Familial Amyloidosis Conference

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Salt Creek Golf Club

Wood Dale IL 60191

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Contents

Amyloidosis Overview – Why do I feel as I do, what's happening with my body?

Dr. Morie Gertz

The symptoms that folks with amyl get vary greatly. You may have none, several, or all of the things below happening, or maybe some during some periods, and others in other periods.

Nerves

Nerves are electrical wires, conducting electrical impulses. They are composed of the wire (axon) and insulation (myelin). Both are needed for transmission. Axonal Neuropathy is where the wire (axon) is damaged, like polio. Myelin damage example: diabetes.

Damaged nerves: the first sign is less sensation – Feet feel calloused or like you are always walking on a rug, or even that you can't feel your feet, so you can't walk well because you don't get the feedback from your feet. The loss of sensation progresses from bottom of feet, to foot, to ankle, to calf. When it hits the calf, then you may start losing sensation in fingertips, so you can't tell a dime from a penny.

Nerves may also "short out" – causing sudden pains (*dysesthesias*) – lancinating pains, burning pains. Eventually, the nerve gets to the point where it does not transmit signals much at all, so these pains stop.

Motor signal nerves go later. This manifests as weakness, starting in the legs.

Automatic nerves and automatic functions: In a normal bowel, from swallowing to defecating, processing of food is automatic, through about 45 feet of digestive tract. If the automatic nerves are damaged, the wave-activity that moves food through the intestine or bowel may not occur well. Bowel movements may occur infrequently or not at all without laxatives. Or the wave is overactive, and you have constant or unpredictable diarrhea. All this is a result of automatic nerves not acting normally.

Blood pressure is like a hose. If you block part of a hose, you raise pressure

Body priorities for blood: 1. Brain 2. Muscles 3. Heart

If you stand up, automatic nerves normally "squeeze" the blood vessels (decreases the diameter) to increase the blood pressure, to send blood to the brain. This is like when you block part of the

opening of a hose, to make the water shoot out farther. But if the automatic nerves controlling blood vessel diameter do not respond normally, blood pressure falls and fainting can occur.

Automatic nerves also adjust heart rate, depending on your body's need (when you are active, like running, your muscles need more blood flow). Damaged automatics nerves can decrease your ability to exercise.

Cardiac

Heart is a pump. Automatic nerves make it squeeze and relax, to pump blood through. When things like poor diet cause plaque to build up in arteries, the heart has a hard time pumping, and the heart can't squeeze hard enough to get enough blood to where it is needed. This is mostly what heart doctors treat, so that is what they look for. BUT THIS IS NOT WHAT HAPPENS WITH AMYL. The Amy problem is that the heart won't relax enough – the problem is not in the 1/3 second squeeze, but in the 2/3 second relaxing between squeezes. The heart becomes less elastic. It relaxes less, so less blood goes in – like trying to fill a leather balloon, rather than a rubber balloon. Likewise, blood comes out less quickly: there is less volume of blood in the heart, so there is less blood to squeeze out, and less pressure in the blood being squeezed out. In normal heart, the heart fills with 3 oz., and 2 oz. get squeezed out: a 66% ejection fraction (a primary measure from echocardiograms). In Amyl. affected hearts, the heart fills with less than 3 oz. (say 2 oz.), but the ejection fraction is the same – so the echocardiogram comes out normal, and the cardiologist say that the heart is fine, but only 3/4 oz. comes out per heartbeat (rather than 2 oz.). This lower volume results in a lower blood pressure – a lower top number in your blood pressure, which a cardiologist may think is a good thing (as it is in most people the cardiologist sees). Cardiologist needs to study your heart while resting to understand that this is a problem. The cardiologist can also examine the thickness of the heart wall: the heart wall will have become thicker with amyloid. Cardiologists usually assume that a thick wall is a sign of some hypertension. When further tests show that is not a problem, the cardiologist often starts grabbing for other causes: tiredness is due to depression, or some lung condition, or something else not due to any circulatory system problem. Or they see some leaking heart valves (often not really a significant problem), and attribute your problems to that.

Amyl heart may be doing all that it can when you are at rest. Then you try to get up, and the heart says, "I can't send out more blood", and the muscles say, "OK, we'll shut down." The result is weakness.

What tests do show that amyl is causing the heart problems?

Where clinicians have experience with amyl, they will recognize that some symptoms and readings could be caused by amyl. But if they never have seen amyl, it can be difficult.

Echo cardiogram coupled with EKG can have results that are fairly specific to amyl.

What is process that causes ejection fraction to drop?

Early in amyl, ejection fraction may be normal, despite circulation problems from amyl. Later, the ejection fraction does decrease.

How should diuretics be used to manage cardiac issues in amyl? (This needs edits)

Symptomatic management of amyl is walking a tightrope. Diuretics are used to manage fluid retention, but can make the kidneys work very hard, and damage them.

[NOTE: I think this is a very critical piece of information that patients need to know, since so many are working with clinicians who do not understand the disorder. Patients need to know this to advocate for

themselves, and help clinicians understand the complexity and tightrope dynamics of this cardiac management.]

Hereditary, Wild Type TTR, Cerebral, Et al.

(Not discussed)

Q & A

How does Alzheimer's differ from amyloidosis?

Alzheimer's is a localized amyl deposit, but amyloidosis is systemic.

Having one does not increase the chance of having the other.

Do environmental issues affect the chance or course of amyl?

Dr. Skinner: we do not know. "I do not think they play a role in the onset."

Are there treatments being studies for SSA (age-related)?

Dr. Skinner: The same treatments that work for familial should work for SSA.

Hereditary Amyloidosis – Historic Perspective

Dr. Martha Skinner

Discovery of TTR

1854 Virchow (Germany). Discovery of amyloid in tissue (Virchow's Arch. Pathol. Anat. Physiol. (6: 268)

1952 Andrade (Portugal). A peculiar form of peripheral neuropathy (Brain 75:408). Dr. Andrade reported an amyloid disease prevalent in one area of northern Portugal. He showed that it was inherited and caused neuropathy in mid-life.

First Symposium

1967 First Symposium, Groningen

Six clinical reports in First Symposium Proceedings (Andrade):

- one on familial amyloidosis associated with neuropathy, FAP
- one on amyloid associated with rheumatoid arthritis
- one on diagnostic tests
- 3 reports on amyloid and aging

"No mild cases" was stated in the summary.

Further studies

1978 Amyloid deposits stained with antibody to prealbumin (TTR)

1981 Amyloid fibrils proven to be prealbumin

1983 First discovery of prealbumin gene mutation (Val-30-Met)

1986 Prealbumin re-named trans thy retin

1983-present More than 100 pathologic TTR mutations discovered

Disorder called Prealbumin at first. Later changed to “transthyretin”

Systemic amyloidosis – which are how common?

- **Systemic non-AL amyloidosis** **20% of all amyloidosis**

- AA (or secondary) 2%
- Age-related (senile) systemic amyloidosis 2-3%
- Familial forms due to gene mutations
- ATTR 10-12%
- Apolipoprotein AI < 1%
- Apolipoprotein AII < 1%
- Fibrinogen A alpha < 1%
- Lysozyme < 1%
- Gelsolin < 1%

When was SSA discovered?

1980 Sletten and colleagues noted the protein type was related to transthyretin (Scand. J Immunol. 12:503)

1983 Cornwell and colleagues reported on the clinical features of age-related cardiac amyloidosis (Am. J. Med. 75:618)

When were rare familial types discovered?

Apolipoprotein A1. 1988
Apolipoprotein AII. 2001
Fibrinogen A alpha 1993
Lysozyme 1993
Gelsolin. 1990

Making the correct diagnosis

1. Get Tissue biopsy positive for amyloid
2. Rule out AL and AA amyloidoses
3. Confirm tissue type by immunohistochemistry with antibody to specific protein (or mass spec, if avail.)
4. Confirm all inherited forms by genetic analysis of patient’s DNA

Diagnostic testing

Assess function of nerves and heart

Systemic non-AL amyloidoses

AA (or secondary) 2%

Age-related (senile) systemic TTR amyloidosis 2-3%

Familial forms due to gene mutations

ATTR 10-12%

Apolipoprotein AI	< 1%
Apolipoprotein AII	< 1%
Fibrinogen A alpha	< 1%
Lysozyme	< 1%
Gelsolin	< 1%

Age-related systemic amyloidosis (SSA)

Caused by wild-type (normal) TTR

Heart predominant organ involved

Older age; mostly men

Also called senile systemic amyloidosis or senile cardiac amyloidosis

SSA diagnosis made by:

Tissue biopsy positive for amyloid

Amyloid deposits positive for TTR

TTR genetic testing negative for a TTR mutation (required)

Clinical picture of older person, most likely with cardiomyopathy and without multisystem disease

Familial (ATTR) amyloidosis:

Most common familial form

Trans thy retin - a transport protein for thyroid hormone and retinol binding protein

Cause: Autosomal dominant inheritance of a mutant transthyretin gene (100+ variants, most cause amyloidosis)

Onset age: 20's-old age; same within family; onset for women is a little later than for men

Survival: 7-15 years from diagnosis. This is a very rough estimate, assuming no treatment. (AL survival used to be 1.5 years, but now is 5-10 years.) And, of course, the diagnosis may occur at various times in the disease course.

