α1-antitrypsin deficiency is a genetic disorder that predisposes to chronic obstructive pulmonary disease (COPD) and chronic liver disease. In this Seminar, we address the history of the deficiency and review its epidemiology and detection, pathophysiology, and genetics. We then discuss the clinical manifestations and diagnostic strategies, natural history, and treatment of this important disorder.

History

The first description of α1-antitrypsin deficiency by Laurell and Eriksson in 1963 affirms Pasteur’s declaration in 1854 that “Chance favours the prepared mind”.

In reviewing all the serum protein electrophoresis gels submitted to his laboratory over a 6-month period, Laurell noted the absence of the α1 protein in five of about 1500 gels.1 Eriksson’s further investigation showed that three of the five patients had emphysema at age 35, 38, and 44 years and that one had a family history of emphysema, thereby establishing the main clinical features of α1-antitrypsin deficiency: absence of a protein in the α1 region, emphysema with onset early in life, and a genetic predisposition.1

Since this landmark description fewer than 50 years ago, much has been learned about α1-antitrypsin and its deficiency, including: the full structure of the protein; the mechanism of its binding to its major substrate, neutrophil elastase; the mechanism of its intrahepatic accumulation; and the main clinical manifestations and natural history of the deficiency. At the same time, major gaps in understanding persist, including the precise mechanism of liver disease, clarification of determinants of emphysema beyond cigarette smoking and occupational risk, and the role of genetic modifiers of disease expression.

Epidemiology and detection

Two major features summarise the epidemiology of α1-antitrypsin deficiency: (1) it is a common disorder; and (2) it is under-recognised by clinicians, which causes important adverse effects. Estimates of the frequency of α1-antitrypsin deficiency have been developed by two methods: indirect epidemiological approaches; and direct population-based screening.

The frequency of α1-antitrypsin deficiency in the USA can be indirectly assessed with data from the National Health Information Survey,4 which estimated that 3·1 million Americans have emphysema. Results of a study, in which 965 consecutive patients with COPD were tested for α1-antitrypsin deficiency, showed that 1·9% had the disorder because of severe deficiency of α1 antitrypsin. Applying this prevalence estimate to the estimated number of Americans with emphysema suggests that about 59 000 have symptomatic COPD due to severe α1-antitrypsin deficiency.

Another indirect approach uses findings of genetic epidemiological surveys. The most frequent mutation that causes severe α1-antitrypsin deficiency arises in the SERPINA1 gene (formerly known as PI) and gives rise to the ZZ allele (see section on Genetics). The approach estimates the mean frequency of the ZZ allele in a given population; this value is then extrapolated to the total population at risk. For the USA, this approach estimates that 59 047 individuals have the ZZ phenotype.5 By review of 373 cohorts with α1-antitrypsin deficiency in 58 countries, de Serres has estimated that there are 3·4 million individuals worldwide with the ZZ, SZ, or SS phenotype.6 On the basis of results of the Alpha-1 International Registry, Lusisetti and Seersholm estimate...
Table 1: Characteristics of selected SERPINA1 alleles

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>Cellular defect</th>
<th>Disease association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M (variant)</td>
<td>Substitution (1 bp)</td>
<td>None</td>
</tr>
<tr>
<td>X (variants)</td>
<td>Glu363lys</td>
<td>None</td>
</tr>
<tr>
<td>Deficiency alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z*</td>
<td>Glu264Val</td>
<td>Intracellular degradation</td>
</tr>
<tr>
<td>Z*</td>
<td>Glu342Lys</td>
<td>Defective inhibition of neutrophil elastase</td>
</tr>
<tr>
<td>Mmineral springs*</td>
<td>Gly67Glu</td>
<td>Defective inhibition of neutrophil elastase</td>
</tr>
<tr>
<td>F</td>
<td>Arg223Cys</td>
<td>Defective neutrophil elastase inhibition</td>
</tr>
<tr>
<td>QOisola di procida</td>
<td>17 kb deletion in exons 2–5</td>
<td>Deletion of coding regions; no mRNA</td>
</tr>
<tr>
<td>Null alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QO1-antitrypsin</td>
<td>Tyr160X</td>
<td>No mRNA</td>
</tr>
<tr>
<td>QO1-antitrypsin</td>
<td>Ile92Asn</td>
<td>No protein</td>
</tr>
<tr>
<td>QO1-antitrypsin</td>
<td>Leu41Pro</td>
<td>Intracellular accumulation</td>
</tr>
<tr>
<td>QO1-antitrypsin</td>
<td>Gly67Glu</td>
<td>Intracellular degradation</td>
</tr>
<tr>
<td>Dysfunctional alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Arg223Cys</td>
<td>Defective neutrophil elastase inhibition</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>Met355Arg</td>
<td>Antithrombin 3 activity</td>
</tr>
<tr>
<td>M (variants)</td>
<td>Gly67Glu</td>
<td>Defective inhibition of neutrophil elastase</td>
</tr>
<tr>
<td>Z*</td>
<td>Glu342Lys</td>
<td>Defective inhibition of neutrophil elastase</td>
</tr>
</tbody>
</table>

