FDA Approves Two Treatments for hATTR Amyloidosis in 2018
by Frederick L. Ruberg, MD - Boston University, BUMC, Amyloidosis Center

What a momentous Summer of 2018 it has been for transthyretin (ATTR) amyloidosis. First, in July 2018, in the same issue of the New England Journal of Medicine, two different phase 3 clinical trials were reported demonstrating the efficacy of two different pharmaceuticals as treatments for ATTR amyloidosis polyneuropathy.

In randomized, double-blinded, placebo-controlled trials, each of these agents showed efficacy in slowing of progression or even improvement of peripheral neuropathy associated with hereditary ATTR (hATTR) amyloidosis.

These trials were accepted as sufficient demonstrations of efficacy to permit the US FDA to approve both patisaran or Onpattro™ (Alnylam Pharmaceuticals) and inotersen or Tegsedi™ (Ionis/Akcea Therapeutics) as the first treatments for ATTR amyloidosis. Both drugs were approved for hereditary ATTR amyloidosis with evidence of neuropathy.

Furthermore, in August, a third phase 3 clinical trial was reported in the New England Journal of Medicine – this one describing the efficacy of yet another medication (tafamidis or VynDAQEL™, Pfizer) but tested in patients with ATTR cardiomyopathy.

This trial (ATTR-ACT, Maurer MS et. al, NEJM 2018), in distinction from those above, showed that tafamidis was superior to placebo for survival among patients with congestive heart failure, meaning that patients randomized to the drug lived longer than those who were not.

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3rd Annual Pittsburgh Amyloidosis Research Benefit a Smashing Success

Montour Heights Country Club was over-flowing with amyloidosis awareness on Friday, October 26, 2018 for our 3rd Annual Pittsburgh Amyloidosis Research Benefit.

Over 100 friends and family came to support this special night, honoring the Chairwoman who started this event, Dr. Darcy Tannehill, who passed away in April.

Her daughter, Courtney A. Sullivan, and son-in-law, Dr. Adam Sullivan, were the Co-Chairs this year and did an amazing job gathering silent auction gifts and over 90 bottles of wine for the annual “wine pull”.

Guests enjoyed a live jazz band, delicious hot appetizers and a gourmet meal plus the opportunity to bid on all the unique silent auction gifts.

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The foundation has several programs that benefit patients and their families. All of these are provided free of charge.

- Webinar recordings posted on our website
- Updated informational pamphlets
- Toll Free Number 1-877-AMYLOID
- Listing of experienced physicians that specialize in amyloidosis. Email us anytime with questions: info@amyloidosis.org

Our comprehensive website has information for patients, caregivers and physicians featuring:

- Treatment Centers (US / International)
- Support Groups
- Newsletters
- Webinars
- Fundraising Toolkits

Stay connected for all the latest information on Amyloidosis:

Web: www.amyloidosis.org
Twitter: @Amyloidosisfdn
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President's Corner

We are excited to announce our new board members, Daniel Lenihan, M.D., FACC and Adrienne Molteni, RN, and look forward to their service and guidance in the coming years. Both have a passion for amyloidosis patients and a commitment to spreading awareness.

If you missed the webinar in October from Dr. Comenzo (or would like to listen again), go to our website to listen to his presentation. Lots of great information plus many patient and caregiver questions are answered. We thank him for his time and unique perspective.

Please consider donating to the Amyloidosis Foundation in your end-of-year giving. We could not do this work without the support of friends like you. We are thankful for your continued generosity over the past 15 years and are hopeful for new therapies in the near future.

Best wishes and happy holidays to you and your family,
Mary E. O'Donnell

Webinar: AMYLOIDOSIS 2030: A SyFy Special

Listen to this informative webinar that was recorded on October 15, 2018, taking a look 12 years into the future at how the risks of AL and ATTR will be managed and the diseases treated.

The webinar was hosted by Raymond Comenzo, MD, Professor of Medicine and Pathology at Tufts University School of Medicine. After the presentation, Dr. Comenzo answered many interesting questions from patients, physicians and family members. Please share this link with your family and friends to spread amyloidosis awareness: http://bit.ly/Amyloid2018. You can also find links to all of our webinars on our website: www.amyloidosis.org.

Our newsletter is published quarterly (Spring, Summer, Fall and Winter) by the Amyloidosis Foundation. We welcome letters, articles and suggestions.

