ARO-AAT: An Investigational Therapeutic for AATD Liver Disease

September 14, 2019
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**Alpha-1 Antitrypsin Deficiency**

- **Normal AAT**
  - Normal blood levels of normal protein protect lungs
  - Normal secretion into the blood

- **Abnormal AAT (Z-AAT)**
  - Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection
  - Abnormal secretion into the blood
  - High accumulation of misfolded Alpha-1 Antitrypsin protein leads to liver injury

**Treated with AAT protein replacement therapy today**

**No current treatment**
Underlying Fibrosis Found in Natural History Study

- 94 ZZ Patients underwent a Biopsy
- 33 (35%) had what was considered significant fibrosis

Clark et., *J. Hep.* 2018

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Z-AAT Globules</th>
<th>Z-AAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>None</td>
<td>No PAS-D</td>
</tr>
<tr>
<td>F1</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>Few</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>Numerous</td>
<td></td>
</tr>
</tbody>
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Abundant PAS-D
Abundant Fibrosis
Why is Liver Injury Problematic?

Liver Functions:

• Removal of toxins

• Produces bile needed for digesting food and absorbing vitamins

• Stores nutrients (e.g. fats, sugars) for use as energy

• Synthesis of proteins important for:
  ▪ Fighting infection
  ▪ Clotting of blood
RNAi-based therapeutics: What is RNAi?

RNAi = RNA interference

- RNAi silences gene expression so specific protein is not produced
- RNAi triggers can be designed and synthesized to target a specific protein
- Not gene therapy or gene editing which may actually modify the genome
ARO-AAT: Mechanism of Action

ARO-AAT designed to stop Z-AAT production by silencing AAT gene expression to:

- Prevent liver accumulation of Z-AAT
- Allow clearance of accumulated Z-AAT protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

Feldmann G et al., Gut 1975

PiZZ phenotype (diseased) → Pi null phenotype (normal liver)
ARO-AAT Reduces Z-AAT and Prevents Globule Accumulation in Young PiZ Mice

Subcutaneous Injection

Baseline (5 weeks old)                  Saline (13 weeks old)
Control siRNA (13 weeks old)           ARO-AAT (13 weeks old)
AROAAT1001 Clinical Study in Healthy Volunteers

• **Subcutaneous Injection**

• Single and Multiple (x3) doses studied in Healthy Volunteers
  
  • Multiple doses = **monthly**

• Dose levels 35, 100, 200, 300 mg

• Assessments of safety, tolerability, pharmacokinetics (drug blood levels) depth and duration of serum AAT reductions
  
  • All cohorts being followed until serum AAT returns to normal or within 20% of baseline

• **Dosing completed**

• 45 total subjects enrolled (including one replacement: 28 active, 16 placebo)
AROAAT1001 Serum AAT Dose-Response

Single dose ARO-AAT

- Placebo (n=17)
- 35 mg (n=4)
- 100 mg (n=4)
- 200 mg (n=4)
- 300 mg (n=4)

Supports quarterly or less frequent dosing
Single dose ARO-AAT

- Placebo (n=17, SEM)
- 100 mg ARO-AAT

AROAAT1001 Serum AAT Reduction Duration

Serum AAT g/L vs. Weeks

LLOQ
### AROAAT2001 SEQUOIA
- Phase 2/3 adaptive design study
- # of ZZ Patients planned=120
- **Location:** Multiple sites in **UK**, EU, US and Canada
- Duration: 2-year minimum treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- Placebo controlled
- At end of study, all placebo will have the option to receive active in an extension study
- Part A Objective: to select a dose level for Part B
- Part B Objective: To evaluate efficacy based on biopsy
- Status: Currently Enrolling

### AROAAT2002
- Phase 2 study
- # of ZZ patients planned=12
- **Location:** UK, Germany, Austria
  - Birmingham, Edinburgh, Cambridge
- Duration: 6 to 24 month treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- No Placebo
- Objective: To assess changes in liver disease activity scale based on biopsy
- Status: Expect to be recruiting by end of year (2019)
In Conclusion…….

• Liver Disease is the silent killer in AATD

• Thanks largely to the Alpha 1 Foundation and Physician/Research Community it is now coming out of the shadows

• ARO-AAT is a RNAi drug designed to halt liver production of AAT in the liver with infrequent, subcutaneous injection

• The SEQUOIA trial (AROAAT2001) is the first trial designed to potentially serve as a pivotal trial for approval

• For more information on ARO-AAT studies, please visit www.clinicaltrials.gov (enter key word: ARO-AAT) and/or speak to your physician