

Augmentation treatment for α 1 antitrypsin deficiency



α 1 antitrypsin is a serine antiprotease secreted by the liver.^{1,2} Its main function is inhibition of neutrophil elastase, a non-specific protease released by activated or dying neutrophils. In individuals with healthy concentrations of α 1 antitrypsin, the fragile alveolar structures of the lung parenchyma are protected from this protease (figure).

α 1 antitrypsin deficiency, discovered by Laurell and Eriksson in 1963,³ is a common hereditary disorder, mainly of Caucasians, characterised by low serum concentrations of the protein, emphysema, and, in some cases, liver disease. Most cases are caused by homozygous inheritance of a single base mutation (Glu342Lys) in the α 1 antitrypsin gene, referred to as the Z variant. The Z form of α 1 antitrypsin produced by the liver aggregates in the endoplasmic reticulum of hepatocytes, with consequently decreased serum protein and, in some cases, liver cirrhosis. Because of these decreased serum concentrations, the lungs of Z homozygotes have little defence against neutrophil elastase and develop clinical manifestations of alveolar destruction (emphysema) aged 35–45 years in cigarette smokers, and aged 50–60 in non-smokers.

In the 1980s, based on the concept that pathogenesis of emphysema can be caused by α 1 antitrypsin deficiency, my laboratory sought to develop a treatment to prevent the progressive loss of lung parenchyma that results in

the clinical manifestations of emphysema. These studies led to approval in the USA of intravenous augmentation treatment for α 1 antitrypsin deficiency. First, using bronchoalveolar lavage, we showed that the epithelial surface of the lower respiratory tract of Z homozygotes was deficient in α 1 antitrypsin and, consequently, antineutrophil elastase capacity.⁴ Second, we purified α 1 antitrypsin from pooled human plasma and showed in individuals deficient in α 1 antitrypsin that intravenous administration of 60 mg/kg of purified α 1 antitrypsin once a week could re-establish healthy serum α 1 antitrypsin concentrations and, importantly, re-establish healthy lung alveolar α 1 antitrypsin concentrations and antineutrophil elastase capacity.^{5,6} On the basis of these studies, the US Food and Drug Administration approved use of augmentation treatment of α 1 antitrypsin deficiency. This approval, and the subsequent use of α 1 antitrypsin augmentation treatment in more than 5000 patients with α 1 antitrypsin deficiency worldwide, was based entirely on biochemical efficacy—ie, that α 1 antitrypsin augmentation treatment is efficacious because it re-establishes healthy serum and lung epithelial lining fluid concentrations and antineutrophil elastase capacity.⁶

Despite the logic underlying the biochemical efficacy of α 1 antitrypsin augmentation treatment, no clinical evidence had existed that this treatment is efficacious.

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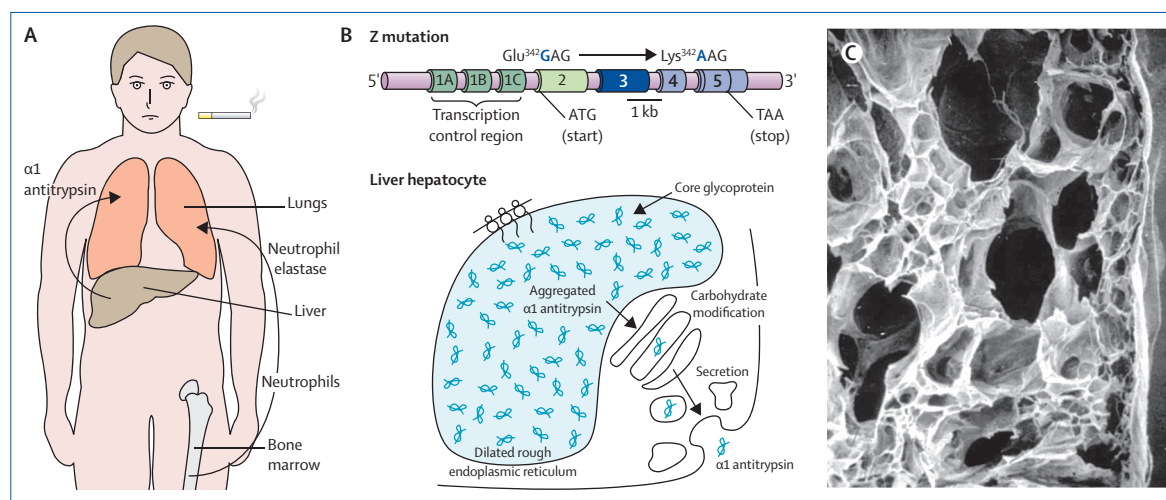


