TREATMENT OVERVIEW

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

Cece has hATTR amyloidosis.

Amyloidosis Research Consortium

ARCI.ORG

KNOWLEDGE IS POWER

ABOUT THE **AMYLOIDOSIS RESEARCH CONSORTIUM**

The Amyloidosis Research Consortium (ARC) is a nonprofit organization dedicated to driving advances in the awareness, science, and treatment of amyloid diseases. ARCs mission is to improve and extend the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery, expand patient access to the most effective care, and improve short- and long-term outcomes. Working with partners in industry, government, and academia, ARC seeks to spark innovation and to bring promising treatments from labs to clinics. Our outreach and educational efforts inform and empower patients, families, caregivers, physicians, and researchers.

To learn more about ARC, visit **www.arci.org** or call **(617) 467-5170**.

Amyloidosis Research Consortium

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INTRODUCTION

We live in a time of rapid advances in genetic know-how and pharmacological technologies. The pace of discovery is accelerating, driving the development of new therapies, with 3 newly approved treatments. The exact course of hATTR varies with each patient, but the outlook holds promise for all. This booklet is designed as a comprehensive guide to help you and your family navigate treatment resources and options that would be most effective for you.

This booklet is not intended to provide medical advice. It is merely an educational tool. Patients should speak with their care team when making any treatment decisions.

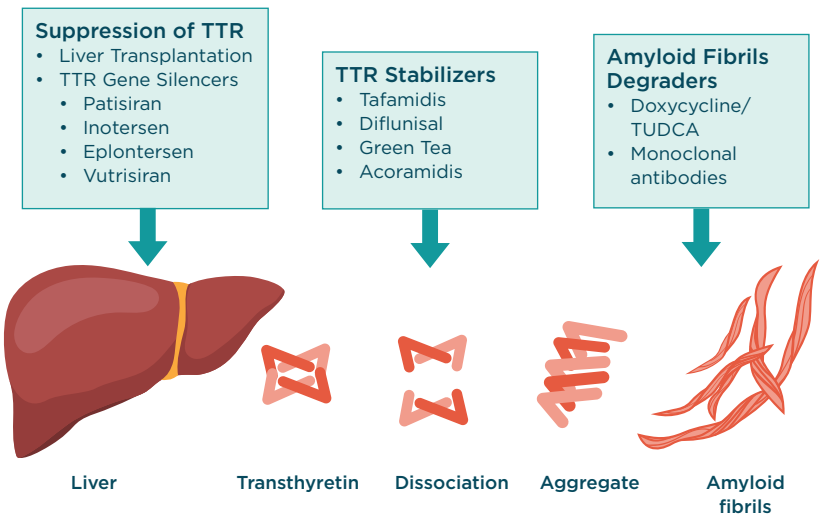
TREATMENT BASICS

While no current therapies can reverse damage caused by amyloid deposits, new drugs can prevent or slow the progression of the disease. Your care will depend on which tissues and organs are affected and how far the disease has advanced.

GOALS OF TREATMENT: AN OVERVIEW

There are a number of ways that therapies approach treating the disease, but ultimately, they have the same goal: to reduce the amount of circulating misfolded TTR. Since TTR is produced in the liver, some treatments target the production at the source using a drug classified as a Gene Silencer, which aims to slow the creation of TTR proteins. Another option, not as frequently used today, is to perform a liver transplant. TTR Stabilizers are another classification of drugs used to treat hATTR. TTR Stabilizers work to prevent the TTR proteins from misfolding and forming amyloid deposits. Another method of treating hATTR is to degrade, or destroy, the amyloid fibrils that have already accumulated. Unfortunately, there are no approved treatments for fibril degradation, but some drugs that were originally designed for other uses are thought to provide this therapeutic benefit in amyloidosis patients. More studies are needed to confirm this.

TREATMENTS THROUGHOUT THE hATTR DISEASE PROCESS



IMPORTANCE OF EARLY TREATMENT

Treatment should start at the first signs of symptom development and once an official diagnosis is made. Early care is essential to slow or prevent progression. For asymptomatic carriers, or those that have had genetic testing and are confirmed to carry a TTR genetic mutation, but do not have any symptoms, the goal is to detect the disease and treat it as soon as symptoms appear. This requires systematic and regular monitoring. Currently, there are no approved treatments for asymptomatic carriers.

If you are a carrier, it is recommended that you are evaluated at an Amyloidosis Treatment Center to create a baseline analysis and discuss the results with a specialist.