TTR mutation: V122I

Variant TTR present in 4% of individuals of African ancestry

Associated with cardiomyopathy of late onset

Incidence of disease unknown

Diagnosis and treatment of familial ATTR amyloidosis

Diagnosis

DNA sequencing necessary for diagnosis of mutation.

☐Important to look for TTR mutation in allblack individuals with cardiomyopathy

Major treatment

Liver transplantation

diflunisal: multicenter international clinical trial in review

Tafamidis (Pfizer): international trial awaits FDA approval. Approved in Europe and Japan

ALN-TTR-NT-001 (Alnylam): clinical trial underway in Europe

ISIS

ATTR supportive treatment

1. For heart:

diuretics; low salt diet; rhythm control, if necessary

2. for peripheral neuropathy:

medications; active exercises; ankle braces; foot care

3. For autonomic neuropathy: BP and GI

Midodrine for low BP, elastic stockings

Low fat diet, meds for diarrhea, food supplements, etc

4. Genetic counseling

Autosomal dominant inheritance

The gene is dominant. Each child has 50% chance of getting the gene.

Having the gene does not always cause the disease, or may not always cause it at the same time in life. Much about this is still a mystery.

Genetic Information Nondiscrimination Act (GINA)

GINA does NOT apply to military personnel. (Department of Defense has its own rules.)

2000 President signed order to protect federal employees from genetic discrimination in employment

2008 Congress finally passed GINA

May 21, 2009 health insurance protection

November 21, 2009 employment protection

For health insurance or employment, GINA prohibits:

Using genetic test results on you

Using genetic tests from a family member,

Using manifestations of a genetic disease in the family

Using the participation of you or family in genetic research

Also GINA prohibits….

Insurers from using genetic information to set health insurance eligibility or premiums

Insurers from requiring an individual to take a genetic test

Using genetic information for hiring, firing, or promotions in employment decisions

Legislation varies by state in protections provided

Allows individuals experiencing discrimination to file a civil suit (damages capped at $300,000. plus back pay)

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Genetic Counseling

Teresa M Kruisselbrink

The personal amyloid journey

Usual medical journey: Symptoms, meet with doctors, testing, diagnosis, treatment

Amyl journey: 1st 3 steps happen in various orders many times, until finally correct diagnosis occurs. Then there are complexities as you deal with family members, who may also have it, and will also be affected by its effects on you, and its treatment and management.

Personal questions after diagnosis

How do I tell my family?

How will they react?

How did I get this?

Who in my family is at risk?

What does Val30Met (and all those other terms) mean?

Genetics of Familial Amyloidosis

Transthyretin (TTR)

Carries thyroid hormone and retinol

Soluble – able to be dissolved

Genetics of FA

We all have 2 copies of all of our genes, including TTR, GSN, APOA1

Familial amyl disorder has Dominant Inheritance: A mutation in 1 of the 2 copies is enough to cause condition

Variation

- Over 100 different mutations
- Specific code change may provide information about symptoms
- T60A – Heart & autonomic nerves
- V30M – Peripheral and autonomic Neuropathy
- V122I – Cardiac
- Same mutation exist in a given family – within a family, everyone has the same specific type, the same variety

Who else is at risk?

All first degree relatives of person with FA

- Children
- Parents
- Brothers and Sisters

Sometimes you can guess about ancestors' status, looking at their cause of death. But that can be misleading.

Should a person with FA have genetic testing?

Part of diagnostic work-up

Important in understanding cause of Amyloidosis (inherited or not)

May provide information about what to expect medically

Will impact treatment and eligibility to clinical trials

Necessary to determine prior to genetic testing other family members

Family Communication

- Understand the condition yourself
- Educational info from providers
- Patient support groups
- Think through how your family members will respond
- Each will respond differently
- Each has their own coping mechanism
- How have they handled other information in the past
- Familial Amyloidosis, NOT AL, NOT Wild Type, NOT Secondary (AA) – Make sure folks google-ing or researching this understand which they should be researching.
- Open the conversation
- Family members will ask questions that are important to them
- You don't have to have all the answers
- Will need more than one discussion

Genetic Testing for Family Members

Benefits

Determine whether you are at risk or not

Relief from uncertainty

Informed decisions about future

Early recognition of symptoms and intervention

"I felt like I needed to know, so I could follow through."

Limitations

Positive test won't tell if or when symptoms may occur

May not be any immediate treatments

May lead to increased anxiety, fear, guilt

Once you know, you know.

"Yesterday I knew I might be at risk, but now I know I am, and I'm now thinking about it all the time."

When to do genetic testing for family members

When is the right time for testing?

"right time" and "right way"

The onset is during adulthood, as is any treatment or other intervention. Genetic testing may have little benefit before then – or may be helpful for planning, or peace of mind. It depends on the person, and is a personal decision.

Individual choice; informed decision: Take into consideration how information will be used. The answer to this will change over time, as treatments are developed.

Genetic testing of children

Testing of young children is not advised – there is not added benefit, and the child should be allowed to reach an age where they can decide themselves about getting tested.

Making informed decisions about pre-symptomatic testing

How will I use the information?

How will I react if my test confirms that I am at risk?

How will I feel if I am not at risk?

How will my family react if some of us are found to be at risk and some are not?

Am I able to handle the medical and psychological impact of a positive result?

Is now the right time?

Testing Logistics

Blood Draw or Cheek Swab

Only looking at FA related genes

Cost ~ $800-$1000 (TTR)

Family specific testing ~ $400-500 (once we know what, specifically, to look for)

Results 2-3 weeks

Set up appropriate time for results

Try to work with a clinical group that understands this. But usually you have to be your own advocate around this; most clinicians do not understand amyl; it is much too rare for them to be familiar with it.

Insurance Concerns

Will my health insurance cover it?

Possibly – your MD may need to explain to insurer why it is medically necessary. Some insurance may exclude this kind of testing from coverage.

Will my health insurance raise my rates or deny coverage? Will my employer discriminate against me?

No – Protected by Federal Law (GINA)

Life Insurance

Note: Life insurance not covered by this law. Some people have had problems getting life insurance after being diagnosed. You may want to have your insurance set up before being tested.

Peripheral Neuropathy, Carpal Tunnel, Etc. (Polyneuropathy and Autonomic Neuropathy)

Dr. Wiesman & Dr. Wang

A Peculiar Form of Peripheral Neuropathy (Andrade, 1952)

"Foot Disease" in Povoa de Varzim, Portugal

- Early impairment of thermal and painful sensibilities, beginning and also predominating in the lower extremities
- Paresis in the extremities, particularly the lower ones
- Gastro-intestinal disorders
- Sexual and sphincter disorders

A Peculiar Form of Peripheral Neuropathy (Andrade, 1952)

- 74 cases from several unrelated families
- Dominant nature of transmission
- Insidious onset in second or third decade
- Progressive nature: 7-10 years

Peripheral Neuropathy

- Polyneuropathy with or without pain
- Small Fiber Neuropathy
- Autonomic Neuropathy

Symptoms of Polyneuropathy

Sensory symptoms

- Tingling
- Burning pain
- Electrical or stabbing sensations
- Hypersensitivity
- Deep aching pain
- Coldness

Non-sensory symptoms

- Imbalance
- Fatigue
- Falls
- Weakness
- Worse in feet
- Worse at night
- Symmetric (usually)

Signs of Polyneuropathy

- length-dependent weakness (feet and hands)
- loss of vibration> proprioception (large fiber) (can't sense a tuning fork)

- loss of temperature and pain (small fiber) (can't sense something hot, or a sharp poke)
- reduced or absent ankle reflexes

Small Fiber Neuropathy

Many clinicians need more training to specifically identify this

- prominent pain and burning in the feet, hands
- distal loss of pain and temperature sensation
- relative preservation of distal vibration sensation
- preservation of ankle reflexes on examination

Autonomic Neuropathy

- Lightheadedness or "dizziness": Do you feel like you may faint, or like you may fall (two different kinds of dizziness, different causes)
- Blurred vision
- Dry eyes, dry mouth
- Cold feet (Starts as just a sensation. Eventually, the feet do become measureably cold)
- Early satiety, constipation, diarrhea
- Urinary retention, incontinence
- Hypohidrosis (hands are dry. Things slip out of hands. Hands don't sweat.)

Delayed Recognition without Dysautonomia (Wang et al. 2008)

If there is an unexplained diagnosis of auto- or poly-neuropathy AND signs of autonomic dysfunction, test for amyloid.

- 65 patients with amyloidosis
- Time to diagnosis
    - 12 months if dysautonomia or small fiber
    - 48 months if no dysautonomia
- Test for autonomic neuropathy if etiology unknown
- Testing abnormal even without symptoms

TTR Variants

- SMN without autonomic symptoms (Cys104- Saraiva et al 1999 and Tyr 77-Quan and Cohen 2002)
- Rapidly progressive PN (Ser 25-Yazaki et al 2002)
- Motor neuropathy (Leu 68-Salvi et al 2003)
- Multifocal demyelinating mononeuropathies
- (Ile 122-Breimberg and Amato 2004)
- Cardiac (Ile122-Jacobsen et al.1997)

Diagnosis

- Polyneuropathy-EMG
- Autonomic Neuropathy-Autonomic testing
- Amyloid deposition-Nerve Biopsy
- TTR-Genetic Testing

Electromyography (EMG)

People with poly-neuropathy have normal EMGs.

