total TTR levels. Patisiran is administered by intravenous infusion every 3 weeks. Patients are pretreated with dexamethasone, oral acetaminophen, ranitidine or famotidine, and diphenhydramine to reduce infusion-related reactions. Patients receiving patisiran should be monitored for infusion reactions and peripheral edema. Alnylam announced that in a 225 patient, 18-month, phase III trial, treatment with patisiran improved the mNIS+7 score by 34 points and quality of life compared with placebo. In addition to an improvement compared with placebo, patisiran-treated patients had an improvement of 6 points compared with their baseline mNIS+7 score. Alnylam also announced that a post hoc analysis of data from this trial estimated a 50% decrease in a composite of all-cause hospitalization and mortality over 18 months.

Author's Note

Information is summarized from selected materials; additional information may be available from other sources. Due to the preapproval nature of the information, non-peer-reviewed data may be utilized. The information provided is meant to provide a way to assess the development status of a new drug and should not be used in making patient care decisions.

Declaration of Conflicting Interests

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References

- Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med*. 2015;47(8): 625-638.
- Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care*. 2017;23(suppl 7):S107-S112.
- Ines M, Coelho T, Conceicao I, Saramago P, Carvalho M, Costa J. Life expectancy and costs of transthyretin familial amyloid polyneuropathy. *Value Health*. 2017;20(9):A553.
- Habka D, Mann D, Landes R, Soto-Gutierrez A. Future economics of liver transplantation: a 20-year cost modeling forecast and the prospect of bioengineering autologous liver grafts. *PLoS One*. 2015;10(7):e0131764.
- Tsuchiya A, Yazaki M, Kametani F, Takei Y, Ikeda S. Marked regression of abdominal fat amyloid in patients with familial amyloid polyneuropathy during long-term follow-up after liver transplantation. *Liver Transpl*. 2008;14(4): 563-570.
- Nelson LM, Penninga L, Sander K, Hansen PB, Villadsen GE, Rasmussen A, Gustafsson F. Long-term outcome in patients treated with combined heart and liver transplantation for familial amyloidotic cardiomyopathy. *Clin Transplant*. 2013;27(2):203-209.
- Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid*. 2006;13(4):236-249.

8. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310(24):2658-2667.
9. Waddington Cruz M, Amass L, Keohane D, Schwartz J, Li H, Gundapaneni B. Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. *Amyloid*. 2016;23(3):178-183.
10. Keohane D, Schwartz J, Gundapaneni B, Stewart M, Amass L. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: additional supportive analyses from the pivotal trial. *Amyloid*. 2017;24(1):30-36.
11. Prescribe Right. Pharmaceutical Pipeline Tracker. 2018. <http://www.prescriberight.com/pharmaceutical-pipeline-tracker.html>. Accessed May 1, 2018.