Early diagnosis and treatment initiation are essential for the best possible outcomes.

STAGING

Staging relies on tests of your peripheral and autonomic nervous systems and imaging to identify amyloid in your heart or other organs. These test results establish if disease is present, progression of the disease, as well as the suitability of various drugs and procedures to treat it. The four stages of hATTR range from asymptomatic to severe impairment. These are shown in Table 1.

TABLE 1. STAGES OF hATTR NERVE INVOLVEMENT	
Stage 0	no symptoms; TTR gene mutation detected
Stage I	unimpaired walking; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
Stage II	assistance required for walking; moderate impairment with progression to lower limbs, upper limbs, and trunk
Stage III	wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

POLYNEUROPATHY VS. CARDIOMYOPATHY

hATTR is defined by dominant symptoms which are outlined in detail in our first booklet, *Hereditary Transthyretin Amyloidosis: Disease Overview*. Patients can experience polyneuropathy (PN) or cardiomyopathy (CM), or a mix of both. Although new drugs are tested and approved for either polyneuropathy or cardiomyopathy, it's not unusual for patients to experience both symptoms. Your health care team will work with you to develop a treatment strategy that addresses your specific needs.

TREATMENT OPTIONS

DISEASE-MODIFYING THERAPIES

While therapeutic support strategies relieve symptoms and manage affected organs (Table 2 on page 13), disease-modifying treatments attack the disease itself. From liver transplants to the frontiers of molecular and genetic medicine, there are many new treatment options to help hATTR patients control their disease.

APPROVED TREATMENTS

ATTRUBY™ (acoramidis)

Acoramidis is a TTR stabilizer approved for use in the U.S. treating patients with transthyretin amyloidosis (ATTR) who have heart involvement (cardiomyopathy). The drug works by binding to the TTR protein and helping to stabilize that protein structure, preventing it from breaking down, misfolding, & forming fibrils.

In the randomized, double-blind, placebo-controlled Phase III clinical trial, acoramidis resulted in a statistically significant better combined outcome that took into account death, hospitalization, biomarker and function.

Acoramidis was generally well tolerated. The most commonly observed side effects in clinical trials were cardiac failure, AFib, COVID-19, acute kidney injury, shortness of breath and constipation. Acoramidis is taken by mouth at 712 mg twice a day. BridgeBio (Palo Alto, CA, USA) www.bridgebio.com.

WAINUA™ (eplontersen)

Eplontersen is a liver targeting, Ligand-Conjugated Antisense (LICA) gene silencing agent that prevents production of TTR protein by binding to messenger RNA (mRNA). In the NEURO-TTR phase III randomized, controlled trial, participants receiving eplontersen experienced a sustained decrease in transthyretin levels, which significantly slowed disease progression. Participants receiving eplontersen also demonstrated significantly improved quality of life and neuropathic symptoms.

Eplontersen is a monthly self-administered subcutaneous (under the skin) injection. The recommended dose is 45 mg, which comes in a pre-filled autoinjector containing 0.8 mL of solution. Reported side effects include decreased vitamin A levels, vomiting, and an increase in protein levels in the urine. Injection site reactions included erythema, pain, and itching. About 6% of participants in the study also experienced cataract or blurred vision.

Eplontersen in approved in the United States to treat to treat stage I or II hATTR-PN. AstraZeneca and Ionis Pharmaceuticals. (Gaithersburg, MD and Carlsbad, CA). www.astrazeneca.com

TEGSEDI® (inotersen)

Inotersen is an antisense oligodeoxynucleotide (ASO), a gene silencing agent that prevents production of TTR protein by binding to messenger RNA (mRNA).

In the NEURO-TTR phase III randomized, controlled trial, it significantly improved quality of life and neuropathic symptoms. It also reduced pain, numbness, weakness, movement problems, diarrhea, constipation, and abnormal heartbeat.

Due to the possibility of severe side effects, including serious bleeding and kidney disease in some patients, distribution is restricted. The drug is only available through the Akcea Therapeutics (Boston, MA USA) TEGSEDI® REMS (Risk Evaluation and Mitigation Strategy) program. Patients need to enroll and agree to weekly blood tests and biweekly urine protein checks, although in-home phlebotomy is an option.

