

4th ATTR/Familial Amyloidosis Support Meeting

October 31 to November 1, 2015

Hilton Chicago O'Hare Airport hotel

Summary of plenary sessions on October 31, 2015

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Welcome

Muriel Finkel welcomed the attendees to the Amyloidosis Support Group biannual meeting, and noted that approximately half were attending for the first time.

Top-table panel of experts:

- Morie Gertz (Mayo Clinic) – chairman
- Martha Skinner (Boston University)
- Mathew Maurer (Columbia University)
- John Berk (Boston University)
- Maria Picken (Loyola University)
- Dan Judge (Johns Hopkins Hospital)
- Jeff Kelly (Scripps Research Institute)
- Mazen Hanna (Cleveland Clinic)
- Muriel Finkel (Amyloidosis Support Group)
- Merrill Benson (Indiana University)
- Sarah Mets (Mayo Clinic)
- Martha Grogan (Mayo Clinic)
- Angela Dispenzieri (Boston University)
- Janice Wiesman (Boston University)
- Lauren Stern (Boston University)

Dr Gertz commented that this was the best assembly ever of experts in hereditary transthyretin (TTR)-mediated amyloidosis (hereditary ATTR amyloidosis) in the US. The meeting began with several plenary presentations.

Why are we here? (Morie Gertz, MD)

Dr Gertz presented data from his amyloidosis center at the Mayo Clinic. Their patient population comprises 62% light-chain (AL) amyloidosis, 25% hereditary ATTR amyloidosis, and 13% with one of 18 other forms of amyloidosis. For patients with hereditary ATTR amyloidosis, age distribution peaks at 61–65 years, and age of symptom onset peaks at 60 years. There is no clustering of TTR gene mutations within the US. The proportions of patients with peripheral neuropathy, autonomic neuropathy, weight loss, or cardiomyopathy vary by TTR gene mutation.

TTR amyloidosis: An overview (John Berk, MD)

Dr Berk explained that diagnosis of amyloid cardiomyopathy usually occurs after the heart wall has thickened. He explained the process that specialist clinics follow to screen patients and identify their type of amyloidosis. The TTR gene is sequenced at specialist centers using mass spectrometry. There are

over 120 different mutations of the autosomal dominant TTR gene, which result in misfolding of the protein monomers, preventing formation of the stable TTR tetramer structure. Dr Berk noted that the incidence rates typically published for hereditary ATTR amyloidosis and the published survival rate data for untreated patients are outdated. He explained the naming system used for the TTR gene mutations (e.g., Val30Met/V30M) and used an example from Sweden to explain the probabilities of genetics for the hereditary disease. He presented the spectrum of disease for hereditary ATTR amyloidosis, from peripheral neuropathy through to cardiomyopathy, and described the familial amyloidosis polyneuropathy (FAP) and polyneuropathy disability (PND) disease staging systems that are used routinely by physicians.

Non-ATTR amyloidosis: An overview (Merrill Benson, MD)

Dr Benson explained that treatment of non-TTR forms of amyloidosis can be more challenging for physicians compared with TTR forms because many patients have kidney amyloid deposits (e.g., LECT2), which necessitate regular kidney dialysis. Organ transplant is a treatment option for some patients with amyloidosis, although patients with apolipoprotein A1 amyloidosis who have had a liver transplant may still have disease progression in their gastrointestinal tract. Dr Benson emphasized that it is essential to identify the amyloid protein for each patient to ensure they are given the correct treatment. He also highlighted the importance of genetic counseling.

TTR and non-TTR amyloidosis: Focus on the kidney (Lauren Stern, MD)

Dr Stern gave an overview of the structure and functions of the kidney, and explained the tests that are routinely used to monitor kidney function (e.g., creatinine levels). She explained that the heart and kidneys function as a team: if heart function decreases significantly, the kidneys may shut down to allow oxygen to continue to reach the brain. Hence, cardiomyopathy can result in kidney problems. Therapeutic options for kidney disease are divided into specific (i.e., based on the amyloid protein) and non-specific (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) therapies, and Dr Stern explained the importance of avoiding nephrotoxins (e.g., most nonsteroidal anti-inflammatory drugs [NSAIDs], herbal supplements). Patients with hereditary ATTR amyloidosis and end-stage renal disease may be offered a kidney transplant, hemodialysis, or peritoneal dialysis.

