Alpha-1 Antitrypsin

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Conflict of Interest and Disclosures

- There are no companies working in Alpha-1 for whom I do not consult
- I will be discussing products in development for Alpha-1
## Burden Of COPD In The U.S.

<table>
<thead>
<tr>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15 million</td>
<td>With COPD</td>
</tr>
<tr>
<td>~15 million</td>
<td>Undetected</td>
</tr>
<tr>
<td>&gt;1.5 million</td>
<td>Emergency department visits</td>
</tr>
<tr>
<td>&gt;15 million</td>
<td>Physician office visits</td>
</tr>
<tr>
<td>~150 million</td>
<td>Days of disability</td>
</tr>
<tr>
<td>~$15 billion</td>
<td>Direct cost of medical care</td>
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Jim Kiley, MD, Director, Lung Division, NHLBI
Alpha-1 Antitrypsin (AAT)

- 52 kDa glycoprotein coded for by single gene on long arm of chromosome 14
- Synthesis predominantly in hepatocytes, but also expressed by many other cells
- Transported to blood where it bathes all tissues
- Prototype SERPIN
- Primary target: neutrophil elastase
- Acute phase reactant
- Anti-inflammatory
- At least 100 different mutations
  - 34 associated with deficiency or dysfunction
AAT Deficiency (Alpha-1)

- Genetic/Hereditary condition causing decreased levels of AAT in blood and tissues
- Usually estimated to be 100,000 people in the US and a similar number in Europe
- Over 20 million carriers of the Alpha-1 gene in the US
- Predisposes to lung, liver, other disease
- The frequency of the Z allele suggests a selective advantage
A Brief History of Alpha-1

- 1963 - Alpha₁-Antitrypsin Deficiency first described
- 1964 - Role of elastase
- 1967 - Discovery of neutrophil elastase
- 1969 - Neonatal cirrhosis
- 1970s - Cigarette smoke capable of destroying alpha₁-antitrypsin function
- 1980s - Plasma deficiency due to blockage of release alpha₁-antitrypsin from liver
- 1987 - Prolastin approved in US
- 2003 - Zemaira and Aralast in US
The “Good” M Phenotype
The Genome and Alpha-1

~ 14,000 base pairs

394 amino acids

Co-dominant allelic expression
Phenotype Pedigree

MZ       MZ

M        M

MM       MZ       MZ       ZZ
Not Rare?

- 100,000 with severe deficiency

About 5% diagnosed

> 95% undiagnosed
Not Rare?

- 100,000 with severe deficiency
- At least 150,000 with severe deficiency and COPD! (Perhaps as many as 300,000)

About 5% diagnosed
> 95% undiagnosed

15 Million Patients with COPD
~1% have undiagnosed Alpha-1
Disease Associated with Alpha-1

Liver

Childhood and adult liver disease
- Fulminant liver failure
- Cirrhosis

Lung

Lung disease – “AAT-COPD”
- Emphysema
- Bronchiectasis
### Disease Associated with Alpha-1

<table>
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<tr>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>- Necrotizing panniculitis</td>
</tr>
<tr>
<td>- Vasculitis (especially Wegener’s Granulomatosis)</td>
</tr>
<tr>
<td>- Hepatocellular carcinoma</td>
</tr>
<tr>
<td>- Susceptibility to atypical TB</td>
</tr>
<tr>
<td>? Susceptibility to chronic active hepatitis</td>
</tr>
<tr>
<td>? Pancreatitis</td>
</tr>
<tr>
<td>? Arterial aneurysm</td>
</tr>
</tbody>
</table>
Risk Factors

• For Lung Disease
  – Smoking
  – 2nd hand smoke
  – Occupational exposures
  – Lung infections

• For Liver Disease
  – Alcohol
  – Infection
    • Hepatitis
  – Liver toxic agents
Why the lungs?

- Major interface with outside world
- 300 million alveoli
- Surface area of an entire tennis court
- Designed to put the outside world in intimate contact with the circulation
- So what protects this delicate organ?
Lung Disease

Protease/Antiprotease Balance

ELASTASE
Burden

ANTIELASTASE
Protection

ELASTASE
Burden

ANTIELASTASE
Protection

NORMAL

ALPHA-1
What’s in a name?