*Defunctional characteristics described are based on altered rates of association and inhibition of neutrophil elastase, and deficiency characteristics. Adapted from reference 20 with permission of the BMJ Publishing Group.
Seminar

80–220 mg/dL by nephelometry). Typically, deficient alleles lead to α1 antitrypsin concentrations less than 20 μmol/L and, for some variants (eg, Z), decreased functional activity of α1 antitrypsin. Of the deficient variants, the mutation in the Z allele—characterised by one aminoacid substitution of lysine for glutamic acid at position 342—is the most common, accounting for about 95% of cases of clinically recognised α1-antitrypsin deficiency. Null variants are characterised by absence of circulating α1 antitrypsin because of transcriptional or translational errors that interrupt synthesis. Finally, dysfunctional variants lead to abnormal function of α1 antitrypsin—eg, with reduced binding to neutrophil elastase (as in the F variant) or, as with Pittsburgh, structural abnormality that causes the protein to serve as a thrombin inhibitor rather than as an antielastolytic protein, causing a bleeding diathesis (figure 1).21

In the context of this classification scheme, testing for α1-antitrypsin deficiency usually begins by establishing the concentration in serum of the protein—eg, by nephelometry, rocket immunoelectrophoresis, or radial immunodiffusion. When concentrations are low (<1000 mg per L, or when pedigree analysis is needed to clarify familial patterns, phenotyping by isolectric focusing is usually used. Molecular diagnostic testing is also available, for which genomic DNA is extracted from circulating mononuclear cells or from mouth swabs and analysed either directly or by allele-specific amplification. Commercial test kits permit detection of S and Z alleles but will not detect null or other rare deficient variants.

Pathophysiology

α1 antitrypsin is the prototypic member of the serine protease inhibitor (serpin) superfamily of proteins, which have a major role in inactivating neutrophil elastase and other proteases to maintain protease-antiprotease balance.22 Conformational instability of the β-sheet structure of the serpins underlies their susceptibility to mutations and polymerisation.23 In the case of ZZ α1-antitrypsin deficiency, retention of polymerised aggregates of α1 antitrypsin in hepatocytes (due to a process called loop-sheet polymerisation, discussed below) might lead to liver cirrhosis. Also, loss of the natural antiprotease screen predisposes to emphysema and, as discussed below, loss of the anti-inflammatory effects of α1 antitrypsin probably has a major role in the pathogenesis of emphysema.

Normal function of α1 antitrypsin

α1 antitrypsin is produced in the liver and reaches the lungs by diffusion from the circulation and by local production in macrophages and bronchial epithelial cells.22,24 Despite its name, α1 antitrypsin reacts with neutrophil elastase much more readily than with trypsin25 and represents a major defence against the elastolytic burden in the lower airways posed by neutrophil elastase, which is produced by neutrophils in the lower respiratory tract.26 Other neutrophil and macrophage-derived elastolytic enzymes have been implicated in the pathogenesis of emphysema—eg, matrix metalloproteinases 9 and 12.26,27

Serpins have been likened to mousetraps complete with bait, a loaded high-energy but unstable state, and a swinging arm. In the case of α1 antitrypsin (figure 1), the bait is a methionine aminoacid side-chain in the

Figure 1: Mechanism of inhibition of proteases by α1 antitrypsin and of polymerisation in serpinopathies

(A) (Upper) Docking of the protease to the reactive centre loop of α1 antitrypsin. (Lower) The protease has cleaved the reactive centre loop, releasing it from its metastable high energy state. The reactive loop swings with the protease in tow into a more stable conformation within the main β-sheet. The process distorts and alters the structure of the protease. (B) Mutations of serpins can result in several diseases. In the case of α1-antitrypsin deficiency caused by a Z mutation, a substitution of lysine for glutamic acid at position 342 widens the β-sheet A. The gap in the β-sheet A can either accept its own loop to form a latent conformation or proceed to polymerisation in an irreversible process. Adapted from: Carrell RW, Lomas DA. Alpha 1-antitrypsin deficiency: a model for conformational diseases. N Engl J Med 2002; 346: 45–53. With permission of Massachusetts Medical Society.

