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# Augmentation Therapy for α1-Antitrypsin Deficiency

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## Abstract

α1-Antitrypsin (AAT) deficiency is a common but under-recognised condition. Since its first description by Laurell and Eriksson in 1963, significant advances have been made in understanding the genetics, physiology and pathophysiology of this condition. The intravenous administration of purified AAT to AAT-deficient individuals has been shown to confer biochemical efficacy by raising the serum AAT level above an epidemiologically established 'protective threshold' while preserving the biochemical properties and functional capacity of the protease inhibitor. Although the lack of a large randomised controlled trial to date has precluded the definitive demonstration of clinical efficacy of intravenous AAT augmentation therapy, substantial evidence supporting its use in AAT-deficient individuals with moderate airflow obstruction has accumulated. For example, both large observational studies comparing rates of forced expiratory volume decline among recipients of augmentation therapy versus non-recipients have shown slower rates of decline among augmentation therapy recipients, especially those with moderately severe airflow obstruction. Also, some evidence suggests that use of augmentation therapy confers an anti-inflammatory effect. For example, a web-based survey suggested that recipients of augmentation therapy experienced fewer respiratory infections than non-recipients.

Despite its high cost, intravenous AAT augmentation therapy remains the only US FDA-approved treatment option for patients with AAT deficiency. Research into new and evolving treatments is currently underway.

First recognised by Laurell and Eriksson[1] in 1963, α1-antitrypsin (AAT) deficiency occurs in approximately 1 in 3000 individuals worldwide but is under recognised.[2,3] Since its first description as a genetic condition associated with lack of proteins in the α1 band of the serum electrophoretogram and early-onset emphysema, considerable advances have been made in understanding the genetics, physiology and pathophysiology of lung disease related to AAT deficiency.[4] With regard to therapy, specific pharmacological therapy of AAT deficiency consists of the administration of purified AAT in order to augment the affected individual's serum levels[5-7] and to confer protection against the unopposed elastolysis that causes emphysema.

This article reviews the specific pharmacological treatment of AAT deficiency, namely with AAT augmentation. We will consider the rationale for such augmentation therapy, available drugs for augmentation therapy, their pharmacokinetic characteristics, costs and the evidence regarding the efficacy of augmentation therapy. As a prelude to this discus-

sion, we briefly review the physiology of AAT, the pathophysiology of AAT deficiency and the genetics of this condition.

## 1. Physiology of $\alpha_1$-Antitrypsin (AAT)

AAT is a 52 kDa, 394 amino acid glycoprotein synthesised primarily in hepatocytes and, to a lesser extent, in mononuclear phagocytes, intestinal epithelium, renal parenchyma and other sites.[8] Although increasing attention is being given to the anti-inflammatory properties of AAT, its classic description is as a protease inhibitor (PI), with its name reflecting early practices of assaying AAT by trypsin inhibitory capacity.[1] Other proteases inhibited by AAT include chymotrypsin, cathepsin G, plasmin, thrombin, tissue kallikrein, factor Xa, plasminogen, proteinase-3 and neutrophil elastase. Indeed, AAT is a member of the serine endopeptidase inhibitor family or so-called 'serpin' family of protease inhibitors and has a major function of inhibiting neutrophil elastase and is responsible for at least 90% of the inhibition of neutrophil elastase at the level of the lung interstitium.[8,9] In view of the fact that unopposed neutrophil elastase is a major elastolytic threat to the integrity of the lung parenchyma, deficiency of AAT (which has an association constant for neutrophil elastase that is 25-fold higher than for other proteases) can predispose to emphysema.

Recent attention has turned to the inflammatory component of the pathogenesis of emphysema and current evidence shows that AAT also serves as an anti-inflammatory protein. Specifically, AAT has been shown to inhibit the lymphocyte response to phytohaemagglutinin, to inhibit chemotaxis and the enhancement of pokeweed mitogen-driven IgG synthesis,[10] and to attenuate smoking-related neutrophil recruitment to the lung.[11,12] Recent research suggests that the oxidised form of AAT, while rendered inactive as a protease inhibitor by oxidation, displays pro- as well as anti-inflammatory properties. Specifically, Moraga and Janciauskiene[13] reported that oxidised AAT can activate human monocytes in culture, leading to elevated levels of monocyte chemoattractant protein, interleukin (IL)-6 and tumour necrosis factor-$\alpha$ expression, while Churg et al.[14] have recently shown that this anti-inflammatory effect is preserved even in the face of oxidation of the active site of the protein. Specifically, oxidised AAT can suppress silica-induced polymorphonuclear influx into the lung and macrophage inflammatory protein-2/monocyte chemotactic protein-1 gene expression in mice, suggesting the inflammatory effect may be separate from the protease inhibition function.