Biopsy: Tissue collection and analysis (Maria Picken, MD)

Light microscopy can be used to detect amyloid deposits in tissue sections, although sections stained with Congo red must be examined in a dark room using polarized light. Electron microscopy can be used to view amyloid fibril formation. Dr Picken explained that amyloid deposits in the early stages of disease are not always seen in routine histology, and it is difficult for pathologists at nonspecialist centers to recognize/rule out the presence of amyloid deposits. Dr Picken explained the process of fat tissue biopsy sampling, but noted the advantages of collecting biopsies from the affected organ. In particular, she showed data from a recent study of patients with ATTR amyloidosis (hereditary or wild type) where the specificity of Congo red staining was 47% for fat tissue versus 100% for heart tissue (Fine et al. Am J

Cardiol 2014;113:1723-7). Dr Picken recommended that family members (of patients with hereditary ATTR amyloidosis) who undergo surgery should request that their surgeon sends a tissue sample to pathology for Congo red staining to investigate amyloid deposits. This is particularly important in cases of bilateral carpal tunnel syndrome.

Genetics (Sarah Mets)

Sarah Mets explained about the structure and role of genes, and introduced the role of the genetic counselor in supporting families with hereditary diseases. Genetic testing is part of the diagnostic work-up for patients with hereditary ATTR amyloidosis, and the results may affect their eligibility for clinical trials and treatment options, and their prognosis including disease progression and the likelihood of complications. She explained the recommended process for informing family members about the disease, and advised it should be an individual, informed decision. She did not recommend genetic testing of children because hereditary ATTR amyloidosis is an adult-onset disease.

Neuropathy: Nerves before and after ATTR (Janice Wiesman, MD)

Dr Wiesman gave an overview of the structure and function of neurons and nerves, and the differences between motor and sensory neurons. She explained that amyloid polyneuropathy is usually the result of nerve axonal damage or fat damage. The longest nerves are typically affected first, which is why patients often experience symptoms in their feet initially, and nerve damage is usually symmetrical within the body. She explained how damaged nerves often 'fire', which is experienced as pain. Treatment options for hereditary ATTR amyloidosis with polyneuropathy may be etiologic (e.g., TTR tetramer stabilizers, liver transplant, RNA interference [RNAi] agents, RNA antisense agents) or symptomatic (e.g., foot rub/massage, topical medications, acupuncture).

Cardiac: Heart before and after ATTR (Martha Grogan, MD)

Dr Grogan summarized the workings of a healthy heart and explained how amyloid deposits result in thickening of the heart muscle, leading to cardiomyopathy. She described the symptoms and complications commonly experienced by patients, and explained the tests used to diagnose amyloid-associated cardiomyopathy (e.g., echocardiography, magnetic resonance imaging, ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) scintigraphy, biopsy analysis, blood tests). She noted that ejection fraction was not a valid test for amyloid-associated cardiomyopathy owing to the significantly reduced heart volume.

Solid organ transplant (Angela Dispenzieri, MD)

Although the liver is the source of amyloid protein in patients with ATTR amyloidosis, most patients have an otherwise well-functioning liver. The three main transplant options are: (1) remove the mutant protein-producing organ; (2) replace the symptomatic organ (commonly the heart or kidneys); or (3) replace both. However, patients with ATTR amyloidosis often do not meet the criteria for a liver transplant because their liver is classed as 'normal'. Dr Dispenzieri shared data on liver transplants from

the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) of approximately 2000 patients, most with the V30M TTR gene mutation. She noted that post-transplant survival is only part of the story, as some patients still have poor quality of life, experiencing diarrhea and light-headedness.

Presentations by pharmaceutical companies with agents in development for hereditary ATTR amyloidosis

Alnylam (Pushkal Garg)

Dr Garg shared data on two investigational RNAi therapies under evaluation for the treatment of hereditary ATTR amyloidosis: patisiran and revusiran. Both agents use a natural process in the body known as RNA interference to lower the levels of TTR protein. Patisiran is currently being evaluated in the open-label extension (OLE) of the phase 2 study, and in the phase 3 placebo-controlled (2:1 randomization) APOLLO trial, in patients with hereditary ATTR amyloidosis with polyneuropathy. In the phase 2 study, patisiran lowered the amount of both wild-type and mutant TTR protein in patients' blood by about 80% over 18 months, including those patients using a tetramer stabilizer. Using the modified neuropathy impairment score +7 (mNIS+7) to monitor neurologic progression, patisiran reduced/improved the mNIS+7 from baseline by a mean of 3.1 points over 12 months. Putting this change in context, other studies have reported an increase/worsening in mNIS+7 of 14–18 points over 12 months. Revusiran is being evaluated in an ongoing phase 2 OLE trial of patients with hereditary or wild-type ATTR amyloidosis with cardiomyopathy, and in a phase 3 trial (ENDEAVOUR) of patients with hereditary ATTR amyloidosis with cardiomyopathy. Dr Garg explained that Alnylam Assist is a dedicated support program for patients and families in the US affected by hereditary ATTR amyloidosis.