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reactive centre of the serpin. Docking of the neutrophil elastase on that residue cleaves the reactive centre, releases α1 antitrypsin from its metastable high energy state, and allows the cleaved reactive loop to snap back, with the protease in tow, to the other pole of the molecule. Because that arm remains fairly short, it distorts and inactivates the elastase molecule by squeezing it on the other end of the α1 antitrypsin molecule. While this process is mutually suicidal and ensures the destruction of both molecules, there is normally an excess of α1 antitrypsin in the lung, thereby providing an adequate protective screen against the elastolytic burden of neutrophil elastase.

**Loop-sheet polymerisation**
A substitution of lysine for glutamic acid at position 342 in the Z protein widens β-sheet A and allows polymerisation, serially linking the reactive loop of one α1-antitrypsin molecule to the β-sheet A of another molecule in an irreversible process (figure 1). Although this mutation might allow spontaneous polymerisation of α1 antitrypsin, factors that encourage polymerisation include an increase in temperature and in the concentration of Z-mutated α1 antitrypsin, and a decrease in pH to less than 6 or an increase in pH above 8. Since polymerisation within the hepatocyte prevents its secretion, only about 15% of Z-mutated antitrypsin is secreted into the plasma.

**Mechanism of emphysema**
Polymerisation, and retention of polymers in the endoplasmic reticulum of liver cells, causes a decrease in the amount of plasma α1 antitrypsin that is available to protect the lung against elastolytic damage. The protease-antiprotease idea posits an imbalance between the α1-antitrypsin protective screen and the neutrophil elastase burden, with consequent unchecked proteolytic activity leading to emphysema. Either a relative increase in elastase burden (which might happen with cigarette smoking or lung infection) or a reduction in antielastase balance unfavourably towards accelerated lung breakdown.

Compounding the quantitative deficiency in individuals with the ZZ phenotype, the antitrypsin molecule with the Z mutation is about five times less effective than normal antitrypsin as an inhibitor of neutrophil elastase. Also, Z-type antitrypsin polymers have been identified in the lung and can be chemoattractants for human neutrophils, thereby potentially increasing inflammation in the lung.

**Anti-inflammatory properties of α1 antitrypsin**
In addition to its role as an antiprotease, α1 antitrypsin has important anti-inflammatory properties. These effects are unrelated to protease inhibition and include blocking the proinflammatory effects of human neutrophil peptide and regulating expression of proinflammatory cytokines such as tumour necrosis factor α, interleukin 6, interleukin 8, monocyte chemoattractant protein 1, and interleukin 1 β.

**Mechanism of liver disease**
Polymers of Z-mutated α1 antitrypsin have been identified by electronmicroscopy as diastase-resistant inclusions within the endoplasmic reticulum of hepatocytes and they are positive for periodic acid-Schiff stain. Intracellular liver inclusions have also been seen with other α1-antitrypsin deficiency phenotypes characterised by polymer formation, including Sα and Mα. Retention of the polymers in the endoplasmic reticulum might be due to an impaired interaction between Z-type protein and its molecular chaperone, calnexin. Also, studies of α1-antitrypsin deficiency caused by the Z mutation have elucidated mechanisms by which misfolded glycoproteins are normally degraded. Emerging understanding suggests that the process of endoplasmic reticulum-associated glycoprotein degradation involves modification of misfolded proteins by the enzyme endoplasmic reticulum mannosidase I, which generates a signal that prompts glycoprotein degradation. Mannosidase inhibitors delay degradation and increase secretion of Z-mutated antitrypsin.

There is striking variability in the phenotypic expression of disease in individuals with the ZZ phenotype, with most escaping liver impairment. Expression of liver disease in these people correlates with a lag in intracellular degradation of Z-type protein.

