Solid organ transplant: *when & which variants do best? Trials – when?*

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Patient Workshop
October 28, 2017

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# Hereditary systemic amyloidoses

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<thead>
<tr>
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<th>Target Tissues</th>
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<td>PNS, ANS, heart, eye, leptomeninges, tenosynovium</td>
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<td>AApoAI</td>
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<td>Heart, liver, kidney, PNS, testis, larynx, skin</td>
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Strange truths about hereditary amyloidosis

• For most types, the source of the ‘disease driving’ building blocks (mutant proteins) is the liver,

• For most types, the disease driving organ (liver) doesn’t ‘appear’ sick
Transplant Approaches

1. Remove mutant protein producer
   • Liver transplant

2. Replace symptomatic organ
   • Possible for kidney or heart
   • Not possible for nerve or guts

3. Do both
ATTR Transplant Trivia

- First OLT for ATTR in 1990
- First domino liver transplant in 1995
- Partial liver transplants since 1995
- ATTR patients do not meet criteria for liver transplant since “normal” liver
• Male 57%
• Age at transplant: 38.2 (range 21-73)
• Duration of disease: 3 years (0-30 years)
Mutation in protein

Transthyretin protein (127 amino acids) stretched out

Normal

Abnormal (amyloid pathway)
Spectrum of genotype–phenotype correlations in transthyretin-related amyloidosis.

112 mutations causing disease (2013)

Claudio Rapezzi et al. Eur Heart J 2013;34:520-528
Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

1940 patients undergoing 2127 liver transplants

Survival post-OLT for Familial ATTR by mutation

10 year Survivorship Post-OLT focusing on most common variants

- Val30Met early onset 85%
- Val30Met late onset 45%
- Val71Ala (N) 85%
- Leu111Met (H) 83%
- Leu58His (H/N) 76%
- Thr60Ala (H/N) 36% if liver Tx only 58% if heart & liver

- Fewer than 50% alive: Ser50Arg, Ser77Phe, Ser77Tyr, Glu89, Gln, Tyr114Cys

Progression noted in heart, vitreous opacities, autonomic nervous system. Typically less cardiac deposition if heart transplant done same time.

Stabilization of symptoms better in Val30Met Patients than non-Val30Met Patients with Liver Transplantation

Improvement in Autonomic Function after Liver Transplant

Thirty-six Japanese transplanted FAP ATTR V30M patients (15 male and 21 female) were assessed.

Diarrhea and orthostatic hypotension could not be assessed due to large variation.

Val30Met Outcomes

• Neuropathy stable or improved in up to 40%
• Nutrition improves in up to 80%
• Cardiac progresses in ~50%
• Kidney involvement unaffected
• Eye deposits progress
Mutant ATTR fibrils Made of mutant TTR

Normal ATTR joining the party

Weeee!
Heart Transplantation for Hereditary ATTR

- Trend for a superior overall survival among those receiving heart and liver transplant versus those receiving liver transplant only
- Mayo Clinic data, and
- Similar finding in the FAPTR registry

Cardiac-Related Death in Liver Transplant Patients

• 212 patients underwent LTx alone
  • 119 (56%) patients died.
  • 45 (38%) of the deaths were heart related

• 52 had combined LTx/HTx
  • 20 (38%) patients died
  • 3 (15%) of the deaths were heart related

What Does It All Mean?

• Known:
  • Survival improved with liver transplant in V30M
  • Most effective if early
  • Major benefit is nutrition
  • Combined liver + heart and liver + kidney feasible
What Does It All Mean?

- Unknown:
  - When is it futile?
  - Which mutations benefit?
  - If heart involved need combined heart + liver?
  - Is amyloid halted, slowed, reversed or accelerated?
In a perfect word, there would be no liver transplant…

• …Safe, effective, affordable drugs would help take care of the problem
Number of ATTR Clinical Trials Registered on Clinicaltrials.gov

- Recruiting
- Not yet recruiting
- Active, not recruiting
- Completed

Number of trials:
- All ATTR trials
- Therapeutic
Hereditary, systemic amyloidoses

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Made entirely in the liver
Fibrinogen A α

- Most common of hereditary renal amyloidoses (Ostertag 1932)
- First mutation described by Dr. Benson, 1993
- Middle age presentation
- If kidney replacement alone, graft fails in 1-7 years with 10-year graft survival of 5% (vs 65%)
First Report of Liver Transplant without Kidney Transplant for Fibrinogen A alpha chain Renal Amyloidosis

Figure 1. Time course of serum creatinine level in patient with liver transplantation without kidney transplantation.

Conclusions

• Liver (± heart) transplant still plays a role in ATTR ValMet30 patients
  • Other mutations, less certain
• Exciting that other means of reducing the ATTR may be on the horizon
• For AFIB, liver + kidney is best
• Early diagnosis, better data collection is imperative regardless