- Two part test:
  - Nerve conduction studies (tests feel like static)
  - Needle electromyography
- Establish diagnosis of polyneuropathy
- Distinguish demyelinating from axonal
- Differentiate radiculopathy, plexopathy
- Normal in small fiber and autonomic neuropathy

Autonomic Testing

- Quantitative Sudomotor Axon Reflex Test
- Heart rate response to deep breathing
- Valsalva Maneuver
- Tilt Table

Nerve Biopsy

- Amyloid deposits in endoneurium (perivascular) or subperineurial areas
- Congo Red, Thioflavine, Methyl Violet, TTR
- Electron Microscopy
  - Unbranched fibrils
- Absent in 10% (multifocal) – i.e., amyloid will sometimes not be detected when this is the cause.

Amyloid Deposition

(A few pictures of tissue samples were shown)

Biopsy-Alternative Sites

- Cardiac, liver, renal
- Fat pad aspiration
- Rectal mucosa (diarrhea)
- Accessory salivary glands (scrape inside of mouth)
- Skin

Symptomatic Treatment

- Weakness
- Pain Management
- Autonomic neuropathy
- Weight loss

Management

Rehabilitation for weakness and balance

It is about safety.

Don’t exhaust yourself and ruin the rest of your day. Be smart about how you spend your energy.

- Physical therapy
  - maintain strength and flexibility
  - balance
  - fall avoidance
  - cane, braces, walker, motorized vehicle
- Occupational Therapy
  - activities of daily living

Table of treatment recommendations

Evidence based Guidelines: MN 2011

	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300–600 mg/day	
Level B	Gabapentin, 900–3600 mg/day	Oxcarbazepine
	Sodium valproate, 500–1200 mg/d	Lamotrigine
	Venlafaxine, 75–225 mg/day	Lacosamide
	Duloxetine, 60–120 mg/day	Clonidine
	Amitriptyline, 25–100 mg/day	Pentoxifylline
	Dextromethorphan, 400 mg/day	Mexiletine
	Morphine sulfate, titrated to 120 mg/day	Magnetic field treatment
	Tramadol, 210 mg/day	Low-intensity laser therapy
	Oxycodone, mean 37 mg/day, max. 120 mg/day	Reiki therapy
	Capsaicin, 0.075% four times per day	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks	

Orthostatic hypotension Management

- get out of bed slowly, in stages
  - Raise head of bed
  - Sit on edge of bed/dorsiflex feet
- Fluids (8 cups/day)
- Salt
- 6 small meals
- Cross legs
- Compression stockings/Abdominal binder
- Walker/wheelchair

Orthostatic hypotension Treatment

- Fludrocortisone
  - Mineralocorticoid
  - 0.1-0.3 mg/day
  - Monitor potassium

    - Supine hypertension
    - Edema
- Midodrine
    - Alpha adrenoreceptor agonist
    - 10 mg three times daily
    - Up to every 4 hours
    - Avoid after 6 pm
    - Goosebumps (piloerection)

Example of a neuropathy exam

This exam determines

Is there an autonomic neuropathy? If so, how severe (what grade)?

Is there a … neuropathy? If so, how severe (what grade)?

Is there a … neuropathy? If so, how severe (what grade)?

Cardiac issues TTR, Non-TTR – Wild Type

Drs. Grogan, Maurer, & Hanna

[I DID NOT GET THE SLIDES]

Cardiac Amyloidosis (3 videos)

Part 1: http://www.youtube.com/watch?v=o6u-nETEj9M&feature=player_embedded

Part 2: http://www.youtube.com/watch?v=9gIB40Imc5U&feature=player_embedded

Part 3: http://www.youtube.com/watch?feature=player_embedded&v=kvPU83VIv2o

Basics of Cardiac Amyloid

Left & Right Atria is where blood goes as it comes back from the body or lungs.

Left & Right Ventricles squeeze the blood back to the body or lungs

Amyloid collects between heart muscle fibers, so the walls become stiff, and move less volume of blood. The ejection fraction (% of blood in heart that gets moved out with each heartbeat) may be normal, but the amount of blood in the heart is less than usual.

Heart tests to diagnose cardiac amyloid

Echocardiogram – often amyloid is first suspected due to abnormal echocardiogram (thickness, stiffness, valve function, pressure in lungs)

MRI

Biopsy

It is not all about heart thickening. Amyl patients with very different heart thicknesses may have very different function.

Blood test for Cardiac Amyloid

Troponin – protein released due to heart attack

BNF or NT pro-BNP – protein released by heart in response to high pressure

Treatment for Cardiac Amyloid

Stop the source

No medication to remove amyloid yet.

Diuretics decrease shortness of breath and get rid of fluid

…[MISSED ONE]

Advanced treatment

Pacemakers

Artificial hearts

Heart transplant.

Summary

Stiff heart, hard to fill

Heart failure & rhythm problems

There is no single number that captures heart function, or that indicates cardiac amyloid

[MISSED ONE]

Q & A

What is difference in what CT vs MRI tells the clinician?

MRI shows heart muscle thickness. CT does not.

Too wet or too dry? (Make sure you get frequent fluid monitoring)

Dr. Maurer (echoed by Dr. Grogan): **Managing an amyloid affected heart is the most challenging type of cardiac management.** Finding the "sweet spot" in diuretic use requires very frequent monitoring. Torsemide (deminex) is better than lasix as a diuretic for amyloid. It is more constant in its effect.

Lunch

TTR – Familial, Wild Type and organ transplants

Dr. Steven Zeldenrust

Rationale

Why liver transplant?

- Removing source only known cure

- Majority of circulating TTR made in liver
- Not for asymptomatic gene carriers

What about transplanting other organs?

If dysfunction is isolated to a single, transplantable organ, than other organ transplant may make sense – but maybe not if the liver is producing amyloid that will then affect some other organ.

Liver Transplant

- First liver transplant performed in Sweden 1990
- The FAP World Transplant Registry:
- Updated 12/31/11
- 2008 liver transplants performed worldwide
- 120 transplants/year
- Portugal, France and Sweden account for over two-thirds – so this may not be informative about your type of amyloid, if it isn't what is common in Portugal, France or Sweden, which is V30Met.

Outcomes

- Low mortality rate (3%)
- Predictors of outcome:
- mBMI – modified body mass index (BMI * albumin level) – the better your mBMI (nutritional status), the better the outcomes.
- Disease duration (shorter duration tends to have better outcomes)
- Mutation (V30M vs non-V30M) (V30M tended to have better outcomes)
- Autonomic neuropathy (worse outcomes than those without)

V30M Liver Transplant Outcomes

- Neuropathy stable or improved in up to 40%
- Nutrition improves in up to 80%
- Cardiac progresses in most
- Kidney involvement unaffected
- Eye deposits progress

Non-V30M Liver Transplant Outcomes

- Small numbers & wide variety of the amyloid strains make prediction difficult
- Neuropathy – autonomic most likely to improve, sensory variable
- GI improves in most
- Eye and brain can worsen due to local production of variant TTR. In some, this can get worse after liver transplant.
- Cardiac progresses in many. Some evidence that pace of deposition can increase after transplant.
- Cardiac deposits develop in those with no heart involvement at TX.
- New amyloid deposits can contain normal TTR made by transplanted liver

Heart Transplant in ATTR

- FAPWTR [Familial Amyloidotic Polyneuropathy. World Transplant Registry]
- Liver + heart 37

- Liver + previous heart 11
- Liver + sequential heart 1
- Liver + heart + kidney 3
- Survival better than those that did not receive transplant
- Some centers advocating combined heart/liver transplant in non-V30M: they say, "Get both, or get neither". In some types that just affect heart, just doing a heart transplant seems to be all that was needed.
- Controversy over timing (combined vs. sequential)
- Bridging with LVAD available – pacemakers & other devices now last a long time, and may be all that is needed (vs. being temporary fixes).

Kidney Transplant in ATTR

- Kidney involvement in most at diagnosis
- Only symptomatic in ~10%
- FAPWTR: Liver + kidney 46
- Survival worse than liver alone, but related to low mBMI. Poor ability to hold and use nutrition

What Does It All Mean?

Known:

- Survival improved with liver transplant in V30M
- Most effective if early
- Major benefit is nutrition
- Heart and neuropathy may not improve
- Combined liver + heart and liver + kidney feasible – multiple transplants are possible, and may be appropriate

Unknown:

- When is it futile? There is a point at which you may be too sick. The transplant may not improve the outcome.
- Which mutations benefit? It is hard to know. There is too little data about most mutations.
- If heart involved need combined heart + liver? Unknown, but some heart-alone transplants have had very good outcomes.
- Is amyloid halted, slowed, reversed or accelerated? We do not know. In some cases, it seems one way, and another way in others.