**Clinical manifestations and diagnosis**
α1-antitrypsin deficiency can predispose to lung disease (eg, emphysema and bronchiectasis), liver disorders (eg, chronic hepatitis, cirrhosis, and hepatoma), skin disease (ie, panniculitis), and vasculitis (especially anticytoplasmic antibody-positive vasculitis such as Wegener’s granulomatosis). Other disease associations have been suggested but are less well established—eg, glomerulonephritis, coeliac disease, lung, colorectal, and bladder cancers, intracranial and intra-abdominal aneurysms, fibromuscular dysplasia, and pancreatitis.

**Lung disease**
With respect to emphysema associated with α1-antitrypsin deficiency, distinctive and suggestive features can include early onset (ie, in the fourth and fifth decades), panacinar pathology, and disproportionate emphysematous involvement of the lung bases (compared with the more apical distribution seen in usual, α1 antitrypsin-replete COPD; figures 2 and 3). As an example of the early onset of COPD, the mean forced expiratory volume in 1 s (FEV1) among 1129 participants in the National Heart, Lung, and
Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of α1 Antitrypsin was 43% predicted, in a population whose mean age was 46 years (SD 10). At the same time, such classic manifestations might characterise a few individuals with severe α1-antitrypsin deficiency-associated COPD, many of whom resemble patients with usual, α1-antitrypsin-replete COPD. For example, symptoms of the 1129 participants in the NHLBI Registry included dyspnoea (84%), usual cough (42%), usual phlegm (46%), and wheezing with upper respiratory infections (76%). In a series of 165 plain chest radiographs of individuals with Z-mutated α1-antitrypsin deficiency, Gishen and colleagues reported that 15% of the films were normal and that only 20% showed the distinctive pattern of emphysema changes confined to the lung bases. Also, among 102 individuals with the ZZ phenotype with evidence of emphysema on CT, Parr and coworkers reported that 64% showed basal predominance of emphysema and that 36% had predominantly apical emphysema.

As in most patients with COPD, partial reversibility of airflow obstruction (eg, as indicated by a 12% and 200 mL rise in the FEV₁, in forced vital capacity post-bronchodilator, or a similar rise) is common in individuals with α1-antitrypsin deficiency; for example, partial reversibility was evident in about 61% of NHLBI registry participants tested with up to three serial spirometries. In keeping with this frequency of partial reversibility of airflow obstruction, 35% of the NHLBI registry participants reported having asthma.

Evidence for the association of bronchiectasis with α1-antitrypsin deficiency is mixed; Larsson originally noted bronchiectasis in 11.3% of 246 individuals with the ZZ phenotype. The NHLBI registry reported bronchiectasis in only 2% of 1129 participants, and, in a case-control study, Cuvelier and colleagues recorded no excess frequency of α1-antitrypsin deficiency in patients with bronchiectasis compared with those without bronchiectasis. In the context of these mixed findings, current recommendations are to check for α1-antitrypsin deficiency when the cause of bronchiectasis remains
null-null: 0% 0% 100%
ZZ: 0·02 2·5–7 20–45 80–100%
SZ: 0·1 8–16 75–120 20–50%
SS: 0·1 15–33 100–200
MZ: 2·7 17–33 90–210 Background
MS: 6·1 18–52 110–340 (approx) Background
MM: 91 20–53 150–350 Background

Table 2: Clinical and serum concentrations of α1 antitrypsin phenotypes

Prevalence (%)† Concentrations in serum of α1 antitrypsin* Risk of emphysema
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Prevalence (%)</th>
<th>True level (mmol/L)</th>
<th>Commercial standard (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>91</td>
<td>20–53</td>
<td>150–350 Background</td>
</tr>
<tr>
<td>MS</td>
<td>6·1</td>
<td>18–52</td>
<td>110–340 (approx) Background</td>
</tr>
<tr>
<td>MZ</td>
<td>2·7</td>
<td>17–33</td>
<td>90–210 Background</td>
</tr>
<tr>
<td>SS</td>
<td>0·1</td>
<td>15–33</td>
<td>100–200 Background</td>
</tr>
<tr>
<td>SZ</td>
<td>0·1</td>
<td>8–16</td>
<td>75–120 20–50%</td>
</tr>
<tr>
<td>ZZ</td>
<td>0·02</td>
<td>2·5–7</td>
<td>20–45 80–100%</td>
</tr>
<tr>
<td>Null-null</td>
<td></td>
<td>0</td>
<td>0 100%</td>
</tr>
</tbody>
</table>

*From references 69 and 70. †From reference 6: represents weighed estimates from Australia, New Zealand, and North America.