- Alpha-1
- Antitrypsin
- Deficiency
Disease Mechanisms

- **Lung disease**
  - *Lack* of protease inhibitor
  - Pro-inflammatory state
- **Liver disease**
  - *Excess* of protease inhibitor
- **Polymerization of Alpha-1**
  - Decreases inhibitory activity
  - ?Pro-inflammatory
Of All Babies Born with Alpha-1

**PIZZ or PISZ Infants**

80% have elevated liver function tests

20% Cholestasis or Hepatomegaly

- 10-25% - Fibrosis
- 75-90% - No Fibrosis

25-50% Liver Transplant In Childhood

No Problems in Childhood

= 0.5 to 2.5 % of all patients
How Often Does Alpha-1 Liver Disease Occur?

- In adults:
  - Data based on small numbers
  - Many times Alpha-1 not diagnosed in adults with liver disease
  - Autopies of Alphas over 60 yo: 71% with cirrhosis
  - We don’t really know the number of Alpha-1 adults there are without any liver or lung disease
  - Hepatocellular carcinoma
American Thoracic Society Documents

American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency

This Joint Statement of the American Thoracic Society and the European Respiratory Society was approved by the ATS Board of Directors, December 2002, and by the ERS Executive Committee, February 2003

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Who should be tested?

- All individuals with COPD
- Asthma with incomplete reversibility on maximal therapy
- Bronchiectasis without other risk factors
- Siblings of AAT deficient individual
- Fam Hx of AAT deficiency or early onset COPD
- Cirrhosis without apparent risk factors
Making the Diagnosis

- Simple to diagnosis
  - Tube of blood
  - Finger stick
  - Buccal swab
  - Level
  - Phenotyping
  - Genotyping

- Alpha-1 is a laboratory diagnosis, not a clinical diagnosis

- Problems
  - Differences between the various testing methods difficult to appreciate

- ACT Study
Making the Diagnosis

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- ACT Study
Advantages of Early Diagnosis

- Careful follow-up of individuals without symptoms
- Lifestyle changes
  - Reduction of risk factors
    - Smoking
    - Liver toxins
    - Immunizations
  - Alpha-1 specific therapy
Alpha-1 COPD is Treatable!

Reduce Risk

- Smoking cessation
- Immunize
- Reduce other exposures

Reduce Symptoms

- Bronchodilators
- Inhaled steroids
- Pulmonary rehabilitation

Reduce Complications

- Treat exacerbations
- Supplemental oxygen

Reduce Lung Destruction

- Augmentation therapy

Education

= therapies shown to improve survival

Augmentation Therapy for Alpha-1

- **1980s** NIH evaluated purified AAT administration
  - Attempt to interest plasma company
  - Re-attempt
- **1987** Prolastin (Cutter => Miles => Bayer => Talecris)
- **1990s** Shortages
- **1999** Direct to consumer allocation
  - Bayer Direct => Talecris Direct => Prolastin Direct
- **2003** Aralast (Alpha Therapeutics => Baxter/Grifols => Baxter)
- **2004** Zemaira (Armor => Cention => Aventis Behring => ZLB Behring => CSL Behring)
Meta-analysis of Studies in Augmentation Therapy for AATD

• 5 studies with a total of 1509 patients
  – 4 nonrandomized trials
  – 1 randomized trial

• Results
  – $\text{FEV}_1$ decline was slower by 23% in patients receiving augmentation therapy
  – Effect predominantly reflected results in patients with baseline $\text{FEV}_1$ 30%-65% of predicted

Augmentation therapy slowed the decline in $\text{FEV}_1$ by 13.4 mL/y among all patients

Summary

- Alpha-1 antitrypsin deficiency (Alpha-1):
  - The most common genetic cause of COPD
  - Accounts for about 1% of all COPD, although most remain undiagnosed
  - Specific plasma-derived therapy is available that improves survival and quality of life
  - The diagnosis of Alpha-1 is a laboratory diagnosis, not a clinical diagnosis
  - All patients with COPD should be tested for Alpha-1
  - Don’t forget the liver