Alpha-1 antitrypsin: now available, but do we need it?

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Summary

Severe α_1-antitrypsin (AAT) deficiency is the best characterised genetic risk factor for the development of emphysema. AAT has a wide spectrum of antiprotease activity and its primary function is inhibition of neutrophil elastase in the lung. Smokers with this genetic defect develop severe impairment in their fifth to sixth decade of life.

Intravenous administration of human AAT is well tolerated and has been shown to increase the levels of AAT in the alveolar lining fluid of individuals with this deficiency. In contrast to the proof of the biochemical effectiveness of augmentation treatment, the favourable clinical effect of AAT on pulmonary function, emphysema progression, morbidity and survival has not been persuasively demonstrated by prospective controlled clinical trials and remains controversial.

Key words: α_1-antitrypsin deficiency; pulmonary emphysema; replacement therapy

History

Almost 45 years ago the clinical chemist Laurell and the clinician Eriksson discovered individuals with reduced blood levels of α_1-antitrypsin (AAT) and suggested a connection with pulmonary emphysema [1, 2]. Additional studies in patients with AAT deficiency and their family members confirmed the association with pulmonary emphysema and suggested a co-dominant pattern of inheritance. Several avenues of research can be traced to this seminal discovery, and deficiency of a protease inhibitor not only revealed a key mechanism underlying the development of pulmonary emphysema but ultimately resulted in identification of the function and dysfunctions of a whole new family of protease inhibitors – the serine proteinase inhibitor or SERPIN superfamily [3, 4].

Pathophysiology

Human AAT, also called α_1-proteinase inhibitor (Pi) is a 394 amino acid, 52 kDa acute phase glycoprotein encoded on chromosome 14q31-32.1. It is predominantly synthesised and secreted by hepatocytes into the blood and to a much lesser extent by alveolar macrophages and possibly lung epithelial cells. This bean-shaped glycoprotein is a highly specialised bait for trapping proteases. AAT has a wide spectrum of antiprotease activity and inhibits several serine proteases found in the lung, its primary function being the inhibition of neutrophil elastase. Point mutations in its mobile domain, which acts as a binding site for the target protease, may result in polymerisation of the protein within the hepatocytes, so that it is not secreted effectively into the blood and this results in low levels within the lung. Since AAT is an effective elastase inhibitor, emphysema is presumed to occur as a result of increased and unopposed elastase activity, destroying the elastin matrix of the lung (Fig. 1).

AAT deficiency is the most widely recognised abnormality of a proteinase inhibitor which causes lung disease. More than 75 protein variants, referred to as Pi phenotypes, have been described and characterised by their migration on isoelectric focusing. A common AAT classification divides the Pi variants into normal, deficient and null categories (no detectable AAT serum level), according to the serum concentration of the AAT protein. The PiM allele is the wild type, and protein variants associated with normal AAT concentrations
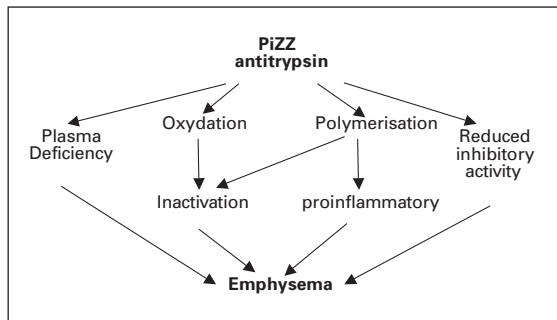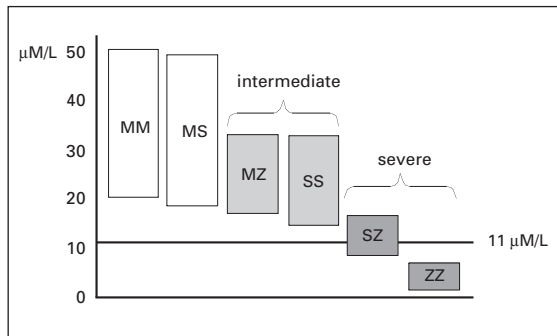
are referred to as PiMM phenotype. The most common deficiency variants PiZ and PiS result from point mutations in the AAT gene, which is very polymorphic. Several rare genetic variants mediate AAT deficiency but the most prevalent mutations in Caucasians are the S-allele (0.6–11%) and the Z-allele (0.3–4%) [5, 6]. Thus, intermediate and severe AAT deficiency phenotypes in Caucasians usually result from combinations of S- and Z-alleles. Severe AAT deficiency (ie, AAT levels below a protective threshold of 11 µmol·L^{-1}) includes subjects homozygous or heterozygous for the Z- or the null-allele. Intermediate AAT deficiency includes subjects with PiMZ, PiSS and PiSZ phenotypes (Fig. 2). Their serum levels range from 20–60% of normal (ie, 11–20 µmol·L^{-1}).