α1-antitrypsin deficiency in Malmo, Sweden, Eriksson observed cirrhosis in 34% (n=14), in whom cirrhosis was suspected during life in 64% (9). Hepatocellular carcinoma was reported in 34% of those with cirrhosis.

The strong association between the ZZ phenotype and liver disease has prompted the recommendation in an international standards document that testing for α1-antitrypsin deficiency should be done in all individuals “with unexplained liver disease, including neonates, children, and adults, especially the elderly.”

Panniculitis

First described by Warter and colleagues in 1972, the association of panniculitis with α1-antitrypsin deficiency has been judged firm on the basis of more than 40 reported cases. However, panniculitis occurs infrequently, with an estimated prevalence of about 1 in 1000 individuals with α1-antitrypsin deficiency.

The panniculitis is characterised by painful, weepy cutaneous nodules at the site of trauma in a third of patients, and might accompany several phenotypes, including ZZ, SZ, SS, and in one report, an individual with the MS phenotype with normal plasma concentrations of α1 antitrypsin. Diagnosis sometimes requires deep excisional biopsy, which shows areas of fat necrosis interspersed with normal-appearing areas. That the cause of panniculitis is unopposed proteolysis is suggested by the pronounced response to intravenous augmentation therapy, which can produce rapid resolution of skin inflammation and pain.

Vasculitis

Over-representation of abnormal α1-antitrypsin phenotypes in people with antiproteinase 3 antibody-positive (ie, c-ANCA-positive) vasculitis in many series has established a relation between α1-antitrypsin deficiency and vasculitis. Specifically, in six series, the prevalence of the Z allele among c-ANCA-positive individuals was 5–6–17–6%, which exceeds by threefold to ninefold the prevalence in healthy people. Although the pathophysiological relation between α1-antitrypsin deficiency and vasculitis remains poorly understood, three potential mechanisms have been proposed. First, because proteinase 3 is a major substrate for α1 antitrypsin, its deficiency might enhance development of autoimmunity to proteinase 3. Second, linkage disequilibrium might promote inheritance of important autoimmunity genes along with abnormal α1-antitrypsin phenotypes. Finally, the polymerisation of Z might prompt autoimmune vasculitic responses. Overall, the strength of the association between c-ANCA-positive vasculitis and α1-antitrypsin deficiency has led to the recommendation that testing for α1 antitrypsin should be undertaken in all adults with c-ANCA-positive vasculitis.

As a practical matter, diagnostic testing for severe α1-antitrypsin deficiency in a symptomatic individual unknown after consideration of the usual causes—eg, cystic fibrosis, hypogammaglobulinaemia, ciliary dysfunction, etc.

As shown in table 2, abnormal phenotypes of α1 antitrypsin are associated with subnormal concentrations in serum of α1 antitrypsin. Normal amounts in blood are 20–53 μmol/L, using a highly purified standard, or about 150–350 mg/dL with commercial standards (depending on the assay technique). Based on the observation that a subset of individuals with the SZ phenotype—ie, those whose serum concentrations fall below 11 μmol/L (table 2)—are at increased risk of emphysema, but that those with amounts exceeding 11 μmol/L are not deemed at increased risk of developing emphysema, the idea of a protective threshold value has emerged. Concentrations in serum of α1 antitrypsin below the protective threshold of 11 μmol/L using a highly purified standard (or, using commercial standards, 80 mg/dL by radial immunodiffusion and 50 mg/dL with nephelometry) are associated with an increasing risk of emphysema.
usually involves first measuring the concentration of α1 antitrypsin in serum, with qualitative testing to assess the genotype if the serum amount suggests values below the protective threshold (eg, <100 mg/dL). Qualitative testing for specific alleles is needed for pedigree analysis in families and for characterising an individual’s specific phenotype.

Natural history of emphysema in α1-antitrypsin deficiency

Although the precise risk of developing emphysema in individuals with severe deficiency of α1 antitrypsin (eg, ZZ) is incompletely understood, and it is clear that some people with the ZZ phenotype can escape developing the disorder, findings of several studies suggest that the likelihood of developing emphysema is high. For example, to lessen selection bias based on attending a chest clinic, Tobin and colleagues assessed the risk of developing emphysema in ZZ siblings of index cases. They reported radiographically confirmed emphysema in 90% of smokers compared with 65% of non-smokers. These data closely agree with those of the Swedish registry, in which only 29% of participants were identified because of lung disease, indicating that in adults homozygous for the Z allele, 29% of never smokers and 10% of ever smokers were healthy, with most having lung disease. Finally, findings of post-mortem series from Sweden and CT studies suggest that only 14–20% of ZZ homozygotes were free of COPD.