Implications

- ATTR clear indication for liver transplant
- Early and accurate diagnosis critical
- Possibility of domino shortens wait time – the amyloid liver gets put into someone who needs a liver (someone elderly, who is not likely to be affected by the amyloid in their lifetime). In Boston, this halves the wait time right now.
- Need for multiple organs lengthens wait time

Future Directions

- Better follow-up needed to answer important questions (disease progression, natural history with & without transplant(s), etc.)
- Impact of new treatments (alternative to transplant vs. adjunct to transplant)

Senile Systemic Amyloidosis (SSA) – Liver transplant does not help

(also called senile amyloid, senile cardiac amyloid, age-related)

- Deposits formed by normal (wild-type) TTR (*note: wild-type and normal are the same)
- Systemic deposits
- Affects predominantly heart in elderly males (little neuropathy, kidney, or lung. But carpal tunnel may be common.)
- Liver transplant not curative in SSA – the new liver produces the same wild-TTR
- Heart transplant possible, but mean age at diagnosis of SSA around 70. 70-year-olds are not high priority for heart transplants.
- Potential benefit from novel therapies

Q & A

What qualifies you for a liver transplant?

You have to have some amyloid, but not too much.

Are liver donors screened for amyloid?

No. Amyloid is so rare that the likelihood is very small that a donated liver would convey amyloidosis.

What is the average time from onset to transplant?

It depends on if your family is aware of the disease. Aware families get onto the transplant lists early, and get transplants much sooner.

Non TTR – including Cerebral & LECT 2 & organ transplants

Dr. Merrill Benson, Indiana University School of Medicine, Department of Pathology and Laboratory Medicine

Familial Amyloidosis, Other Than TTR

1. TTR most common
2. Non-TTR more challenging.
    a. Diagnosis – DNA testing. Can be expensive: There are many of them. There are 110+ known strains for which to test.
    b. Treatment – Organ involvement
3. Research – Limited financial support.

Types

There are many, many types.

Some "Common" Types	1st clinical description	1st biochemical characterization	Where 1st discovered
ApoAI	1969	1988	USA
Fibrinogen Aa-Chain	1975	1993	USA
Lysozyme	1982	1993	UK
ApoAII	1973	2001	USA
Gelsolin	1969	1990	Finland
Cystatin-C	1972	1986	Iceland
LECT2	2008	2008	USA

The symptoms vary, and are not completely consistent for any single type.

Having one vs. two of your genes with the amyloid (heterozygous vs. homozygous) produces a greater affect for some strains, but not for others.

10/02/2013

TRANSTHYRETIN AMYLOIDOSIS

MUTATION	CODON CHANGE	CLINICAL FEATURES*	GEOGRAPHIC KINDREDS
Cys10Arg	TGT - CGT	Heart, Eye, PN	USA (PA)
Leu12Pro	CTG - CCG	LM	UK
Met13Lys	ATG - AAG		France
Asp18Glu	GAT - GAA	PN	South America, USA
Asp18Gly	- GGT	LM	Hungary
Asp18Asn	- AAT	Heart	USA
Val20Ile	GTC - ATC	Heart, CTS	Germany, USA
Ser23Asn	AGT - AAT	Heart	USA
Pro24Ser	CCT - TCT	Heart, CTS, PN	USA
Ala25Ser	GCC - TCC	Heart, CTS, PN	USA
Ala25Thr	- ACC	LM, PN	Japan
Val28Met	GTG - ATG	PN, AN	Portugal
Val30Met	- ATG	PN, AN, Eye, LM	Portugal, Japan, Sweden, USA (FAP I)
Val30Ala	- GCG	Heart, AN	USA
Val30Leu	- CTG	PN, Heart	Japan, Sweden
Val30Gly	- GGG	LM, Eye	USA
Val32Ala	- GCG	PN, AN, Heart	Singapore (Chinese)
Val32Gly	- GGG	PN,AN	France
Phe33Ile	TTC - ATC	PN, Eye	Israel
Phe33Leu	- CTC	PN, Heart	USA
Phe33Val	- GTC	PN, Eye	UK, Japan, China
Phe33Cys	- TGC	CTS, Heart, Eye, Kidney	USA
Arg34Ser	AGA - AGC/T	PN, Heart	USA
Arg34Thr	- ACA	PN, Heart	Italy
Arg34Gly	- GGA	Eye	UK (Kosovo)
Lys35Asn	AAG - AAC	PN, AN, Heart	France
Lys35Thr	- ACG	Eye	USA
Ala36Pro	GCT - CCT	Eye, CTS	USA
Asp38Ala	GAT - GCT	PN, Heart	Japan
Asp38Val	- GTT	PN, Heart	Guiana
Asp39Val	GAC - GTC	Heart	Germany
Trp41Leu	TGG - TTG	Eye, PN	USA
Glu42Gly	GAG - GGG	PN, AN, Heart	Japan, USA, Russia
Glu42Asp	- GAT	Heart	France
Phe44Ser	TTT - TCT	PN, AN, Heart	USA
Phe44Tyr	- TAT	PN, AN	France
Ala45Thr	GCC - ACC	Heart	USA
Ala45Asp	- GAC	Heart, PN	USA
Ala45Ser	- TCC	Heart	Sweden
Ala45Val	- GTC		France
Gly47Arg	GGG - CGG/AGG	PN, AN	Japan
Gly47Asp	- GCG	Heart, AN	Italy, France
Gly47Val	- GTG	CTS, PN, AN, Heart	Sri Lanka
Gly47Glu	- GAG	Heart, PN, AN	Turkey, USA, Germany
Thr49Ala	ACC - GCC	Heart, CTS	France, Italy
Thr49Ile	- ATC	PN, Heart	Japan, Spain
Thr49Pro	- CCC	Heart, PN	USA
Thr49Ser	- AGC	PN	India
Ser50Arg	AGT - AGG	AN, PN	Japan, France/Italy, USA
Ser50Ile	- ATT	Heart, PN, AN	Japan
Glu51Gly	GAG - GGG	Heart	USA
Ser52Pro	TCT - CCT	PN, AN, Heart, Kidney	UK
Gly53Glu	GGA - GAA	LM, Heart	Basque, Sweden
Gly53Ala	- GCA	PN, An, Heart, Eye, LM	UK
Gly53Arg	- AGA	LM	USA
Glu54Gly	GAG - GGG	PN, AN, Eye	UK
Glu54Leu	- TTG	Heart	Belgium
Glu54Lys	- AAG	PN, AN, Heart, Eye	Japan
Leu55Arg	CTG - CGG	LM	Germany
Leu55Gln	- CAG	Eye, PN	USA, Sweden
Leu55Pro	- CCG	Heart, AN, Eye	USA, Taiwan
His56Arg	CAT - CGT	Heart	USA
Gly57Arg	GGG - AGG	Heart, PN	Sweden
Leu58His	CTC - CAC	CTS, Heart	USA (MD) (FAP II)
Leu58Arg	- CGC	CTS, AN, Eye	Japan
Thr59Arg	ACA - AGA	Heart, AN	Japan
Thr59Lys	- AAA	Heart, PN, AN	Italy, USA (Chinese)
Thr60Ala	ACT - GCT	Heart, CTS	USA (Appalachian)
Glu61Lys	GAG - AAG	PN	Japan
Glu61Gly	- GGG	Heart, PN	USA
Glu62Lys	- AAG	PN	Italy
Phe64Leu	TTT - CTT/TTG	PN, CTS, Heart	USA, Italy
Phe64Ile	- ATT		
Phe64Ser	- TCT	LM, PN, Eye	Canada, UK
Gly67Arg	GGG-AGG	Eye, PN	USA
Ile68Leu	ATA - TTA	Heart	Germany
Tyr69His	TAC - CAC	Eye, LM	Canada, USA, Sweden
Tyr69Ile	- ATC**	Heart, CTS, AN	Japan
Lys70Asn	AAA - AAC	Eye, CTS, PN	USA
Val71Ala	GTG - GCG	PN, Eye, CTS	France, Spain
Ile73Val	ATA - GTA	PN, AN	Bangladesh
Tyr75Ile	ACC - ATC	Heart	France
Ser77Tyr	TCT - TAT	Kidney	USA (IL, TX), France
Ser77Phe	- TTT	PN, AN, Heart	France
Tyr78Phe	TAC - TTC	PN, CTS, Skin	France
Ala81Thr	GCA - ACA	Heart	USA
Ala81Val	- GTA	Heart	Russia, Poland
Ile84Ser	ATC - AGC	Heart, CTS, Eye	USA (IN), Hungary (FAP II)
Ile84Asn	- AAC	Heart, Eye	USA
Ile84Thr	- ACC	Heart, PN	Germany, UK
His88Arg	CAT - CGT	Heart	Sweden
Glu89Gln	GAG - CAG	PN, Heart	Italy
Glu89Lys	- AAG	PN, Heart	USA
His90Asp	CAT - GAT	Heart	UK
Ala91Ser	GCA - TCA	PN, CTS, Heart	France
Glu92Lys	GAG - AAG	Heart	Japan
Val93Met	GTG - ATG	PN	UK
Val94Ala	GTA - GCA	Heart, PN, AN, Kidney	Germany, USA
Ala97Gly	GCC - GGC	Heart, PN	Japan
Ala97Ser	- TCC	PN, Heart	Taiwan, USA
Arg103Ser	CGC - AGC	Heart	USA
Ile107Val	ATT - GTT	Heart, CTS, PN	USA
Ile107Met	- ATG	PN, Heart	Germany
Ile107Phe	- TTT	PN, AN	UK
Ala109Ser	GCC - TCC	PN, AN	Japan
Leu111Met	CTG - ATG	Heart	Denmark
Ser112Ile	AGC - ATC	PN, Heart	Italy
Tyr114Cys	TAC - TGC	PN, AN, Eye, LM	Japan, USA
Tyr114His	- CAC	CTS, Skin	Japan
Tyr116Ser	TAT - TCT	PN, CTS, AN	France
Ala120Ser	GCT - TCT	Heart	Afro- Caribbean
Ala120Thr	- ACT	PN, CTS	Japan
Val122Ile	GTC - ATC	Heart	USA
ΔVal122	- ΔΔΔ	Heart, PN	USA (Ecuador), Spain
Val122Ala	- GCC	Heart, Eye, PN	USA

* = CLINICAL FEATURES: AN = Autonomic Neuropathy; CTS = Carpal Tunnel Syndrome; Eye = Vitreous Deposits; LM = Leptomeningeal; PN = Peripheral Neuropathy; ** = Double Nucleotide Substitution

Treatment

Type	Liver transplant?	
Apo AI	Yes	Affected organ transplant – kidney, heart
Fibrinogen Aα	Yes*	Affected organ transplant – kidney
Lysozyme		Affected organ transplant – liver, kidney
Apo AII		Affected organ transplant – kidney
Gelsolin		Affected organ transplant – cornea
Cystatin C		Avoid fever (one report indicates fever may speed amyloid production)

* for fibrinogen, liver transplant is probably curative, since only mutant amyloid accumulates in fibrinogen amyloid. It is arguable that liver transplant should be done as early as possible, to avoid kidney transplant.