Figure: Pathogenesis of α 1 antitrypsin deficiency

(A) α 1 antitrypsin produced in the liver functions to protect the lungs from the burden of neutrophil elastase. (B) With the Z mutation in the α 1 antitrypsin gene, the α 1 antitrypsin Z protein aggregates in the liver, resulting in low α 1 antitrypsin concentrations in the lungs. (C) The effect is progressive lung destruction, resulting in emphysema (scanning electron microscopy).

However, the study by Kenneth Chapman and colleagues,⁷ published in *The Lancet*, sets out to examine this issue. With a classic randomised, placebo-controlled design, the study was done for 2 years in patients with $\alpha 1$ antitrypsin deficiency randomly assigned to $\alpha 1$ antitrypsin augmentation treatment or placebo, using chest CT to quantify the extent of emphysema. The authors have provided some evidence that augmentation treatment slows down progression of lung destruction.

Two technologies are accepted as valid, non-invasive clinical measures of lung alveolar destruction—lung function studies and chest CT. Chapman and colleagues⁷ wisely chose chest CT as their primary endpoint because lung function studies, particularly measures of forced expiratory airflow, are indirect measures of lung destruction; and diffusing capacity, a more direct measure, is sufficiently variable that a much higher number of patients and longer follow-up would be needed than if chest CT was used. By contrast, chest CT can be used as a direct, reproducible, quantitative measure of emphysema, much like the classic anatomical description of the disease.^{8,9}

All patients in Chapman and colleagues' study had $\alpha 1$ antitrypsin serum concentrations of less than the 11 μM threshold for risk of emphysema and spirometry evidence of airflow obstruction. Of the 180 patients recruited, 153 completed the trial, including 84 patients given 60 mg/kg of $\alpha 1$ antitrypsin infusion every week and 69 receiving placebo. Importantly, quantitative chest CT showed that the annual rate of lung density loss (a direct measure of the extent of emphysema) was significantly lower in the treated patients assessed over 2 years when measured at total lung capacity alone (-1.45 g/L per year vs -2.19 g/L per year; difference 0.74 g/L per year [95% CI 0.06–1.42]). The authors conclude that intravenous $\alpha 1$ antitrypsin augmentation treatment might slow progression of emphysema associated with $\alpha 1$ antitrypsin deficiency.

One unanswered question is when to initiate $\alpha 1$ antitrypsin augmentation treatment. The study by Chapman and colleagues⁷ enrolled patients with $\alpha 1$ antitrypsin deficiency with mild to moderate airflow obstruction (forced expired volume in 1 s 35–70% predicted). With evidence of clinical efficacy now shown,

use of augmentation treatment earlier than at present, before onset of decline in lung function, should be explored. Diagnosis of $\alpha 1$ antitrypsin deficiency is a single blood test, and the data⁷ would suggest that treatment could begin earlier and lung parenchymal destruction could be prevented.

Finally, the challenge remains of a means to augment $\alpha 1$ antitrypsin concentrations in patients with $\alpha 1$ antitrypsin deficiency without the need for intravenous infusions every week, and to do so in a less costly manner (present treatment costs US\$ 100 000 per individual per year). We^{10,11} and others¹² are therefore exploring gene therapy strategies to augment $\alpha 1$ antitrypsin concentrations using adeno-associated viral gene transfer vectors, a treatment that can potentially replace $\alpha 1$ antitrypsin augmentation with a single administration.

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I declare no competing interests.

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