Please contact us anytime at: info@amyloidosis.org, 1-877-AMYLOID (877-269-5643) or 7151 N. Main Street, Ste. 2, Clarkston, MI 48346

If you wish to receive a printed version, please send us an email:

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Celebrating Kevin Sullivan and Raising Funds for Research

On Thursday, September 27 the family and friends of Kevin Sullivan came together to hold a fundraiser in his memory and raise amyloidosis awareness, in a beautifully restored home in Grand Rapids, MI.

It was a beautiful night, everyone enjoyed hors d’oeuvres and drinks and then bid on the silent auction. Nancy, her children Keenan, Kelsie and Connor all shared stories and memories of Kevin throughout the evening. Dr. David Fermin, Kevin’s cardiologist from Spectrum Health in Grand Rapids, spoke about Kevin’s strength and spirit, plus gave a short presentation. Over 70 people came out to support the family and the AF.

In total, they raised over $13,900 for research. Thank you to everyone who attended the event and donated to honor Kevin, a special event for an extra special man. AF

2nd Annual AF Run/Walk in Michigan

It was a chilly start, but the sun was shining for our 2nd annual “Run for Your Life” 5k/10k event on Saturday, October 13, 2018. We had over 70 participants plus many friends and family cheering everyone on at the beautiful Independence Oaks County Park in Clarkston, MI.

Thanks again to all of our volunteers, sponsors and donors. Join us next year! AF

3rd Annual Pittsburgh Amyloidosis Research Benefit a Smashing Success

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Over $53,000 was raised thanks to our generous donors, attendees and sponsors: University of Pittsburgh Medical Center, Eidos, Alnylam, Allegheny Health Network, Akcea and Takeda.

A great night was had by all and we thank the Pittsburgh community for continuing to make this annual event a success. AF

www.amyloidosis.org
2018 NORD Summit Update by Kathi Luis, Amyloidosis Foundation

Day 1: A panel discussed how patient engagement is driving research and drug development. It was said that the patient is the best advocate. With collaborations with patient organizations, evidence and hearing from the patients, innovative collaborations and progress is happening.

The next session, ‘Solving the diagnosis challenge’, is something the AF receives calls about on a daily basis. Delay in diagnosis remains to be a serious problem for all of us in the rare community. Scientific and financial challenges were discussed. Education of medical professionals seems to be the biggest challenge.

The FDA has approved more than 600 medicines since passage of the Orphan Drug Act in 1983. More than 560 drugs are in the current biopharmaceutical pipeline. Even with recent progress, there is much more work to be done. Only 5% of rare diseases have an approved treatment.

Decisions made at the state level are having a huge impact on patients and families. It is important to be your own advocate. Representatives from the Rare Action Network spoke about the challenges of advocating, making connections, exciting experiences and new opportunities.

The next panel discussed how to achieve a balance with value, pricing and patient experience. Pricing was the main topic, as many in the rare community cannot afford their drug options. Different programs within pharmacology were spoken of, as well as foundations that offer patient assistance.

Day 2: A panel discussed how there are 250 new rare diseases every year, and that it would take 2000 years before every rare disease is treatable. Gene therapy was discussed with nsgc.org where genetic counselors throughout the country can be found.

In the keynote, amyloidosis was mentioned in regards to the FDA approving two new therapies for hATTR. There are more than 150 gene therapy and clinical trials in progress. Patients, caregivers, organizations and pharmaceutical companies that represent several rare diseases shared thoughts, hopes and concerns regarding promising new treatments.

In the breakout session, we discussed clinical trials. Overall thoughts are that things are moving toward a more patient-centric practice. It was said that it is easier to recruit and retain with the changes of clinicaltrials.gov. There are many different views on strategies for patient access to clinical trials, and how they should be promoted. Online communities have helped with this. There was a general consensus that the rare patient is not rare.

I really enjoy traveling and making new connections in the rare disease arena. I’m confident good things are around the corner. AF
FDA has yet to act on approval of this agent, but the community of patients and caregivers with ATTR amyloidosis with cardiomyopathy is eagerly awaiting its decision.

Each of these 3 new drugs acts through different mechanisms to achieve the same clinical objective – that is to arrest or reverse the progression of neuropathy or heart failure associated with ATTR amyloidosis. Thus, we have gone from a disease without pharmaceutical treatment (previously only treated with organ transplantation) to one where we now have 3 effective agents, albeit with different target populations, in a few short months.

Each of these new agents already approved by FDA was done so through accelerated pathways including Fast Track, Priority Review, and Breakthrough Therapy designations. In addition, the drugs have received Orphan Drug designation, which FDA defines as: “The Orphan Drug Designation Program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.” Cost remains a key sticking point, as now that we have approved drugs, discussions/negotiations are ongoing between sponsors (ie, pharmaceutical companies) and 3rd party payors (insurers) over pricing.