Regarding production of the protein, once synthesised within the hepatocyte, normal so-called M-type AAT undergoes glycosylation and secretion from the hepatocyte into the bloodstream, where normal serum levels range between 20 and 53 μmol/L, or approximately 100–350 mg/dL, depending on the individual laboratory.[15,16] Indeed, because the purity of commercial standards of AAT for serum level determination varies, normal laboratory ranges vary, as does the accuracy of testing. Under normal conditions (i.e. in the individual who has homozygous M-type AAT), serum levels, which bathe the lung interstitium, suffice to offset any excessive proteolytic threat to the lung. However, in the context of deficient serum levels, which may accompany genetic variants that produce so-called 'deficient' proteins, serum levels may fall below a designated 'protective threshold' at which the risk of emphysema increases.[17] Specifically, based on epidemiological studies regarding the prevalence of emphysema with various phenotypic variants of AAT, the protective threshold has been identified as 11 μmol/L or approximately 80 mg/dL.[17-19] Individuals whose serum levels exceed 11 μmol/L are felt to be protected, whereas those whose serum levels fall below 11 μmol/L (such as *PI*ZZ* and a minority of *PI*SZ* individuals) show an increasing risk of emphysema with decreasing serum levels, such that individuals who lack AAT in serum completely (i.e. *PI** null null) are deemed to be at the highest risk of developing emphysema. In the context of this protective threshold, the rationale for augmentation therapy in AAT-deficient individuals with chronic obstructive pulmonary disease (COPD) is to raise serum levels above the protective threshold and to

maintain levels in the serum and lung throughout the dose administration interval.

Importantly, the pathogenesis of liver disease in AAT deficiency is different than that of emphysema.[4] Although the precise mechanism of liver disease is incompletely understood, liver dysfunction relates to the accumulation within the hepatocyte of unsecreted abnormal AAT in individuals whose phenotypes are associated with abnormal protein folding (e.g. Z, $M_{malton}$ and $M_{duarte}$). In such individuals, liver biopsies generally reveal the presence of intra-hepatocyte inclusions that are periodic acid-Schiff positive and diastase resistant. Analysis of these inclusions shows that they represent unsecreted AAT related to abnormal folding of proteins produced by these abnormal alleles.[20-23] Specifically, as shown by Carrell and Lomas,[8] the presence of a single amino acid substitution of a lysine for a glutamic acid residue at position 342 is responsible for abnormal folding of the Z-type AAT molecule, such that polymerisation of adjacent molecules may occur in a mechanism dubbed loop-sheet polymerisation (figure 1). Loop-sheet polymerisation leads to accumulation within the hepatocyte of unsecreted protein, thereby causing serum levels to be below normal and, in the case of selected phenotypes (e.g. *PI*ZZ), below the serum protective threshold. *In vitro* data suggest that this process can be accelerated by fever.[8] Notably, because the pathogenesis of liver disease relates to the intrahepatocytic accumulation of unsecreted protein rather than to any deficiency predisposing to elastolytic breakdown, treatment strategies to augment serum levels of AAT above the protective threshold confer no protection against the liver disease as they may against emphysema (see section 3).

## 2. Genetics of AAT and AAT Deficiency

AAT deficiency is inherited as an autosomal codominant condition.[24] To date, approximately 100 different alleles of the AAT gene have been identified and have been categorised according to a '*PI**' (*SERPINA1**) classification scheme.[25] As shown in table I, available variants have been categorised as normal, deficient, dysfunctional or null variants. A full description of the spectrum of abnormal phenotypes is beyond the current discussion and the reader is referred to recent reviews (e.g. Luisetti and Seersholm[26]). For the purpose of the current discussion, we focus on the deficient variants, because these are most clinically prevalent and because these variants are associated with low serum levels that may fall below the aforementioned protective threshold and which are the target for pharmacological therapy currently.