Inotersen is approved in the U.S. and Europe to treat stage I or II hATTR-PN. It is self-injected weekly using a prefilled syringe. The injection is sub-cutaneous (under the skin). Akcea Therapeutics (Boston, MA USA) www.akceatx.com

ONPATTRO® (patisiran)

Patisiran is an RNA interference (RNAi), another type of gene silencer that prevents production of TTR in the liver and reduces levels in the blood. In the phase III APOLLO clinical trial, it significantly improved symptoms of polyneuropathy as well as walking, quality of life, and activities of daily living. Some patients also experienced improved cardiac function.

Patisiran is administered via an 80-minute intravenous (IV) infusion, usually in a clinic, once every three weeks. Reported side effects include mild or moderate infusion-related reactions and vitamin A deficiency. It is important to note that "pre-drugs" are also prescribed, which include corticosteroids, acetaminophen, and antihistamines to prepare for the infusion. Patisiran is approved in the U.S. and Europe to treat stage I or II hATTR-PN.
Alnylam Pharmaceuticals (Cambridge, MA, USA) www.alnylam.com

AMVUTTRA® (vutrisiran)

Amvuttra (vutrisiran) is another RNA interference (RNAi) gene-silencer designed to inhibit production of the transthyretin (TTR) protein in the liver, thereby reducing the levels of TTR in the body, preventing amyloid build-up and organ damage. Amvuttra has been approved for hATTR patients with polynuropathy (nerve damage) and is being investigated for both hATTR and ATTRwt patients with cardiomyopathy. Amvuttra is delivered through a subcutaneous (under the skin) injection administered by a health care professional in a hospital or clinic setting once every three months. In the phase III HELIOS-A clinical trial, it significantly improved neuropathy impairment, including reversal of polyneuropathy symptoms, as well as walking, quality of life, nutritional status, and activities of daily living. Amvuttra offers hATTR patients with polyneuropathy symptoms an additional treatment option to the two treatments currently approved: Onpattro® and Tegsedi®. (Alnylam Pharmaceuticals) www.amvuttra.com

VYNDAQEL®/VYNDAMAX® (tafamidis)

Tafamidis is a selective TTR stabilizer that works by binding to TTR protein to prevent misfolding that leads to amyloid fibrils. The drug slows disease progression in early-stage hATTR-PN (stages I - III), and is approved for that use in Europe, Mexico, Japan, Argentina and other countries. In the U.S., it is approved to treat cardiomyopathy in adults with hATTR.

In a phase III randomized clinical trial in patients with hATTR-CM, tafamidis significantly reduced all-cause death and heart disease-related hospitalizations in patients with early disease. It also slowed loss of function and helped maintain quality of life.

Tafamidis has very few reported side effects in patients with cardiomyopathy. It is taken orally in once-daily 80 mg or 61mg dose. Pfizer (New York, NY USA) www.pfizer.com

Liver and other organ transplants

Most of the transthyretin (TTR) produced in the body is created in the liver. Orthotopic liver transplant (OLT) replaces the major source of TTR proteins to slow the course of the disease. OLT has historically been used as a treatment for patients with early-stage polyneuropathy, but it not as common today due to mortality, cost, and disease recurrence after transplant. The best time to be referred for an orthotopic liver transplant (OLT) is early in stage I. Depending on damage to the heart or other organs, a heart or other organ transplant may also be considered.

Transplantation, though well-established, is costly and high-risk. Post-transplant complications are common. Outcomes depend on age of onset and type of mutation. Other factors include age at the time of transplant and nutritional status. Transplant slows the disease but does not stop it.

Off-label treatments are prescribed by physicians based on expert opinion, small study outcomes, or clinical experience. Because the claims can often be misleading, you should discuss them with your health care provider to find out if they might be right for you.

ALTERNATIVE TREATMENTS AND OFF-LABEL USAGE

Some drugs or therapies that were originally created for the treatment of other diseases or ailments have been found to also provide therapeutic benefits to amyloidosis patients. Since they are not approved for the treatment of amyloidosis, using them would be considered "off-label." Your health care team can help you make informed treatment decisions about what might be the best choice for you.

DOLOBID® (diflunisal; Off-label)

Diflunisal is an NSAID (non-steroidal anti-inflammatory drug) that also works as a TTR stabilizer. NSAIDs are common medications to reduce inflammation and diflunisal is also used in patients to decrease arthritis pain. It may be prescribed off-label for treating ATTR polyneuropathy, with limited data in ATTR cardiomyopathy usage.