Conformational changes in the reactive loop of PiZ allow the reactive loop of a second molecule to dock on at this location. This results in the formation of AAT polymers with an accumulation in the liver, causing liver cell damage and eventually liver disease in AAT deficient infants or adults [3, 4].

Epidemiology

Although large numbers of cohorts have been investigated, only a few population-based studies on AAT allele frequencies, chiefly based on blood donor screening, are available. In 200,000 neonates screened in Sweden, the number of babies with the Z variant was 122, ie, one in 1639 [7], and one in 4455 in 107,038 screened newborns in Oregon, USA [8]. The prevalence of the three major AAT variants (PiM, PiZ, and PiS) is reported in most surveys as gene frequencies which are then used to estimate the total number of carriers (PiMS and PiMZ) and subjects with deficiency variant combinations (PiSS, PiSZ, and PiZZ) based on the Hardy-Weinberg equilibrium formula. For Switzerland the calculated number (95% confidence interval) is 955 (426–2103) for PiZZ and 6468 (3496–11821) for PiSZ based on a population of 7.45 million [5]; 1.9% of 965 consecutive COPD patients in the United States were found to have a PiZZ phenotype [9].

Pulmonary manifestation

The hallmark of AAT deficiency is the development of early-onset pulmonary emphysema in persons with the ZZ genotype. The disease in these patients typically starts earlier than in patients with chronic obstructive pulmonary disease (COPD) without AAT deficiency, and is often out of proportion to their smoking history [10]. Lung function tests in symptomatic patients show airflow obstruction, indicated by a reduced forced expiratory volume in one second (FEV$_1$) and a reduced FEV$_1$ to FVC (forced vital capacity) ratio, pulmonary hyperinflation as well as a reduced diffusing capacity. Almost half of the patients with AAT deficiency complain of chronic sputum expectoration and experience more frequent exacerbations than patients with COPD but without AAT deficiency. Emphysema associated with AAT deficiency is typically panlobular, characterised by uniform destruction of the pulmonary lobule. In contrast to centrilobular emphysema, the classical type of emphysema in pure smokers, the destruction is generalised and more prominent in the lower lobes (Fig. 3) [11]. Cigarette smoking is the biggest risk factor for the development of emphysema and airflow obstruction in AAT deficiency, and current smokers have an accelerated decline in FEV$_1$, compared with ex-smokers and never-smokers, and AAT deficiency [12, 13]. In smokers who are unable to stop smoking, average life expectancy is below 20 years after diagnosis of AAT deficiency. However, it should be noted that non-smoking individuals with the homozygous Z phenotype have remarkably delayed onset of symptoms and some may enjoy an almost normal life span [14]. In a Swedish cohort of 127 individuals with PiZZ out of 200,000 screened children,

lung function remained normal during the first two decades of life [15]. Studies of the natural history of AAT deficiency show that emphysema leading to early death usually becomes symptomatic in the third and fourth decades of life. In one study of life expectancy in 246 subjects the median age at death for smokers was estimated to be some 40 years and for never-smokers approx. 65 years [16].