The deficient variants include the Z, S, $M_{malton}$, $S_{iiyama}$ and various other less common alleles. The most common variant associated with disease is the Z variant, named because of its slow migration within an isoelectric field of pH 4–5. As mentioned in section 1, the Z variant involves a single amino acid substitution at position 342, such that a lysine residue replaces the normal glutamic acid.[8,25] This substitution occurs at a strategic position along the protein, affecting its conformational stability and allowing intercalation of an A sheet from a neighbouring molecule into a gap in the adjacent molecule, the mechanism of loop-sheet polymerisation (figure 1).[8] In addition to the associated serum deficiency, Z-type AAT protein has an association constant for neutrophil elastase that is lower than the normal M-type protein, thereby requiring twice the time for Z-type AAT to inhibit neutrophil elastase as the M-type protein.[27]

As shown in table I, the S allele is associated with mildly reduced serum AAT levels and relates to a substitution of a valine for a glutamic acid residue at position 264. To the extent that the Z homozygous state accounts for approximately 95% of all clinically recognised cases of severe AAT deficiency, deficient variants other than Z are far less common.[28] So-called null variants are even less common and relate to transcriptional or translational errors that interrupt protein synthesis completely, causing the serum to be completely devoid of AAT. Because no protein is synthesised in null variants, *PI** null null individuals are generally not at risk for intra-hepatocyte accumulation or consequent liver disease.

Clinical recognition of AAT-deficient individuals is based on clinical suspicion and confirmatory

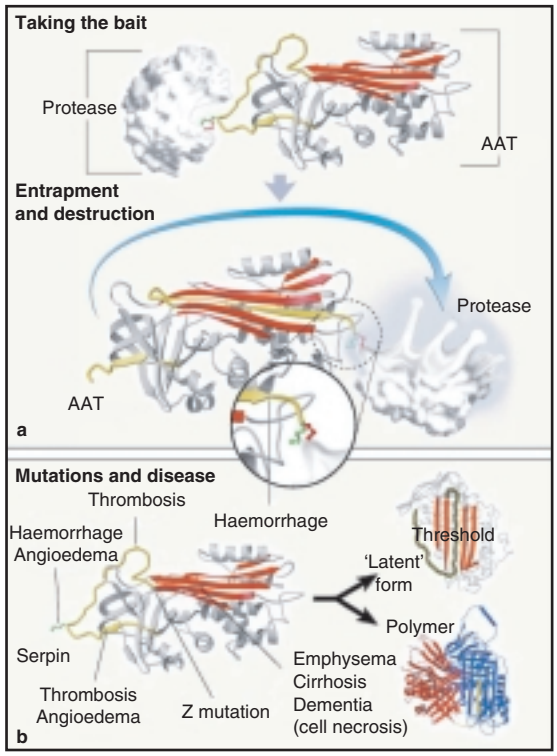


**Fig. 1.** Mechanism of inhibition of proteases by serine endopeptidase inhibitors or serpins, and mutations resulting in $\alpha_1$-antitrypsin (AAT) deficiency. The mechanism of inhibition of the serpins, represented in panel (**a**) by AAT, is like that of a mousetrap, with a spring-like shift from a metastable to a hyperstable state. The protease attacks the reactive centre loop (yellow) of AAT, with the active serine of the protease (small red side chain) forming a link to the amino acid at the base of the reactive centre (small green side chain) of AAT. The resulting cleavage of the reactive loop allows it to snap back into the main β sheet (red ribbons with arrows) of the AAT. This spring-like movement flings the tethered protease to the opposite end of the AAT molecule, distorting its active site (inset) and altering its structure so that it can be destroyed. Some 200 different mutations in serpins are known to result in disease (**b**). In particular, mutations affecting antithrombin confer a predisposition to thrombosis, those affecting C1 inhibitor confer a predisposition to angioedema, and those affecting antiplasmin confer a predisposition to haemorrhage. Mutations at the reactive centre result in a loss of function (e.g. causing familial angioedema) or, more rarely, result in change in function (e.g. causing haemorrhagic disease). The insertion of an amino acid into the peptide loop containing the reactive centre of another serpin, $\alpha_2$-antiplasmin, reduces the distortion of the catalytic site (inset) of plasmin, allowing its release, with consequent fibrinolysis and haemorrhage. The most common cause of loss of function of serpin molecules are mutations affecting the critical mobile hinges of the molecule. These lead to spontaneous changes in conformation that allow either the insertion of the intact reactive loop into the main (β) sheet, resulting in the formation of a 'latent' form, or the insertion of the loop of one molecule into the β sheet of the next, resulting in the formation of polymers. Polymerisation occurs in AAT with the common Z variant and with mutations at the opening of the sheet, leading to emphysema and cirrhosis. Mutations at the same site in a neuron-specific serpin result in neurodegradation and dementia (reproduced from Carrell and Lomas,[8] with permission. © 2002. Massachusetts Medical Society. All rights reserved).