Cerebral Amyloid Angiopathy

Amyloid probably being produced in central nervous system

…

LECT2: What we know

1. Mainly kidney pathology
2. Systemic disease – Liver (hepatic) amyloid deposition
3. Predominantly affects Hispanics (Mexicans)
4. DNA (gene) analysis –
    a. No mutation in LECT2 gene
    b. To date, all gene sequences have shown homozygosity for the Val 58 polymorphism

LECT 2: What we do not know

1. Frequency of LECT2 amyloidosis in different populations.
2. Is there a mutation in a gene, other than LECT2, that determines development of amyloidosis? (e.g. as seen in some forms of hereditary Alzheimer disease).
3. If there is a gene mutation, what percent of people with the mutation get the disease?

LECT 2: Importance of making the diagnosis

1. Avoid treating the patient as AL (primary) amyloidosis (no chemotherapy).
2. Counseling – LECT2 amyloidosis appears to be a slowly progressive disease.
3. LECT2 patients are probably candidates for organ transplantation (kidney, liver).

Q & A

Where to go for testing for rare TTRs?

Indiana, Boston, Mayo, Baylor, … many places test. See http://www.ucl.ac.uk/amyloidosis/national-am-centre for a good list of types of amyloid (National Amyloidosis Centre, University College London Medical School) [I COULD NOT FIND THAT LIST ON THEIR WEBSITE]

Pathologists' Perspective

Dr. Maria Picken

See also: Picken MM, Doğan A, Herrera GA. Amyloid and related disorders surgical pathology and clinical correlations. New York: Humana Press; 2012. Available at: http://www.springer.com/medicine/pathology/book/978-1-60761-388-6 .

Why amyloid forms?

Structural abnormalities render the proteins amyloidogenic,

Excess production

Genetic predisposition

Congo Red stain: gold standard to identify amyloid

- β-pleated sheet conformation confers unique staining properties
- (affinity to Congo red) & fibrillar ultrastructure common to ALL types of amyloid

Congo Stain history

1. first synthesized in 1883 by Paul Bottiger (Friedrich Bayer Company, Germany) as a textile dye
2. the company was not interested, so Bottiger filed the patent under his name and sold it to the AGFA company of Berlin
3. AGFA marketed the dye under the name "Congo red" (bright red color) (1884 Berlin West Africa Conference, colonization of Africa)

Fat biopsy process

A special syringe is used to get fat globules from the belly, or pulled through a cut (surgical biopsy – can get fat that is more likely to have the amyloid (not just subcutaneous, and larger sample)

If there is a high index of suspicion & the fat biopsy is negative, it may be appropriate to biopsy the affected organ.

Pathology of Familial Amyloidoses

1. Detection of amyloid in the index patient
   - lack of a family history
   - new mutation
2. Examination of family members/known carriers
   - experience from domino liver transplants
3. Staging, definition of organ involvement

Different organs may be affected

	Heart	Nerve	Kidney	Gastrointestinal
Transthyretin	X	X	X	X
Gelsolin		X	X	
Apolipoprotein I	X	X	X	
Apolipoprotein II			X	
Fibrinogen A α-chain			X	
Lysozyme			X	X
Lect2			X	
Cystatin C				

When to do Congo red stain?

- to confirm suspicion of amyloid
- to rule out amyloid

Kidney: Proteinuria/NS

Heart (native): routinely
Heart failure, orthostatic hypotension
Nerve bx: routinely
GI: ischemia, collagenous colitis
Bleeding, malabsorption, weight loss,
constipation, diarrhea
Liver: hepatomegaly
Spleen: splenomegaly
Thyroid, Adrenal gland: hypofunction, enlargement
Unexplained kidney, heart or systemic disease

Clinical Trial Presentations

Diflunisal & Doxycycline

Dr. John Berk

Data are under review, due to the stage of review of the potential treatment

Diflunisal – aspirin-like, non-steroidal anti-inflammatory drug (NSAID)

Study Design

- ~8 site, international randomized clinical trial
- Outcome measure: NIS+7 (a composite Neurologic Impairment Score)

Subjects

Requirements

- Age 18-75 (Skewed toward upper end)
- Biopsy-proven amyloid deposits
- mutant TTR
- diagnosed neuropathy

Demographics

- Amyloid Types: 55% V30M, 11% T60A, 12% L58H, 22% other
- More males than females (~2/3 to 1/3)

Results

May be out in a month, or maybe in many months

ISIS

Dr. Merrill Benson

Studying ISIS-TTRRx for the Treatment of Transthyretin Amyloidosis

What is ISIS-TTR_{Rx} & How does it Work?

- Isis' drug, ISIS-TTR_{Rx} is an antisense drug that works by reducing the amount of mutant and normal TTR protein made by your body
- The build-up of TTR can cause nerve damage and/or heart disease.

- Most patients with TTR amyloidosis produce both normal and mutated forms of the TTR protein.
- It has been shown that both forms of TTR protein build-up in tissues as amyloid deposits.
- It is predicted that lowering the amount of TTR protein will result in a lower amount of amyloid deposits that build-up in tissues, thus slowing or halting disease progression.
- As with liver transplantation, ISIS-TTR_{Rx} decreases the amount of mutant TTR produced, however ISIS-TTR_{Rx} also lowers normal TTR, offering a unique approach to treating this disease. Because normal TTR can continue to deposit as amyloid fibers after liver transplant, this distinction may even represent a therapeutic alternative or advantage.

The basic theory

- Proteins Are Made from RNA
- Antisense Drugs Bind to & Destroy the RNA

ISIS-TTR_{Rx} Phase 1 Study

- Healthy volunteers
- Studied 5 different single and multiple doses of ISIS-TTR_{Rx}
- Designed to test effects of ISIS-TTR_{Rx} on:
  - Side Effects = Safety
  - Amount of Drug in Blood = Pharmacokinetics
  - TTR Levels in Plasma = Pharmacodynamics
- Study Completed

Potent & Durable Reductions in Transthyretin Levels in Healthy Volunteers Treated with ISIS-TTR_{Rx}

Dose-response seen in Transthyretin reduction in healthy volunteers up to 300 mg

ISIS-TTR_{Rx} Phase 3 Enrolling Now

Purpose

- Does ISIS-TTR_{Rx} slow or stop the nerve damage caused by TTR deposits
  - mNIS+7 test will be used to help make this determination

Inclusion Criteria

- Must have signs of polyneuropathy
- Late Stage 1 or Early Stage 2
- Patients with liver transplantation are not eligible

Patients

- 195 TTR Amyloidosis Patients

Evaluate Safety

- Determine the safety of ISIS-TTR_{Rx} given for 15 months
  - Blood tests, eye exams and other tests will be used to make this determination

ISIS-TTR_{Rx} Phase 3 Study Design

- Double-blind and Placebo Controlled

    - Neither the Study doctors, nor the patients will know who is getting placebo and who is getting ISIS-TTR_{Rx}
- 2:1 Randomization
    - 2/3 of the patients will receive drug
    - 1/3 of the patients will receive placebo
- OLE (open-label extension) – After finishing the Phase 3 study, patients can participate in the OLE study. In the OLE study all patients will receive ISIS-TTR_{Rx}
- Seven Participating Trial Sites in the United States

ISIS-TTR_{Rx} Phase 3 Study Process

Treatment

15-month treatment

Weekly injections

Subcutaneous injections

Both Placebo and ISIS-TTR_{Rx} are given as a shot under the skin

Home Administration

Patients take the drug home

Patients & caregivers are trained and given detailed instructions to take home

Self-administered by patient or by family members/caregivers

mNIS+7: An Important Phase 3 Test

mNIS+7 will help evaluate if ISIS-TTR_{Rx} is helping slow the progression of disease in patients with TTR FAP.

Tests Include:

- Neuropathy Impairment Score (NIS)
- Nerve conduction tests
- Tests to measure your ability to feel heat or touch

Interested in Knowing More?