As table 3 shows, estimates of the annual rate of decline of FEV1 in Z homozygotes varies from 41 to 109 mL. Important predictors of increasing rate of decline include smoking status (ie, current vs ever vs never), male sex, age 30–44 years, FEV1 35–79% of predicted value, decreased serum α1-antitrypsin concentration, and bronchodilator response.

The most common cause of death in patients with α1-antitrypsin deficiency is respiratory failure (accounting for 50–72% of deaths) followed by liver cirrhosis (10–13%); the observed overall yearly mortality rate ranges from 1·7% to 3·5%. Findings of the US NHLBI registry show that factors associated with increased mortality include older age, lower education, lower FEV1, predicted, lung transplant, and not receiving augmentation therapy. In another study, only age and CT assessment of proportion of emphysema predicted respiratory and all-cause mortality.

Treatment

Standard treatment for COPD

Treatment for individuals with COPD due to α1-antitrypsin deficiency should include usual therapy for COPD (eg, smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen when indicated, rehabilitation, etc), with the possible exception of lung volume reduction surgery. Such surgery has been shown to enhance survival and functional status in some subsets of COPD individuals but in a small available series of α1-antitrypsin-deficient individuals, it generally conferred shorter-lived benefits.

Augmentation therapy

Beyond usual treatment of COPD, specific treatment of α1-antitrypsin deficiency currently consists of infusion of purified pooled human plasma α1 antitrypsin, known as augmentation therapy. The goal of this treatment is to raise and maintain serum α1 antitrypsin concentrations above the protective threshold. Three different preparations of purified α1 antitrypsin from pooled human plasma are currently available and have been approved for use by regulatory agencies in several countries to date (table 4).

Two kinds of criteria—biochemical and clinical—have been used to assess the effectiveness of augmentation therapy. Questions about assessment of biochemical effectiveness include: does the drug produce serum levels that exceed the protective threshold value, ideally over the entire interdose interval; and is the functional capacity of the infused α1 antiprotease preserved? Questions assessing clinical effectiveness and usefulness include: does augmentation therapy slow the rate of decline of lung function; does augmentation therapy enhance functional status, ameliorate symptoms, or prolong life; is augmentation therapy safe; and is augmentation therapy cost effective?

Various studies have assessed and shown the biochemical effectiveness of intravenous augmentation therapy with pooled human plasma α1 antitrypsin. For example, Wewers and colleagues showed that infusion

### Table 3: Effect of smoking on the rate of FEV1 decline among individuals with α1-antitrypsin deficiency

<table>
<thead>
<tr>
<th>n</th>
<th>Never smokers</th>
<th>Ex-smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janus 1997</td>
<td>21</td>
<td>-80 (SE 38)</td>
<td>-61 (SE 43)</td>
</tr>
<tr>
<td>Hutchison 1997</td>
<td>82</td>
<td>-66 (SD 55)</td>
<td>-44 (SD 56)</td>
</tr>
<tr>
<td>Wu 1998</td>
<td>80</td>
<td>-61 (SD 100)</td>
<td>-81 (SD 70)</td>
</tr>
<tr>
<td>Seersholm 1995</td>
<td>161</td>
<td>-86 (SD 107)</td>
<td>-52 (SD 80)</td>
</tr>
<tr>
<td>Seersholm 1997</td>
<td>198</td>
<td>-66 (SD 107)</td>
<td>-52 (SD 80)</td>
</tr>
<tr>
<td>Seersholm 1997</td>
<td>97</td>
<td>-75 (95% CI 61–87)</td>
<td>-75 (95% CI 61–87)</td>
</tr>
<tr>
<td>NHLBI Registry 1998</td>
<td>1129</td>
<td>-67 (95% CI 56–78)</td>
<td>-54 (95% CI 46–63)</td>
</tr>
<tr>
<td>Piitulainen 1999</td>
<td>608</td>
<td>-47 (95% CI 41–53)</td>
<td>-41 (95% CI 36–48)</td>
</tr>
</tbody>
</table>