diagnostic testing with serum level determinations and/or phenotype confirmation.[25] As recently discussed in The American Thoracic Society (ATS)/European Respiratory Society (ERS) evidence-based standards document regarding the management of individuals with AAT deficiency,[4] circumstances that should prompt clinical suspicion of AAT deficiency include:

- early-onset emphysema (age ≤45 years);
- emphysema in the absence of a recognised risk factor (smoking, occupational dust exposure);
- emphysema with prominent basilar hyperlucency;
- otherwise unexplained liver disease;
- necrotising panniculitis;

- anti-protease 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis);
- family history of any of the following: emphysema, bronchiectasis, liver disease or panniculitis;
- bronchiectasis without evident aetiology.

Serum AAT levels are commonly determined by nephelometry.[15] When indicated, phenotyping can be performed using isoelectric focusing or genotyping using polymerase chain reaction analysis for specific DNA sequences characterising the respective deficient types.[25]

## 3. Rationale for AAT Augmentation Therapy

On the basis of the understanding that the emphysema risk in AAT deficiency relates to deficient serum and interstitial levels of AAT that predispose to unopposed elastolysis, and that emphysema risk increases as serum AAT levels fall below the protective threshold value, the rationale for augmentation therapy in individuals with COPD is to raise and maintain serum AAT levels above the protective threshold. Currently available drugs achieve augmentation of serum AAT levels by intravenous infusion of purified pooled human plasma AAT. Indeed, the criteria to establish efficacy of so-called intravenous augmentation therapy involve both biochemical and clinical considerations.

Biochemical efficacy criteria include demonstration that the infusion of purified AAT can raise serum levels above the protective threshold value and maintain levels above this threshold value throughout the entire dosage interval. Also, although direct measurement of interstitial AAT levels in humans is not technically possible, another criterion of biochemical efficacy is the demonstration that infused AAT enters the lung interstitium by demonstrating augmentation of levels in the epithelial lining fluid (ELF), as sampled by bronchoalveolar lavage. Finally, biochemical efficacy requires not only that serum and ELF protein levels are raised, but that the infused protein pre-

**Table I.** Selected protease inhibitor (*PI*) variants with characteristics including type of mutation, cellular defect and disease association (reproduced from DeMeo and Silverman,[25] with permission from the BMJ Publishing Group)

| *PI* allele | Type of mutation | Cellular defect | Disease association |
|---|---|---|---|
| **Normal alleles** | | | |
| M (various subtypes) | Substitution (1bp) | None | Normal |
| $X_{christchurch}$ | Substitution (1bp) | None | Normal |
| **Deficient alleles** | | | |
| S | Substitution (1bp) | IC degradation | Lung |
| Z* | Substitution (1bp) | IC accumulation | Lung, liver |
| $M_{malton}$ | Deletion (3bp) | IC accumulation | Lung, liver |
| $S_{iiyama}$ | Substitution (1bp) | IC accumulation | Lung |
| $M_{heerlen}$ | Substitution (1bp) | IC degradation | Lung |
| $M_{procida}$ | Substitution (1bp) | IC degradation | Lung |
| $M_{mineral\ springs}$ | Substitution (1bp) | IC degradation | Lung |
| **Null alleles** | | | |
| $QO_{granite\ falls}$ | Deletion (1bp) | Stop codon; no mRNA | Lung |
| $QO_{ludwigshafen}$ | Substitution (1bp) | No protein | Lung, liver |
| $QO_{hongkong\ 1}$ | Deletion (2bp) | Truncated; IC accumulation of a truncated protein | Lung |
| $QO_{isola\ di\ procida}$ | Deletion (17 kbp) | Deletion of coding regions; no mRNA | Lung |
| **Dysfunctional alleles** | | | |
| Pittsburgh | Substitution (1bp) | Antithrombin 3 activity | Bleeding diathesis |
| $M_{mineral\ springs}$ | Substitution (1bp) | Defective inhibition of neutrophil elastase | Lung |
| Z | Substitution (1bp) | Defective inhibition of neutrophil elastase | Lung, liver |