Figure 3

High resolution CT of the lung of a 55-year-old male with PiZZ AAT deficiency. The emphysematous destruction is more prominent in both lower lobes than in the upper lobes. Note the marked bronchial and peribronchial inflammatory changes.
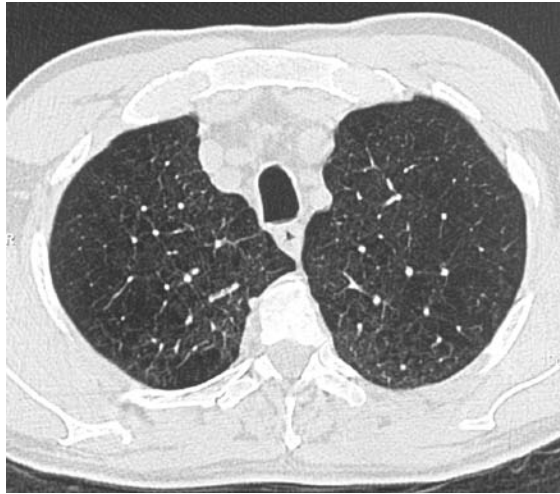
Diagnosis

Several methods are available for measurement of plasma AAT levels (eg, radial immunodiffusion, nephelometry). In the interpretation of an individual plasma level, not only the method-specific normal ranges should be considered but also the fact that AAT is an acute-phase reactant which may augment the plasma concentration in Z heterozygotes in inflammatory conditions [17]. It should be noted that a "protective" threshold level of 11 umol/L corresponds to 80 mg/dL (Fig. 2) if measured by radial immunodiffusion and to 50 mg/dL if measured by nephelometry. The "protective level" concept evolved from the observation that individuals with heterozygote phenotypes whose levels of AAT are above this limit usually do not develop pulmonary emphysema. The most widely used method for identifying AAT variants, ie, for phenotyping, is their separation on the basis of isoelectric point by means of thin layer isoelectric focusing. This technique requires experience and should be performed in reference laboratories. Genotyping is performed on genomic DNA which is extracted from circulating blood cells. Known mutations may be detected by all allele-specific amplification. The most prevalent defect alleles S and Z can be identified by commercially available kits.

Large-scale screening of newborns or adults is not recommended for reasons of cost and issues of personal vulnerability related to the presence of an inherited defect, as well as the fact that individuals must sustain the emotional tension of living with this information at a time when they may feel perfectly healthy. Since avoidance of smoking may improve the prognosis of persons with AAT deficiency there is some justification for early individual detection. Measurement of AAT blood level is recommended in patients with early-onset COPD with or without a history of cigarette smoking, and in siblings of AAT deficient persons for prognostic reasons. The idea is that the smokers among them can be more effectively advised to stop smoking and non-smokers not to start the habit. Subjects with low or borderline normal AAT plasma levels (12–35 μmol/L or 90–140 mg/dL) should undergo qualitative testing, ie, pheno- or genotyping.

Treatment

The treatment of symptomatic patients with AAT deficiency and COPD does not differ basically from symptomatic therapy of COPD not related to this genetic condition, and follows published guidelines [17, 18]. Particular emphasis is placed on smoking cessation, since smoking is a particularly important prognostic factor for the outcome of patients with AAT deficiency. Lung transplantation remains the most efficient therapeutic intervention in patients with advanced pulmonary emphysema and AAT deficiency. Since such patients experience their functional impair-

Table 1

Published studies on the clinical efficacy of AAT augmentation therapy.