Isis Pharma (Lisa Ackermann)

Dr Ackermann explained that ISIS-TTR_{Rx} is an antisense agent that specifically targets the mRNA of wild-type and mutant TTR to reduce TTR protein expression. The phase 1 study in healthy volunteers is completed, and identified 300 mg as the optimal dose to evaluate in the ongoing placebo-controlled (2:1 randomization) phase 3 trial in patients with hereditary ATTR amyloidosis with polyneuropathy. Data from the phase 1 study showed about 70% TTR knockdown in blood. The phase 3 trial is monitoring efficacy (using the mNIS+7) and safety. In the OLE stage of the trial, patients can self-administer the subcutaneous dose at home.

Pfizer (Lesley Amass and Rodger Kobes)

Tafamidis prevents tetramer dissociation, and is taken as a daily oral dose. Because tafamidis is an investigational drug and is not approved in the US, Dr Amass was unable to talk about the data at this patient meeting (this would be considered as pre-approval promotion by the Food and Drug Administration [FDA] and is not permitted). The drug is currently approved in the European Union and additional countries in Latin America and Asia-Pacific regions for the treatment of hereditary ATTR amyloidosis with polyneuropathy. The tafamidis clinical development program in the US includes a second efficacy study, the phase 3 placebo-controlled ATTR-ACT study in patients with ATTR amyloidosis

with cardiomyopathy. In this trial, approximately 50% more patients are on tafamidis than placebo. In 2007, Pfizer established the THAOS registry of patients with ATTR amyloidosis, which focuses on the natural history of the disease and its progression. Over 2900 individuals are currently registered in THAOS from 55 sites across 25 countries.

Non-clinical trial treatments (John Berk, MD)

Dr Berk gave an overview of several agents that are commercially (off label) available in the US for ATTR amyloidosis:

Curcumin, a natural polyphenol, has been shown to break up amyloid fibrils in laboratory in vitro tests, and has been evaluated in a mouse model of very early amyloid aggregations. The data may not be applicable to patients as the blood curcumin levels reported in mice would be unachievable in humans.

Resveratrol stabilizes TTR tetramer conformation, but there are insufficient data in humans and the effective dose has not been determined.

Epigallocatechin gallate (EGCG) ('green tea') stabilizes TTR tetramers. In an uncontrolled trial of 59 patients with AL amyloid cardiomyopathy, reductions in left ventricular thickness were reported. Dr Berk noted that this was a very selected population and reserved judgment on the data.

Early data on **doxycycline/tauroursodeoxycholic acid (TUDCA)** showed 'substantial stability' of nerves. Dr Berk expected new data on this combination to be presented at a congress in Paris in early November 2015. Dr Berk has experience of using doxycycline/TUDCA in 25 patients, and noted that tolerability appeared to be an issue.

Diflunisal, an NSAID, has been evaluated in a randomized controlled clinical trial in patients with hereditary ATTR amyloidosis with polyneuropathy. The NIS+7 score showed significant improvements from baseline at 12 and 24 months in a subanalysis of 'completer patients' (population noted in the Q&A session), although there was bias toward an absence of effect in the intention-to-treat (full) trial population. Improvements in quality of life measures were also reported. Dr Berk concluded that diflunisal inhibits neurologic progression in patients with hereditary ATTR amyloidosis with polyneuropathy, which shows effective repurposing of an old drug.

Familial survey results (Isabelle Lousada)

Isabelle Lousada from the Amyloidosis Foundation explained that data from patient surveys will be instrumental in discussions with the FDA about trial designs for patients with ATTR amyloidosis. She acknowledged 'survey fatigue', and appreciated the support of the patients who had completed the survey. She highlighted that what doctors believe about a disease is not always the same as what patients think, so these surveys are important to determine patient opinion and experiences.

Overall 64 patients (mean age 58 years) with hereditary ATTR amyloidosis with polyneuropathy, cardiomyopathy, or both, completed the survey in September 2015. The majority of patients had

neuropathy and 77% had a family history of disease. The results showed that the pathway to diagnosis can be complex, involving many specialists, and can be prolonged if disease is not recognized early after symptom onset. Of note, family history does not always reduce delay in diagnosis. Fine motor skills are commonly affected by the disease, and difficulty is also observed in performing more common tasks, such as walking upstairs or taking a shower. Mobility is affected by the disease, with over 25% of patients dependent on a cane or wheelchair most or all of the time. About two-thirds of patients are taking an amyloidosis directed treatment or investigational therapy; the most common medication is diflunisal (19/64), although a variety of investigational agents are being used.