- Ask your doctor
- Talk to physicians here at the meeting
- Talk to Isis representatives here at the meeting
- Go to www.clintrials.gov for more information

Alnylam

Dr. Jared Gollob

ALN-TTR02 and ALN-TTRsc

Transthyretin Amyloidosis Programs

.

RNA Interference (RNAi)

A Breakthrough Discovery in Biology

- "Silence" disease-causing genes
- Create whole new class of medicines

Therapeutic Approach to Harnessing RNAi

Interfere with production of RNA by putting a short piece of interfering RNA in each cell.

Alnylam Development Pipeline

About 6 products are in the pipeline. The "TTR-Mediated Amyloidosis" is farthest along (in phase 2 of 3 phases)

Transthyretin (TTR)

- TTR amyloidosis is a fatal, autosomal dominant, multisystem disease caused by abnormal extracellular deposits of TTR amyloid (mutant and WT)
- TTR is a primarily liver-expressed tetrameric protein that binds and transports serum retinol binding protein (RBP)/Vitamin A and minor fraction of serum thyroxine (T4)
- Mutations in TTR gene lead to destabilization of TTR tetramer with deposition of mutant and WT protein and fibril/amyloid formation in a variety of tissues, including:
- Nerves (FAP): 10,000 patients, commonly associated with Val30Met (V30M) mutation
- Heart (FAC): 40,000+ patients
- Therapeutic options for early stage FAP
- Liver transplantation: eliminate mutant protein
- Tafamidis: stabilize TTR tetramer

RNAi Therapeutic Approach

Blocking Liver Production of TTR

ALN-TTR siRNA Selection

RNAi Delivery to Liver Solved

IV and SC Platforms: Pre-clinical

Enables advancement of innovative medicines to patients

- Potent, rapid, and durable target gene silencing with lipid nanoparticle (LNP) technology and IV dosing
- Potent, rapid, and durable target gene silencing with proprietary GalNAc-conjugate technology and SC dosing with wide therapeutic index

ALN-TTR Programs

For the Treatment of Transthyretin Amyloidosis

ALN-TTR02 for Familial Amyloidotic Polyneuropathy (FAP): Intravenous delivery

ALN-TTRsc for Familial Amyloidotic Cardiomyopathy (FAC): subcutaneous delivery

ALN-TTR02 in clinical development

- Positive Phase I results in human volunteers
    - Data published in New England Journal of Medicine
- Positive Phase II results in FAP patients
    - Interim data at Peripheral Nerve Society, June 30, 2013
    - Final data at FAP Symposium, November 10–13, 2013 in Rio de Janeiro, Brazil

- Open-label Phase II extension study initiated
    - Includes clinical endpoints measured every 6 months
- Phase III start planned for late 2013
    - Successful completion of long-term non-clinical studies supporting chronic dosing in humans

ALN-TTR02 Study Results

Phase I: RNAi-Mediated TTR Knockdown (80% decrease in TTR for about a month in healthy volunteers)

Phase II: Found a dose response, and duration tapering after about a month in Familial Amyloidotic Polyneuropathy patients

Phase II: [I DIDN'T GET THESE RESULTS]

ALN-TTR02 Safety and Tolerability

Generally safe and well tolerated in human volunteers (n=17) with single dose1

- All AEs associated with drug administration mild or moderate in severity
    - Moderate infusion reaction in one subject at 0.5 mg/kg
- No SAEs, no discontinuations due to study drug
- No laboratory abnormalities
    - LFTs, renal function, or hematologic parameters

Generally safe and well tolerated in ATTR patients (n=19) with multi-dose2, 3

- All AEs associated with drug administration mild or moderate in severity
    - Mild infusion reaction in one patient at 0.3 mg/kg
- Self-limiting episode of upper limb cellulitis due to drug extravasation at infusion site in a patient with poor IV access (SAE)
- No laboratory abnormalities
    - LFTs, renal function, or hematologic parameters
- Additional safety data reported at PNS meeting
    - No additional AEs reported in 6 additional patients dosed at 0.3 mg/kg with simplified/reduced pre-medication regimen

ALN-TTRsc For Familial Amyloidotic Cardiomyopathy (FAC)

ALN-TTRsc in clinical development

- Positive Phase I study results
    - Normal healthy volunteer study in UK
    - Data presented at Annual Scientific Meeting of Heart Failure Society of America, September 23, 2013
- Pilot Phase II study start expected in late 2013
- Phase III start planned for 2014

ALN-TTRsc Phase I Study: TTR Knockdown in Multi-Dose Cohorts

- Statistically significant knockdown of serum TTR at all doses evaluated ($p<0.01$)
- Consistent level of TTR knockdown with weekly dosing; durable effects lasting weeks after last dose
- Mean TTR knockdown of 87.5% and 92.4% at 5.0 and 10.0 mg/kg, respectively

- Maximum TTR knockdown of up to 94%

ALN-TTR02 Safety and Tolerability

Phase I Study: Multiple doses of ALN-TTRsc generally safe and well tolerated

- Transient (<2 h), clinically mild erythema at injection site in minority of subjects
- No abnormalities in liver function tests, renal function, or hematologic parameters
- No evidence of inflammation (cytokines, CRP)

Acknowledgments

ALN-TTR02 Phase II Investigators

- David Adams; Hospital de Bicetre, Le Kremlin-Bicetre, France
- Teresa Coelho, Ana Silva; Hospital de Santo Antonio, Porto, Portugal
- Ole Suhr;Umea University Hospital, Umea, Sweden
- Isabel Conceicao; Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisboa, Portugal
- Juan Buades; Hospital Son Llatzer, Palma de Mallorca, Spain
- Josep Campistol; Hospital Clinic Barcelona Instituto, Barcelona, Spain
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- Hartmut Schmidt; University Hospital of Muenster, Muenster, Germany
- Marcia Waddington-Cruz; Hospital Universitário, Rio de Janeiro, Brazil
- John Berk; Boston University, Boston, MA USA

Pfizer: Tafamidis

Tafamidis Overview

- Status of discussions with FDA regarding TTR-Polyneuropathy (TTR-FAP)
- New collaborative research initiatives
- Update on tafamidis in Europe and Japan
- New clinical study with tafamidis for TTR-Cardiomyopathy (TTR-CM)

Status of Tafamidis FDA Discussions

- Pfizer is in active discussions with the FDA to find a path forward for approval
  - Our approach is focused on a novel biomarker
  - As discussions are ongoing with FDA, we cannot share specific details
- We are focusing our efforts on obtaining regulatory approval of tafamidis in the US which we believe is the best way to make this medicine available
- Pfizer stands firmly behind tafamidis and is committed to pursuing the development program for the drug in the US

Pfizer registry & research initiatives

Pfizer is about to launch a research grant program for research into the treatment of TTR-polyneuropathy. In 2014, research topics will focus on the early diagnosis of people with TTR-FAP.

New Collaborative Research Initiatives in TTR-Polyneuropathy

- Largest disease registry on TTR-Amyloidosis: focusing on understanding of the disease and its progression

- Over 2000 patients registered, over 45 sites in 17 countries, with 20 sites in the US
- Supported by Pfizer – established in 2007
- THAOS.net provides information for people with TTR-Amyloidosis, their caregivers and physicians
- Grants program to advance medical knowledge through clinical research in the treatment of TTR-polyneuropathy
- 2014 research topics will focus on the early diagnosis of people with TTR-FAP
- Open in the near future to investigators worldwide

Tafamidis in Europe and Japan

- Tafamidis approval for the EU (European Medicines Agency) granted in November 2011
- Tafamidis is currently available in 13 European Countries
- Clinical experience in individual patients for more than 5 years
- Tafamidis was approved in Japan in September 2013

New Study in TTR-Cardiomyopathy Starting This Year

- A multicenter, global evaluation of the efficacy, safety, and tolerability of tafamidis in people diagnosed with transthyretin cardiomyopathy
- Largest study of its kind:
    - Up to 400 patients to be enrolled with either familial TTR-Cardiomyopathy or non-hereditary (wild-type/senile systemic amyloidosis) cardiomyopathy
        - Approximately 250 tafamidis treated patients, 150 placebo
        - 20-25 sites in the US; additional sites globally
        - 30-month treatment duration
- All patients who complete the study will have the opportunity to receive tafamidis treatment in a long-term extension study.

Acknowledgements

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- Leslie Amass, PhD, US Medical Director, Tafamidis
- Emil Androsko, US Vice President, Rare Disease
- Pat Fay, Global Lead, Tafamidis
- Pedro Huertas, MD, PhD, Global Medicines Development Lead, Tafamidis Polyneuropathy
- Jennifer Schumacher, PhD, US Regional M edical Research Specialist Tafamidis

Concurrent Workshops

Peripheral Neuropathy: Prevent, avoid, cope, & treat

Neurologists Weisman, Wang

Cardiac: Symptoms, coping, & treatment

Cardiologists Grogan, Maurer, Hanna

Solid Organ Transplants: Yes, No, Which ones?

Drs. Despenzieri, Zeldenrust, & Picken

Genetic Issues

Teresa M. Kruisselbrink

ALA60: What makes us different?