Reference (Year)	Type of Study	Infusion interval	Outcome parameters and results
Seersholm (1997) [22]	observational concurrent controls	weekly	FEV_1-decline 53 ml/yr in 97 controls and 35 ml/yr in 198 treated patients ($p = 0.04$); FEV_1: 31–65% pred.
NHLBI (1998) [23]	observational concurrent controls	51% weekly 25% biweekly	FEV_1-decline slowed by 27 ml/yr in patients with FEV_1 35–49% pred. 22% monthly ($p = 0.02$) in 392 treated as compared to 32 not treated patients
Dirksen (1999) [26]	randomized controlled trials	four-weekly	loss of lung tissue: 2.6 g/L with placebo (n: 26) and 1.5 g/L on treatment (n: 39); ($p = 0.07$)
Liebermann (2000) [24]	observational	56% weekly 26% biweekly	number of infections decreased from 3–5 to 0–1 (n: 89)
Wenker (2001) [25]	observational	weekly before – after	FEV_1-decline 49.2 ml/yr before and 34.2 mL/yr after ($p = 0.019$) augmentation (n: 96)

ment at a much earlier age than smokers with COPD without AAT deficiency, these patients make up a considerable fraction in every lung transplantation programme. Among the 224 transplanted patients at our hospital, 23 of 56 with end-stage pulmonary emphysema were known to have severe AAT. Although the functional improvement after lung volume reduction surgery is not usually long-lasting in this particular population, we continue to perform this type of surgery in selected cases as a bridging procedure to transplantation [19, 20].

Treatment modalities targeting the molecular basis of AAT deficiency rather than its consequences are a topic of ongoing research. Such approaches include inhibition of polymerisation of PiZZ, eg, by chemical chaperones, or the replacement of defective or absent genes, eg, by various vectors by portal vein injection, airway instillation or intramuscular injection. The major focus of treatment for patients with emphysema due to severe AAT deficiency has been on correcting the deficiency. It is reasonable to speculate that if the deficiency could be corrected, the progression of emphysema might be halted or at least delayed. Purified human AAT concentrates have been licensed and augmentation therapy has been covered by health insurance for several years now in, for example, Germany, Austria, France, Italy, Spain and the USA. In contrast, augmentation therapy is not recommended and not at present covered by health insurance in Great Britain, the Scandinavian countries and the Netherlands. In Switzerland, a purified AAT from pooled human plasa (Prolastin®) has recently been approved for clinical use by Swissmedic.

Intravenous administration of human AAT was shown to increase the levels of AAT in the bronchoalveolar lavage fluid of AAT deficient individuals more than twenty years ago [21]. The protective serum level is maintained over an entire interdose interval, and the functional capacity of the infused AAT to oppose neutrophil elastase is preserved. However, in contrast to the proven biochemical effectiveness of augmentation treatment, the clinically favourable effect of AAT on pulmonary function, emphysema progression, morbidity and survival has not been persuasively demonstrated by prospective controlled clinical trials and hence remains debatable. AAT replace-

ment seems to be safe and is well tolerated. Serious side effects such as anaphylaxis are rare and there have been no reported cases of bloodborne diseases (eg, hepatitis, HIV, prion disease).

Published studies (table 1) of the clinical efficacy of augmentation therapy embrace various study designs and include observational studies [22–25] with concurrent or historical controls and, up to the present, only a single randomised controlled trial [26]. Outcome measures include the rate of FEV_1 decline, the frequency of acute exacerbations, mortality rate and the change in lung density as measured by CT scanning.

In a first attempt to study the effect of augmentation therapy, the annual decline of FEV_1 was compared in a non-randomised group of ex-smokers in Germany with that in an untreated group of ex-smokers in Denmark [22]. No differences were found in the subgroup of 103 patients with a baseline $FEV_1 \leq 30\%$ and in the 25 patients with FEV_1 of >65% predicted, but a difference of 21 mL per year ($p = 0.04$) was found in the group with FEV_1 in the middle range.