In a 24-month randomized clinical trial in patients with hATTR-PN, diflunisal slowed progression and preserved quality of life. It also led to a two- to threefold improvement in neuropathy impairment scores. In a nonrandomized single-center study in patients with hATTR-CM, it delivered a significant survival benefit.

The drug is taken orally (250 mg) twice a day and is widely available at low cost. Side effects are kidney disease, gastrointestinal upset or bleeding, and worsening of fluid retention thus, it is not suitable for all patients. Merck and Co., Inc. (Whitehouse Station, NJ USA) www.merck.com

Doxycycline (Off-label)

Doxycycline is an antibiotic that may disrupt or degrade amyloid fibrils. Doxycycline studies in patients with ATTRwt have not yet been conducted, but in small clinical trials in people with advanced cardiac disease, it helped relieve symptoms. Possible side effects include loss of appetite, nausea and vomiting, diarrhea, rash, sensitivity to the sun, and hives.

Doxycycline plus TUDCA (OTC)

A phase II open-label study of the antibiotic doxycycline (100 mg twice daily) plus the bile acid TUDCA (250 mg three times a day) stabilized the disease in patients with ATTR amyloidosis. The treatment was well tolerated and halted progression of heart disease as well as neuropathy for at least one year.

TASMAR® (tolcopone; off-label)

Tolcapone is an FDA-approved drug used to treat Parkinson's disease. It inhibits the catechol-O-methyltransferase enzyme. A proof-of-concept clinical trial in 17 asymptomatic carriers and patients showed significant increases in TTR stabilization without serious side effects. Tolcapone is approved to treat Parkinson's disease in the U.S. and is being investigated for treatment of ATTR amyloidosis. Bausch Health (formerly Valeant Pharmaceuticals; Laval, Quebec, Canada) www.bauschhealth.com

EGCG (green tea; OTC)

Green tea contains Epigallocatechin-3-gallate (EGCG), a well-known major polyphenol which may inhibit formation of TTR amyloid fibrils and help break up amyloid deposits. Preliminary clinical data of patients consuming approximately 550 mg EGCG daily for 12 months, showed significant reductions in heart wall thickness and left ventricular myocardial mass. This early evidence suggests that green tea can slow the progression of ATTR cardiomyopathy. The extract from green tea is available in a capsule. More research is needed to confirm the benefits.

IN THE PIPELINE

FIBRIL DEGRADERS

Researchers are testing new ways for drugs to deliver their therapeutic benefits; this includes the use of monoclonal antibodies. Monoclonal antibodies have the ability to target a specific protein or harmful cell. Current studies involve the use of monoclonal antibodies to remove pre-existing amyloid deposits within the heart.

Clinical trials are underway to study the effects of **NNC6019-0001**, a monoclonal antibody that targets TTR deposits. In a phase 1 trial, the tolerability of NNC6019-0001 was proven amongst hATTR and ATTRwt patients with cardiomyopathy. Its safety and effectiveness are being studied further in an ongoing phase 2 trial. (Novo Nordisk A/S) clinicaltrials@novonordisk.com

NI006 is an additional amyloid depleting monoclonal antibody currently in the pipeline. A phase 1 trial has been completed, in which a cohort of patients demonstrated a decrease in cardiac amyloid load after a period of 12 months. A phase 3 trial is expected to begin initiation in early 2024. (AstraZeneca and Nuerimmune) www.astrazeneca-us.com

GENE-EDITING

NTLA-2001 is a CRISPR-Cas9 gene-editing agent designed to treat ATTR amyloidosis by reducing TTR protein levels. A phase 1 trial has been completed, in which patients demonstrated a decrease in TTR levels 28 days after a NTLA-2001 infusion. A phase 3 trial is expected to begin initiation in early 2024. (Intellia Therapeutics) www.intelliatx.com/pipeline

SYMPTOM MANAGEMENT

SUPPORTIVE CARE

hATTR has wide-ranging effects on body tissues and systems. Supportive care involves the treatment of symptoms and the management of disease in the heart and other organs (Table 2). Other therapies may include replacement of the liquid part of

the eye (vitrectomy) and carpal tunnel surgery. While a well-planned treatment strategy can substantially improve quality of life, a multidisciplinary approach is essential for the best possible outcome.

For more symptom management options to explore, please see our companion booklets - Neuropathy and Amyloidosis, and Gastrointestinal Amyloidosis Symptoms and Management, or contact an ARC Patient Support Specialist.