Dr. Benson

Coping: Traveling, Managing GE Problems, Eye Problems, Orthostatic Hypertension, Diarrhea

Drs. Gertz & Skinner

Clinical Trials: Investigators

Dr. Berk

Caregiving

Carole, Liz, Jim, Sue, & Paula

Sunday, October 27

Questions & Answers

Dr. Gertz & Muriel Finkel

Dr. Merrill Benson, Indiana

Dr. Jeff Kelly, Scripps

Dr. Mazen Hanna – Cleveland Clinic

Dr. Matthew Maurer, Columbia U

Dr. Martha Skinner, Boston

Dr. Steve Zeldenrust, Mayo

Dr. Annabel Wang, Irvine

Dr. Janice Wiesman, Boston

Dr. John Berk, Boston

Dr. Angela Dispenzieri, Mayo

The programs testing new agents for FAP verify their ability to reduce TTR?

Yes, they will be tested for that. We'll find out if they are effective. They will look at change in protein & RNA levels. The patients in the trials are making an important contribution for us all.

How do you verify the progression (benefits) of treatment in clinical trials?

Dr. Wang: We are looking to see that there is no progression in specific quantitative markers

How long after phase 3 trial will drug become available?

Phase 1: dosing level – 1st human testing (animal testing is done before phase 1). Usually groups of 3 patients get a dose, and are carefully observed for side effects. Then another group gets a higher dose, to find the most promising dose.
Phase 2: safety – Not for efficacy, but rather for safety.
Phase 3: full clinical trial. Drugs that seem to have some efficacy & are safe are compared to standard of care. For amyloid, standard of care is nothing (placebo).
Most companies provide phase 3 trial subjects with medication during the gap between the end of the phase 3 trial and the medication going onto the market

I have a cough in the morning that is so severe it hurts

Sometimes fluid builds in the lungs when you lay down. This is associated with congestive heart failure – a backup of blood into the lungs causes fluid in the lungs. Let your doctor know about it.

I am told that my numbness in toes is not caused by amyloid. How do they know?

- Having numbness in fingers and toes may indicate other causes. Usually, toe numbness comes 1st, and finger numbness come after numbness is much further up the leg.

Explain how doxycycline works

- Doxycycline has enzymes that seem to break down existing amyloid deposits, and may improve discomfort of neuropathy. Whether there is long term improvement is not known.

Agents that affect amyloid formation

- Amyloid changes from functional form to a form that aggregates. The agents either change their form so they are not as likely to aggregate, or decrease the concentration of the protein (so they don't bump into each other as much, and so aggregate less).

At what age & how often should family members be tested for amyloid

- Depends on family's age of onset. It is helpful to have a baseline study before onset, and then maybe every 5 years (until onset), and maybe every year after the usual age of onset.
- Be your own advocate. If you start to see symptoms, it can help to see your doctor promptly rather than waiting a year or three

If you have the gene, but no symptoms, is there some medication I should be taking?

- Currently, we can't recommend a medication to slow down the progression of the disease, before onset. We recommend monitoring, not pre-onset treatment.

Are taste bud changes related to amyloid, and will my taste ever return to normal

- Dr. Wang: Amyloid can affect sense of taste and of smell. Once it is gone, it seldom returns. Zinc can also cause loss of taste or smell. Zinc can also decrease copper in body, with effects like loss of B12. Don't go beyond RDA of zinc.

Would you take diflunisal? If you had no symptoms?

- Dr. Benson: Many folks take aspirin every day. Diflunisal is a pretty safe NSAID. It could be OK.
- Matt: But patients with fluid retention or congestive heart failure should be careful about NSAID use. NSAIDs can complicate this condition. Be careful about diflunisal or other NSAID use if you have heart failure.

Are their triggers that might start TTR amyloid deposits?

- There may be some, but we don't know of any.

Is the protein intake in my diet important in the amount of amyloid that is produced?

There are many proteins. The ones you eat are digested in your stomach, and do not build amyloid.

Will carpal tunnel surgery resolve my hand numbness?

- Usually no. A second surgery may temporarily relieve the problem when it recurs.
- Benson: have the surgeon do a thorough release – the amyloid squeezes the nerves beyond the carpal tunnel segment
- Nerve conduction studies can tell whether the nerve is being pinched at the wrist, elbow, neck, peripheral neuropathy, or several of those. The set of symptoms can also reveal important clues – although in 25% of people, there are mild anomalies in how the nerves are organized, so you need a knowledgeable neurologist.
- Looking at both hands, even if one is unaffected, is helpful in the diagnosis.

When will some Amyl. meetings occur in the South, to accommodate some patients.

- Talk to your local advocacy group leader about recruiting a doctor to your local meeting, to address your questions.

I have fluid in my knees. Is that due to amyloidosis?

- If you have peripheral edema in your legs, it can (rarely) collect in knees

What is the best test for cardiac amyloid involvement?

- There is an invasive test that is riskier than most, but more conclusive than most. There are many types and variations of tests. You need to have a long discussion with your practitioner to decide which. The test needs to be adjusted to the question to be answered, your family history, your doctor's expertise, and more.

An echocardiogram is certainly one of the best first tests for screening.

An anteroseptal-MI finding without Hx of a heart attack, or thick walls with low voltage both should greatly increase the suspicion of amyloid

Can blood tests indicate heart involvement with amyloid?

- Blood tests can help in monitoring known heart involvement, but they don't currently know how they can be used to detect heart involvement.

Discuss beta blockers for wild-type TTR and cardiac amyloid

- In most heart conditions, beta-blockers are very good (toprol, coreg, corveta.., atenavol They slow down the heartbeat. But in amyloid, to compensate for small volume of blood per beat from a stiff, thick-walled heart, you need a faster heartbeat, so beta-blockers may not be helpful (except if you have tachycardia, arrhythmia, and autonomic neuropathy or in some other situations). Don't stop beta-blockers without talking to your doctor.
- When you exercise, heart rate usually increases. If you exert yourself, heart usually gets a bit bigger & beats faster, to move more blood. Beta blockers obstruct that, so can increase fatigue.

Discuss digoxin and other medications to slow the heart, relative to amyloid

- When amyloid patients go into atrial fibrillation (irregular heart beat), they do worse. So there can be some benefit from heart medications (like amioderone (cordarone, coreg)) that help you stay in rhythm.
- Digoxin (digitalis) slows heartbeat, especially for those in atrial fibrillation. So do other medications. Years ago, a study of sudden deaths among folks taking digoxin found that digoxin bound very tightly to amyloid particles. The thought is that, over time, the digoxin may have built up (having stuck around, being bound to the amyloid).
- Very sick amyloid patients may have atrial fibrillation, and may be given digoxin. But choosing the right heart medication is a tightrope – a "less of the evils" question. Digoxin may be used, but must be used carefully, usually at lower than normal doses, with careful monitoring.
- Digoxin can be very effective in folks with irregular heart beat and can be simply monitored by taking your pulse regularly.

Medication for the heart: talk more about medications cardiologists use for amyloid patients

- Cardizem, verapamil (calan), & other calcium channel blockers are NOT helpful for cardiac amyloid, except in very unusual situations.
- Ace inhibitors (blood pressure medicines, also for folk with weak hearts): lisinopril captopril, diovan, … If your MD thinks "heart failure", they may use these. But these **can be harmful** for amyloid patients.
- It is important to make the cardiac amyloid diagnosis early, so cardiologists know what not to use.
- Low blood pressure (from amyloid) aggravated by medications that lower your blood pressure can lead to fainting, falling, banging heads when you fall, etc. Be very wary of these medications.
- There is variation. In the end, it is a matter of finding what medications work for each specific patient.

Dr. Kelly: People are working hard to increase clearance of amyloid.

Do TTR levels fall after the age of 60? Does buildup occur at age 40, and then just manifest later in life?

Dr. Kelly: We don't know. We are trying to understand when the accumulation starts.

Does TTR level fall due to being sick?

Dr. Skinner: Yes. Infections & malnutrition do drive down TTR levels.

We understand why trials exclude liver transplant recipients. Is it time for trials specifically on folks with liver transplant?

Folks with liver transplants are very complicated. It is overly ambitious now, before treatments are defined in less complicated patients.

Off label prescribing: Would you advise a patient regarding off-label use of tafamidis for amyloid?

Doctors do prescribe available medication for uses that the FDA has not approved them for.
The insurance company may not pay for uses not approved by the FDA.
Consider impact on livers. If your liver fails, you are in trouble.
The new, rare disease medications will all cost about the same, and probably about $100,000 per year. Let the insurance and drug companies argue about that. Let's figure out which is most effective.
But it is challenging for physicians to decide how to use a medication when that use has not been carefully studied.
Safety is a complicating factor, especially regarding drug interactions with these patients who are commonly on so many different medications already.

What is being done to prevent peripheral neuropathy deterioration is post-transplant patients?

You can't go back once you have a transplant. You can't undo the transplant. We do not know of post-transplant medications for neuropathy.
Liver transplants tend to come after neuropathy is already present. Then you rest for a long time, which may be increasing neuropathy. There may not be increase of neuropathy after transplant, or it may be wild type TTR accumulation.
You can accelerate the production of pearls by putting a grain of sand in the oyster. There may already be "grains of sand" (abnormal TTR deposits) in your body before the transplant, which may continue to accumulate wild type (normal) TTR from the new liver.
Amyloid patients with low modified BMI do worse after liver transplants than do patients who are better off nutritionally. (albumin = "egg white protein" – the most common protein in the body).

If I have a type other than TTR, will diflunisal hurt me?