The largest observational cohort study (n: 1129) is based on the NHLBI Registry for individuals with severe AAT deficiency [23]. The subjects receiving augmentation therapy had decreased mortality (risk ratio [RR] = 0.64, 95% CI: 0.43 to 0.94, $p = 0.02$) as compared with those not receiving therapy. There was no difference in FEV_1 decline between augmentation-therapy groups. However, among subjects with a mean FEV_1 between 35% and 49%, predicted FEV_1 decline was slower for subjects receiving than for those not receiving augmentation therapy (mean difference = 27 mL/yr, 95% CI: 3 to 51 mL/yr; $p = 0.03$). Because this study was not a randomised trial either, the possibility that these differences may have been due to other factors such as socioeconomic status cannot be ruled out. The authors reasoned that definitive conclusions would require a randomised controlled trial.

Liebermann [24] sent a questionnaire to patients with a ZZ phenotype for AAT deficiency to explore whether those receiving augmentation therapies experienced any subjective benefit, and in particular whether the therapy had an effect on the frequency of exacerbations. 96 patients receiving AAT responded, as did 47 similar patients not receiving augmentation therapy. 74 of 89 patients

who had received infusions for over one year believed that they had definitely benefited, and 56 claiming a benefit attributed this to a reduction in the number of lung infections since starting therapy. Before starting AAT replacement, the majority of patients estimated they had had 3–5 infections per year, and 0–1 infection per year during AAT therapy (p <0.001).

96 patients with severe AAT deficiency receiving weekly augmentation therapy with AAT 60 mg/kg bodyweight, and a minimum of two lung function measurements before and two lung function measurements after augmentation therapy, took part in a multicentre retrospective cohort study [25]. Lung function data were followed up for a minimum of one year both before and during treatment (mean 47.5 months and 50.2 months respectively). Patients were grouped according to severity of lung function impairment. The change in FEV_1 was compared during non-treatment and treatment periods. In the whole group the decline in FEV_1 was significantly lower during the treatment period (49.2 mL/yr vs 34.2 mL/yr, p = 0.019).

The first, and thus far only, randomised, parallel, double-blind, placebo-controlled trial of AAT augmentation therapy was performed with 26 patients from the Danish AAT deficiency registry and 32 patients from a similar Dutch registry [26]. All patients had AAT deficiency of PiZZ phenotype and moderate to severe emphysema (FEV_1 30% and 80% of predicted). Patients received infusions every four weeks of either AAT (250 mg/kg bodyweight) or placebo (human albumin) for three years. Self-administered spirometry was performed every morning and evening. The degree of emphysema was quantified by the 15th percentile point of the lung density histogram derived from computed tomography with scanners regularly calibrated using water and air phantoms to allow for comparison between examinations. No significant difference was found in FEV_1 decline between treatment and placebo. The loss of lung tissue measured by CT (mean ± SEM) was 2.6 ± 0.41 g/L/yr for placebo as compared with 1.5 ± 0.41 g/L/yr for AAT infusion (p = 0.07).

As mentioned previously, the pathophysiological proof of concept for the potential value of AAT augmentation was published twenty years ago [21]. Unfortunately, at that time the opportunity for a prospective, randomised, controlled clinical trial comprising an appropriate number of patients which would permit firm conclusions on appropriate functional and clinically relevant endpoints was missed. With the exception of the Danish-Dutch trial [26] all other studies are methodologically flawed and hence their results remain unconvincing. Confounding variables in retrospective studies consist of potential differences in, for example, socioeconomic status and contact to health care between the treatment and the control groups.

A 2-year multinational, European placebo-controlled trial with parallel groups including 78 patients with PiZ and FEV_1 >25% of predicted has recently been completed (EACTLE Trial). The treatment consisted of weekly intravenous Prolastin® 60 mg/kg (placebo: 2% albumin). The primary endpoints are frequency of exacerbations and progression of emphysema as assessed by CT lung density measurements. The results of this trial are eagerly awaited and will have a major impact on AAT replacement recommendations in Switzerland.

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