TABLE 2. SUPPORTIVE CARE FOR hATTR

Signs and Symptoms	Treatment
Arrhythmias/ palpitations	Pacemaker/ ICD implantation, medications
Heart failure (leg swelling, abdominal swelling)	Diuretics, salt and fluid restriction, cardiac rehab
Orthostatic hypotension	Medications to increase blood pressure (droxidopa, midodrine, florinef), thigh high compression stockings, stopping medications that lower blood pressure, standing up slowly
Diarrhea	Loperamide, tincture of opium, lomotil, avoid fatty foods, avoid medications that cause diarrhea
Constipation	Laxatives, fiber supplement, avoid medications that are constipating
Slow motility (delayed stomach emptying)	Metoclopramide, eat small frequent meals
Neuropathic pain	Pregabalin, gabapentin, amitriptyline, duloxetine. Topical lidocaine (OTC). Avoid alcohol
Carpal tunnel syndrome	Surgery or wrist splints

TABLE 2. SUPPORTIVE CARE FOR hATTR, CONT.	
Signs and Symptoms	**Treatment**
Dry mouth	Potassium dihydrogen phosphate, cevimeline
Hypoglycemia	Glucose loading, monitor glucose at home
Urinary incontinence	Medications (Distigmine, Detrol), voiding schedule
Hypothyroidism	Medications, determine underlying cause
Ocular amyloidosis (floaters)	Vitrectomy, trabeculectomy

CARDIAC CARE

Commonly prescribed drugs for cardiac conditions are under new scrutiny as we learn more about their effects on patients with hATTR. Many need to be used with caution, started at low doses, and closely monitored.

Digoxin strengthens heartbeat but can bind to amyloid fibrils, causing the amount of digoxin in the body to rise to toxic levels, causing problems with your nervous system, heart rate, and electrolytes.

Hypertension medications—beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs)—may be poorly tolerated in patients with amyloidosis, especially in those with low blood pressure. One class of calcium channel blockers, non-dihydropyridine, is contraindicated in patients with hATTR-CM, and typically should be avoided. Your physician may have good reason to prescribe these medications to you, but amyloidosis patients should be very closely monitored while taking them.

CLINICAL TRIALS

UNDERSTANDING AND PARTICIPATING IN RESEARCH

Clinical trials are research carried out with patients to assess the safety and efficacy of treatments, drugs, or medical devices. These studies are the proving grounds for new ways to prevent, diagnose, and treat different diseases.

Studies are done in phases, each designed to learn specific information.

The table below summarizes the different phases:

CLINICAL TRIAL STAGES			
	Phase 1	**Phase 2**	**Phase 3**
Objectives	Optimal dose Side effects Metabolism	Preliminary effectiveness Additional safety	Definitive effectiveness and safety
Treatment	Single arm (all patient receive experimental therapy)	Single arm Two arms of different treatments or doses: patients randomly assigned to an arm	Two arms: patients randomly assigned to receive experimental therapy or standard therapy
Study size	Small (<50)	Varies	>200

Statistical techniques are used to make sure that the data accurately reflect outcomes and that findings are unbiased. Patients are randomized to receive either treatment or a placebo; neither patients nor physicians know the group assignment; and test drugs are evaluated according to prespecified criteria.

Phase III multicenter, double-blind, randomized, placebo-controlled clinical trials only succeed if they meet prespecified endpoints. If outcomes are statistically significant (highly unlikely to be due to chance), the next step is regulatory approval to bring the drug to market.

After approval and marketing, the new drug might be combined with other medications to treat a specific disease in a select group of patients.

SHOULD I JOIN A CLINICAL TRIAL?

Clinical trials are entirely voluntary and come with benefits and risks. You might receive a new, state-of-the-art drug, and more testing and follow-up than you might otherwise receive in your standard care. You might also receive the placebo instead of the new drug. Your treatment could be free or provided at reduced cost. Expenses are typically covered by the company or agency that sponsors the trial.

Not all side effects and risks are known at the start of the trial. You may experience unknown adverse effects as well as unexpected benefits. You will be informed of known risks during the informed consent process. The pros and cons of participating should be weighed against those of other treatment options and the natural course of the disease.

Clinical trials in the U.S. are listed on a government site (www.clinicaltrials.gov). Trials on this site can be searched by company, drug, or disease. ARC also keeps amyloidosis clinical trial information up to date on the My Amyloidosis Pathfinder (MAP) website.

MAP | My Amyloidosis Pathfinder

MAP is a free, easy-to-use tool that captures your treatment preferences, goals, and challenges so you can effectively communicate with your amyloidosis care teams.