There is no reason to believe that diflunisal will help any amyloid besides the TTR amyloid diseases.

What's unique about ILE122?

This should be the most common variant in the US, being in about 4% of African Americans. But is clinically under-recognized. It has a particular, cardiac manifestation. Several drug companies are showing interest in developing treatments for this.

Atrial flutter, pros & cons of ablation

Flutter and fibrillation are different
Ablation success of non-amyloid patients is 80% or more. Usually reserved for patients who fail usual therapy (anticoagulant & rate control).

Ablation is rhythm control.
MD should talk to patient about symptoms and impact of symptoms. Frequent, severe symptoms weigh toward an ablation.
Flutter is more amenable than fibrillation to ablation treatment. But both often come together.

Heart Biopsy – it sounds scary. Is it a big deal?

2 patients who have had about 10 each: It takes ½ day. The only pain is when they numb the spot they go through. It is not that big a deal.

Erectile dysfunction

Erectile dysfunction is a common autonomic manifestation of amyloid. It is often mis-attributed to aging, rather than neuropathy. Viagra & similar medications do work for erectile dysfunction from amyloid.
In Amyloid, you have fewer nerves triggering the release of the nitrous oxide that triggers the erection. Viagra and the like slow the break-down of that nitrous oxide. The same mechanism happens in women, but there is much debate about Viagra for women.

Foot care

Foot care is very important in amyloid with peripheral neuropathy. Look at your feet each night. Take care of any breaks in the skin promptly. Prevention is much easier that cure, when you have poor blood-flow and poor sensation. Have a podiatrist trim your toenails.

Don't most senile cardiac amyloid patients have atrial fibrilation?

About 35% have atrial fibrillation.
The 1st principle of treatment is rate control, if required, and anti-coagulation (because clots and consequent stroke risk is notably elevated).
There is a cardiac tightrope with heart rate (not too fast, not too slow) and with fluid (not too much, not too little).

Is it possible to have 2 types of amyloidosis at once?

It is possible, but is very rare.

Will the slides be available? When and where?

Notes will be emailed to everyone very soon, and posted on the websites. As soon as Muriel gets presentations, she will let us know.

Do you need a drug with cardioversion?

Do you need ameodarone with cardioversion
Afibrillation begets afibrillation: the chance of recurrence is probably about 50% in the general population, and maybe greater in amyloid patients. But the treatment requires a lot of thought and discussion with your MD.

If I want to be in a doxycycline trial, what should I do?

The diflunisal trial is closed, but the doxycycline trial is open. Call Boston Medical Center's Amyloidosis Center, and talk to the trial coordinator.

If I am taking a blood thinner and doxycycline, is there some concern?

Dr. Skinner: I know of no contra-indication between these medications

Is the cause of amyloidosis the amyloid protein?

We don't know for sure what causes amyloidosis. There is evidence that the protein may be an effect, rather than the cause, and that some symptoms may be caused by something other than the protein.
The benefits of drugs that clear amyloid occur very quickly – that is, the amyloid protein is cleared. But the symptoms do not.
Not clear that having the gene causes the disease. A much better predictor,
once you have a family member identified with the disease.

What causes autonomic sufficiency? Does Celexa work for it? Does Florinef? How about sodium levels in diet?

Dr. Wang: I don't know Celexa well. A lot of what I do is trying to increase blood pressure, to increase safety and avoid orthostasis. Most of it is not with medication, but with the proper walking aids, walkers with chairs, having enough salt in diet, caffeine & ice cold water with meals (or other times), compression stockings …
Blood pressure can fall after meals, as blood goes to the digestive tract. Caffeine with meals can help – but be careful standing up after a meal.
Dr. Benson: Florinef helps you retain sodium. Diuretics can lead to you pee-ing out all of your sodium. I've prescribed florinef to help assure the body retains enough salt, and keep blood pressure up. But it is that fluid-tightrope issue – so monitor frequently, and keep in contact with your doctor.
Excessive salt and fluid restriction may be harmful even in usual heart patients, and should be viewed with skepticism in cardiac amyloid patients.
The kidneys, working well, do a lot to regulate sodium levels.

Sweating

You sweat every day, to control body temperature. You need your autonomic nervous system to sweat. As your feet and extremities lose their ability to sweat, you will sweat more from your face and core, to control your body temperature.

What medications help with tingling and pain from peripheral neuropathy?

I don't use cymbalta for neuropathy tingling and pain. Warm water foot massage machines can relieve it long enough to allow you to sleep.
I have not found effective medications. Ketamine (a cream produced by a compounding pharmacy) is available, but require frequent application. Some folk have had success with acupuncture, or spraying solarcaine on their feet to numb them long enough to fall asleep.
Patient: Getting good shoes and arch supports helped me a lot.

I am 40. Can I get into a clinical trial?

First, confirm that your symptoms are due to amyloid. Then see if you qualify.

I have numbness in feet and ankles, but only intermittent numbness in the soles of my feet (and can sense temperature?). Is that not amyloid, since the numbness is not progressing in the right order?

Dr. Benson: We doctors describe the median or average case. But there is a lot of variation.

Why am I told to avoid salads when I'm on warfarin?

If you get a lot of vitamin K, your INR can increase such that blood clots are more likely. The trick is more to have a constant intake, rather than no intake.

Likely suspect for causing amyloid is … [I MISSED THIS ENTIRELY] Kelly

When is the next international amyloid conference (in Indianapolis)?

See http://www.amyloidosis.nl/indpls/indpls_index.html (Google "Amyloidosis ISA", click on symposium, then Indianapolis). It starts April 27 2014, and ends May 1. There may be a patient meeting on the afternoon of May 1.
Rooms are $150 to $200 in the main hotel (JW Marriott). There are many other hotels in the area.

I'm a liver transplant recipient. Is it likely that my sibling's symptoms will differ much from mine?

Within a family, the disease presentation and course strongly tends to be very similar between everyone. There are examples of when this is not the case.

How do we educate doctors about amyloid?

These are rare diseases. We publish papers and present at meetings. But patient advocacy is very important.
Matt: I suggest that patients who have experienced delayed diagnoses of amyloid, write up their experience, and send it to the doctor(s) who missed the diagnosis.
Get your name into the media – get your story into local papers, get some TV show to use your story for an episode.
… (the Afr Am type) is somewhat common, but the rest of the amyloidosis types are rare.

I have Lucine 58. What trial should I try to get into?

(Dr. Benson reviewed the history of its discovery.)

I think I am in the placebo arm of a clinical trial. What should I do?

The placebo arm is essential to finding out if a drug is effective. If you stay in the trial, when it ends, you usually will get the medication at no cost. So it is important and beneficial to stay in the trial.

Some studies showed that green tea reduced amyloid in the heart. What is the current understanding of this?

Zeldenrust: The reports are not conclusive. Green tea is probably good for you in moderation, but I would not recommend drinking gallons per day, due to basic fluid management issues.

I have an enlarged tongue. …

Enlarged tongue is very rare in TTR amyloid. It is likely not to be due to amyloid.

Is Congo Red sufficient to confirm that I have amyloid, or do I need to get it typed?
If you already know the type that runs in your family, then just confirming the presence of the protein is sufficient for treatment and management decisions. Clinical trials may require that the type is known; they may be limited to certain types.

How to manage colon incontinence

Amyloid alters peristalsis, so the flow through the GI tract is altered. There are meds that slow the flow of the GI tract (Imodium,). Timing your meals and managing their content can help, for some folk. A final solution is colostomy, which can greatly improve quality of life for patients with no colon control.
Bladder incontinence: harder to manage. There are spasm control meds, …, or even catheters.

TTR ocular vitrious amyloid with glaucoma – please discuss current treatment

Dr. Benson: Find someone with experience with this, including to get a victrectomy, if that is the plan. A problem: the amyloid can be around the muscle and nerves of the eye, so make sure that you get checked frequently for glaucoma afterward (any ophthalmologist can do that); don't just wait for the usual 'a year.' Make sure you get frequent evaluations.

Might the new drugs help with TTR ocular vitreous amyloid?

Dr. Benson: No. These meds won't get into the eye & brain, where these problematic amyloids are produced.

Is there a link between TTR amyloidosis and spinal stenosis, and any treatments?

Amyloid goes everywhere, and so can go into the spinal column. Amyloid in the blood vessels supplying the nerves may be causing the problems. The symptom may be getting very weak in the legs after walking a short distance.
Treatments: surgeries probably will not help much, unless it is a big, laminectomy for confirmed stenosis (vs. a nerve problem that looks like stenosis).

Final comments

Dr. Kelly: It is extraordinary that we have several drugs racing toward development, before there is even a medication for Alzheimer's. That is due to you advocates.
Dr. Benson: Get in the trials, and keep the medication development moving.
Dr. Grogan: Think about planning for the future. Plan in advance to get an autopsy. That provides important information. Increase awareness.
Dr. Maurer: it is an exciting time of developing solutions. Participate in the clinical trials.
Zeldenrust: It is exciting to be working with this group of patients and advocates. In HIV, tremendous progress came very quickly when the advocates got active. In 20 years, I expect us to look at amyloid like that – a curable condition.
Dispenzieri: It is an exciting time, and you are a key part of that.
Gertz: The society has smaller gathering throughout the year. Find out about them through the website.
Muriel: We have a terrible disease, but the best doctors.