### Table 4: Available preparations of purified α1 antitrypsin

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Source</th>
<th>Purification method</th>
<th>Countries in which regulatory approval received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokastin</td>
<td>Talecris Biotherapeutics (Research Triangle Park, NC, USA)</td>
<td>Pooled human plasma, Pasteurization</td>
<td>USA, Germany, Italy, Canada, Spain, Argentina, Austria, Brazil, Ukraine</td>
</tr>
<tr>
<td>Aralast</td>
<td>Baxter (Deerfield, IL, USA)</td>
<td>Pooled human plasma, Solvent detergent purification, nanofiltration</td>
<td>USA</td>
</tr>
<tr>
<td>Zemaira</td>
<td>ZLB-Behring (King of Prussia, PA, USA)</td>
<td>Pooled human plasma, Pasteurization</td>
<td>USA</td>
</tr>
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</table>
of 60 mg/kg once a week of purified α1 antitrypsin derived from healthy donors raised serum concentrations above the protective threshold of 11 μmol/L over the entire dosing interval and increased antielastase activity in bronchoalveolar lavage fluid. Studies of alternate dose regimens, such as 120 mg/kg once every 2 weeks or 250 mg/kg once a month, are less promising biochemically, in that serum concentrations of α1 antitrypsin were maintained above the protective threshold for only part of the interdose intervals.95–97

Available studies of the clinical effectiveness of augmentation therapy (table 5) are of various designs, including several observational cohort studies and a small randomised controlled trial.38,81,85,97–101 Several outcome measures have been studied, including the rate of FEV1 decline, change in CT densitometry, and frequency of exacerbations.

The largest observational cohort study, the NHLBI Registry for Individuals with Severe Deficiency of α1 Antitrypsin,69 assessed 1129 participants, of whom 747 received augmentation therapy at some point during follow-up. Recipients of the treatment showed a reduced mortality rate (relative risk of death 0·64, 95% CI 0·43–0·94; p=0·02).38 Differences between augmentation therapy recipients and non-recipients in the rate of FEV1 decline were not significant for the group overall, though subgroup analysis showed that FEV1 decline slowed (by 27 mL/year; p=0·03) in recipients with values of FEV1 of 35–49% predicted.69 As emphasised by the authors of these and other observational studies (table 5),38,81,85,97–101 and in the American Thoracic Society/European Respiratory Society evidence-based review of α1-antitrypsin deficiency,95 cautious interpretation of these results is warranted because of the risk of bias in comparing outcomes of cohorts in observational studies.

In a randomised, double-blind, placebo-controlled trial of augmentation therapy, Dirksen and colleagues randomly allocated 56 patients with the ZZ phenotype either 250 mg/kg of augmentation therapy at 4-week intervals or a placebo of monthly albumin infusions.95 Over at least 3 years of follow-up, the primary outcome of FEV1 decline did not differ between augmentation and placebo recipients, although a trend towards slower loss of lung tissue (by CT scan) was noted in augmentation therapy recipients (p=0·07).97

Overall, notwithstanding the lack of definitive evidence, findings suggest that intravenous augmentation therapy satisfies criteria for biochemical and clinical effectiveness (table 5).43 In keeping with this view, available standards documents endorsed by the Canadian Thoracic Society102 and by a group of organisations including the American Thoracic Society, the European Respiratory Society, the American College of Chest Physicians, and the American Association for Respiratory Care,69 endorse selected use of augmentation therapy. Specifically, the 2003 international, evidence-based standards document states:

“Recognizing that support of efficacy comes from concordant observational studies but not from a randomized controlled clinical trial, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from α1 antitrypsin deficiency. Evidence that augmentation therapy confers benefit (eg, slowed rate of FEV1 decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (eg, FEV1 35–60% predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (eg, FEV1 <35% predicted) or mild (eg, FEV1 >50–60% predicted) airflow obstruction are less clear . . . Insufficient evidence regarding the benefits of augmentation therapy in patients who have undergone lung transplantation for α1 antitrypsin deficiency precludes a firm recommendation. However, it has been observed that inflammation results in free elastase activity in epithelial lining fluid in individuals who have undergone lung transplantation (eg, during acute rejection and infection). In the context of available data regarding this issue, this observation leads the Task Force to favor augmentation therapy for lung transplant recipients during such episodes.”