**bp** = base pair(s); **IC** = intracellular; **mRNA** = messenger RNA.

serves its functional capacity to inhibit neutrophil elastase on arrival in the blood and lung.

Clinical efficacy criteria involve showing that AAT augmentation therapy confers protection against the development and/or progression of emphysema. Ideally, augmentation therapy would be shown to confer a survival advantage and to achieve this benefit with minimal and tolerable morbidity. Finally, though beyond consideration of clinical or biochemical efficacy, desirable characteristics of a drug would be affordability and demonstrated cost effectiveness.

The discussion in section 4 reviews available evidence regarding the biochemical efficacy and characteristics of pooled human plasma AAT and evidence regarding the clinical efficacy of intravenous AAT augmentation therapy. Although randomised clinical trials of augmentation therapy have been advocated,[29] impediments to their performance have included the challenges of assembling a sufficiently large cohort, the long duration of follow-up needed using spirometric endpoints and the expense.[30] Indeed, only a single, small randomised trial (n = 56) has been conducted to date.[31]

On the basis of available evidence, three pooled human plasma AAT commercial products have received US FDA approval for use: Prolastin® [1] (Bayer, West Haven, CT, USA), Aralast™ (Baxter, Deerfield, IL, USA), and Zemaira™ (ZLB Behring, King of Prussia, PA, USA). The preparations differ by the methods of viral activation with pasteurisation (Prolastin®, Zemaira™) or solvent detergent and nanofiltration techniques (Aralast™) and specific functional activity of AAT (e.g. <0.55mg and 0.7mg of functional $\alpha_1$-protease inhibitor per milligram of total protein in Aralast™ and Zemaira™, respectively).

## 4. Biochemical Characteristics and Effectiveness of AAT Augmentation Therapy

### 4.1 Biochemical Efficacy

Several studies have addressed the biochemical efficacy of intravenous AAT augmentation. In a landmark study in 1987, Wewers et al.[5] assessed the biochemical efficacy of a sterile lypophylised preparation of partially purified AAT obtained from pooled plasma from healthy donors (Prolastin®), and administered at a dosage of 60 mg/kg once weekly. Specifically, 21 subjects with the *PI*ZZ* deficiency received this drug weekly over 30 minutes for up to 26 weeks. An immediate sharp rise in serum AAT level (>300 mg/dL) was followed by a decline thereafter. Three weeks after the initiation of intravenous augmentation therapy, all 21 patients displayed serum trough AAT levels above the 11 μmol/L (80 mg/dL) protective threshold (figure 2). Furthermore, a 4-fold sustained increase in the AAT levels in the ELF was observed, as was a 2-fold increase in neutrophil elastase inhibition, an essential criterion for biochemical efficacy. Also, the stability of the serum half-life of 4.4 days over a 6-month period argued against any immune response or development of immune complexes. Finally, the lack of acute reactions or severe adverse effects following 507 infusions of AAT addressed the safety of the preparation.