As part of your MAP experience, you can also find and compare specialty treatment centers and receive personalized matches to clinical trials.

Treatment Center Selector

Clinical Trial Finder

www.myamyloidosispathfinder.org

KEY QUESTIONS TO ASK YOUR HEALTH CARE TEAM

Therapeutic education and genetic counseling can answer many questions. Research in medical journals and information from advocacy groups like ARC may answer others. Some common questions about treatment are listed in Table 3.

TABLE 3. QUESTIONS TO ASK YOUR HEALTH CARE TEAM	
1	Where is the closest specialized amyloidosis treatment center? Will you provide a referral for me?
2	What tests will be required before I start treatment?
3	What will these tests show? How reliable are they?
4	How will I know if I've had all the necessary testing done?
5	How will my treatment strategy be determined? Who is on my care team?
6	Who is the key treatment team contact and how do I reach him or her?
7	Who will coordinate care and arrange for regular monitoring and follow-up?
8	What specialists will be involved in my care, and why?
9	Am I eligible for treatment with new drugs?
10	Is my treatment covered by my insurance? Who can I talk to if I have questions about my insurance coverage?
11	What can I expect as we move forward with my treatment plan?

GLOSSARY

Angiotensin-converting enzyme (ACE) inhibitors. A class of drugs prescribed to control high blood pressure, prevent kidney disease, and treat and prevent heart attacks and heart failure.

Angiotensin receptor blockers (ARBs). A class of drugs prescribed to control blood pressure, treat heart failure, and prevent kidney failure in people with diabetes or high blood pressure.

Anticoagulants. Drugs that thin the blood to prevent blood clots that can cause strokes or heart attacks.

Antisense oligodeoxynucleotides (ASOs). Short, chemically modified oligonucleotides that bind to TTR mRNA to prevent production of TTR protein.

Beta blockers. A class of drugs prescribed after a heart attack or to treat abnormal heart rhythms (arrhythmias); widely used to treat high blood pressure but are no longer first line therapy for most patients.

Calcium channel blockers. Drugs that stop calcium from entering cells of the heart and blood vessel walls to lower blood pressure. Catechol-O-methyltransferase (COMT): An enzyme involved in the inactivation of catecholamines such as dopamine, epinephrine, and norepinephrine.

Contraindication. A specific situation in which a drug, procedure, or surgery should not be used because it may be harmful.

CRISPR/Cas9. A tool developed by scientists to edit genes by cutting DNA.

Digoxin. A drug used to treat congestive heart failure and slow the heart rate in patients with atrial fibrillation.

Diuretics. Medications that help flush excess fluid and sodium from the body; used to treat congestive heart failure, liver disease, and kidney disease.

Double-blind masking. A clinical trial design strategy in which neither the participants nor the researchers know who is receiving a certain treatment.

Drug repurposing (also drug repositioning). The investigation of existing drugs for new therapeutic purposes.

hATTR-CM. Hereditary transthyretin amyloidosis with cardiomyopathy.

hATTR-PN. Hereditary transthyretin amyloidosis with polyneuropathy.

Hemodialysis or dialysis. The process of purifying the blood in a patient whose kidneys are not working properly.

Hypoglycemia. Low blood sugar.

Messenger RNA (mRNA). A large family of RNA molecules that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression.

Monoclonal antibodies (MABs). A type of protein made in a laboratory that can bind to substances in the body, including cancer cells.

Off-label prescribing. When a physician gives a drug that the FDA has approved to treat a condition other than the one a patient has; the practice is legal and common.

Orthostatic hypotension. A condition that causes blood pressure to fall when standing up or sitting.

Orthotopic liver transplant. Removal of a diseased liver and replacement with a healthy liver from a deceased donor.

Placebo-controlled. A clinical trial in which the drug being tested is compared to a placebo (a substance containing no medicine).

RNA interference (RNAi) therapeutics. Double-stranded, small interfering RNAs (siRNA) that bind to TTR messenger RNA (mRNA) to preventing production of TTR protein.

Staging. Exams and tests to learn the extent of disease progression.

Trabeculectomy. A surgical procedure to treat glaucoma.

TTR tetramer stabilizers. A treatment option that works by binding to the TTR protein to prevent the production of amyloid fibrils.

Vitrectomy. A surgical procedure where the vitreous humor gel that fills the eye cavity is removed to provide better access to the retina for vision correction.

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