With respect to the safety of augmentation therapy, available data over more than 15 years of α1 antitrypsin augmentation therapy use suggest that overall, the
treatment is generally well tolerated and is without important side-effects. Two large studies (table 6) have specifically addressed this issue.103,104 Wencker and colleagues104 reported the experience of 443 recipients of α1-antitrypsin, of whom 65 had a total of 124 adverse events. The most common adverse reactions were fever and chills (17 patients), urticaria (18), nausea and vomiting (21), and fatigue (7). No deaths or instance of viral transmission (ie, HIV or hepatitis) were recorded.104

In a study of 747 recipients of α1-antitrypsin, Stoller and colleagues104 reported the experience of 443 recipients of α1-antitrypsin in the NHLBI registry,54 765 (2001) Expert opinion Markov analytic model validated QALY, ICER The ICER for lifetime treatment per QALY No assumption decreasedICER to

The overall incidence of adverse events was very low (about 0·02 events per patient-month).104 In a study of 747 recipients of α1-antitrypsin in the NHLBI registry,54 765 (2001) Expert opinion Markov analytic model validated QALY, ICER The ICER for lifetime treatment per QALY No assumption decreasedICER to

Although these incremental cost-effectiveness ratios exceed the thresholds for interventions conventionally deemed cost effective, the authors suggest weighing these unfavourable ratios in the context that augmentation therapy remains the only specific treatment currently available for individuals with severe α1-antitrypsin deficiency. Still, these studies encourage development of alternative treatments.

New and emerging treatments

Promising treatments include gene therapy (by injecting adeno-associated virus carrying the human α1-antitrypsin gene),110 strategies to inhibit intracellular polymerisation of α1 antitrypsin,111,112 promotion of hepatic secretion,45,113 inhibition of neutrophil elastase by small-molecule inhibitors, and pegylation of α1 antitrypsin to prolong its serum half life.114

In the context of substantial progress made in α1-antitrypsin deficiency since its description less than 50 years ago, prospects for major advances in diagnosis and treatment are bright. Important challenges include improved detection of affected individuals to make effective therapies available and the pursuit of strategies to effect a genetic cure.

<table>
<thead>
<tr>
<th>Natural history</th>
<th>Augmentation cost per year (US$)</th>
<th>Utility weight</th>
<th>Method of calculation</th>
<th>Outcome indices</th>
<th>Major conclusions</th>
<th>Sensitivity analysis</th>
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<tr>
<td>Hay106 Larsson106</td>
<td>30 000 (1990)</td>
<td>Arbitrary: 0.75</td>
<td>Life expectancy: natural history data; outcome efficacy: 55% (based on registry data)</td>
<td>CLYS</td>
<td>At 30% efficacy the CLYS would be $50 000–128 000 and comparable with other medical interventions</td>
<td>Outcomes most sensitive to efficacy and therapy costs assumptions</td>
</tr>
<tr>
<td>Alkins106 NHLBI registry106</td>
<td>$1 948 (1998)</td>
<td>Not included: 1</td>
<td>Life expectancy: DEALE, outcome efficacy: 55% (based on registry data)</td>
<td>ICYS</td>
<td>At 55% efficacy, the ICYS for patients with FEV1 &lt;50% would be $13 971</td>
<td>Outcomes most sensitive to efficacy and to a lesser degree therapy cost assumption</td>
</tr>
<tr>
<td>Guild106 NHLBI registry106</td>
<td>$4 765 (2001)</td>
<td>Expert opinion based on COPD stage: stage I: 0.93; stage II: 0.75; stage III: 0.36</td>
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<td>QALY, ICER</td>
<td>The ICER for lifetime treatment per QALY gained is $13 971</td>
<td>No assumption decreased ICER to less than $100 000 unless augmentation cost was reduced to $14 000</td>
</tr>
</tbody>
</table>

DEALE=declining exponential approximation of life expectancy; life expectancy is inverse of mortality at 1 year. Mortality=−(1/t)(ln(survival at time t)). CLYS=cost per life-year saved. ICYS=incremental cost per life-year saved. QALY=quality-adjusted life-year. ICER=incremental cost-effectiveness ratio (US$ per QALY). Utility weight adjusts measure of quality based on impact of disease; ranges from 0=health state equivalent to death, 1=perfect health.

Table 7: Comparison of cost-effectiveness studies of augmentation therapy for α1-antitrypsin deficiency
Conflict of interest statement

J K Stoller has served as a scientific adviser for Baxter, ZLB Behring, and Bayer. L S Abouassouan has no conflict of interest.

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Seminar