As a care provider for patients with ATTR amyloidosis, I am grateful that so many of our partners in industry looked to ATTR amyloidosis as a space in which to develop desperately needed treatments. Further, I think we all can agree that the sponsors which invested great resources in dollars and time should be permitted the opportunity to recover their investment. However, the cost of these new drugs, which would in theory be given for years to decades (i.e., the duration of a patient’s life), must be balanced with the cost to the patient directly, and further the cost to our healthcare system. Such decisions are even more difficult when we are speaking about individuals, with real symptoms, and real disabilities.

Determination of a drug cost naturally considers the numbers of potential patients who can be treated. If more patients can be treated, than the cost per unit can be lower for a similar return. As I noted above, FDA considers hATTR amyloidosis an Orphan disease affecting < 200,000 people at any given time, and while this appears undoubtedly true for hATTR polyneuropathy, is it also true for ATTR cardiomyopathy? A disease is rare because it truly doesn’t affect a large number of people, or it is rare because it is unrecognized. In the case of ATTR amyloidosis cardiomyopathy, which includes both hereditary and wild-type amyloidosis (ATTRwt) the answer is probably a combination of the two.

This October, in the Journal of the American College of Cardiology, a team of cardiologists and orthopedic surgeons at the Cleveland Clinic collaborated on an innovative screening study for amyloidosis. Led by Mazen Hanna, MD (Sperry JW, J Am Coll Cardiol 2018), the investigators looked at sequential patients undergoing carpal tunnel release surgery and analyzed the resected tissue under the microscope for the presence of amyloidosis.
Bilateral carpal tunnel syndrome has long been associated with systemic amyloidosis, but up to this point no one has actually examined whether one could use carpal tunnel release surgery as a means to screen for the disease. The authors placed relatively few exclusions on their study population casting the broadest possible net to include all men over age 50 years, all women over age 60 years, and excluded only those with known amyloidosis, prior trauma, or rheumatoid arthritis.

Of the 319 surgeries performed over the course of a year, 98 patients were included in the final analysis, and previously unrecognized amyloidosis was found in 10 total (or 10%) patients. As predicted, 100% of patients with amyloidosis had a history of bilateral carpal tunnel syndrome, but so did 83% of those without amyloidosis. What we learned from this important study is that bilateral carpal tunnel syndrome is indeed common in systemic amyloidosis, but it is also common in patients without systemic amyloidosis, so as a clinical filter it is relatively non-specific. But we also learned that unsuspected amyloidosis can be diagnosed with carpal tunnel surgery, and furthermore, amyloidosis in this population may be seen in as many as 1 in 10.

Uncommon yes, but not a rare disease. So, if this rate proves accurate in larger populations, there are likely more patients with amyloidosis than currently appreciated. How many is not yet clear. Such data feed directly into the determination of cost for these promising new agents.

Another important aspect of this study is that screening afforded a means to identify patients early in their amyloidosis disease course. In fact, 3 of the 10 identified (1 case of AL amyloidosis, 1 ATTRwt, and 1 hATTR) were given amyloidosis specific therapy. Early identification is critical in any medical disease, but particularly so in the case of systemic amyloidosis where the damage done by amyloid deposits is either slow to reverse (as in the case of neuropathy) or largely irreversible (as in the case of cardiopathy) with currently available treatments. In fact, in the ATTR-ACT trial of tafamidis, those who had less severe congestive heart failure (a marker of earlier disease) did better. Unlike in cancers such as breast or prostate, we have yet to settle upon the best screening approach for amyloidosis to apply to larger populations. In addition, we know that for AL amyloidosis patients often remain undiagnosed for months to years and see many providers before the final diagnosis of amyloidosis is made correctly (Lousada I, Advances in Therapy 2015).

The same is likely also true for ATTR amyloidosis. Studies showing therapeutic success in prominent medical journals, FDA approvals, and high-profile screening reports all raise awareness of amyloidosis. These advances all work synergistically to bring amyloidosis onto the clinician’s differential diagnosis when seeing potential new cases. Screening algorithms will definitively involve integration of different modalities of testing and collaboration between providers. It is now our challenge to translate these new discoveries into clinical practice. AF

Disclosures

Dr. Ruberg acknowledges consulting income from Pfizer and research support from Eidos Therapeutics.
Celebrating 15 Years of Research

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