Prompted by the desire for less frequent dose administration and, hence, fewer intravenous administrations, two later studies have examined longer dose administration intervals. The earlier study was conducted in 1988 by Hubbard et al.,[6] who administered 4-weekly infusions of purified pooled human plasma AAT. Specifically, AAT 250 mg/kg was administered at 28-day intervals to nine patients (eight *PI*ZZ*, one *PI*null null*) with AAT deficiency and emphysema over a 12-month period. Using 80 mg/dL as the threshold level of serum AAT below which the risk of emphysema is increased, the investigators showed the serum AAT level exceeded

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

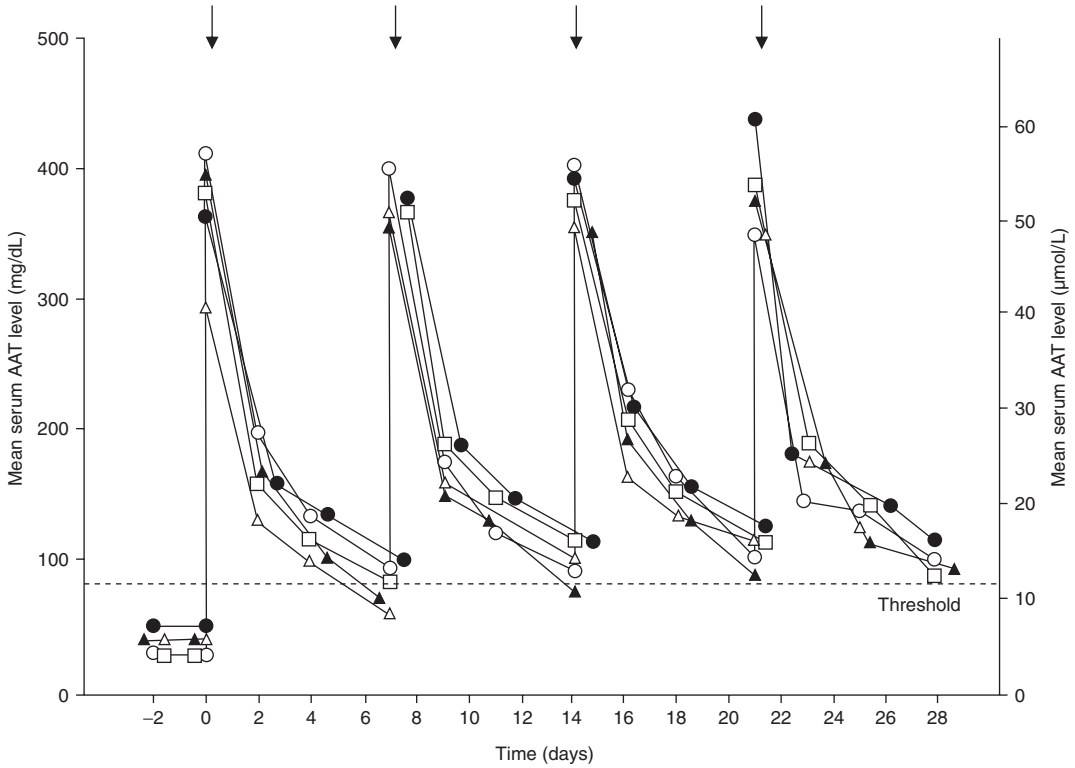


**Fig. 2.** Serum levels of $\alpha_1$-antitrypsin (AAT) following weekly infusions of 60 mg/kg of purified pooled human plasma AAT. Data shown for five AAT-deficient individuals (represented by five symbols) represent mean serum levels of AAT at day 0 (before infusion), 30 minutes, 2 days, 4 days and 7 days post-infusion. The broken line represents the epidemiologically established protective threshold. The left ordinate (mg/dL) represents the mass concentrations based on the commercial standard while the right ordinate (μmol/L) represents the molar concentrations based on the true laboratory standard (reproduced from Wewers et al.,[5] with permission. © 1987. Massachusetts Medical Society. All rights reserved).

the threshold for an average of 25 of 28 days (figure 3). More importantly, the ELF nadir level was 5-fold greater than the pre-infusion level and the neutrophil elastase inhibitory capacity of the nadir ELF was 3-fold above pre-infusion levels. Finally, and in agreement with the findings of Wewers et al.,[5] there were no significant adverse effects and no evidence for immunological responses. Assessment of pulmonary function in the study subjects showed no significant change in lung function as reflected by stable chest radiographs, ventilation/perfusion scans and forced expiratory volume in 1 second ($FEV_1$) values over the study period.

A study of biweekly intravenous AAT augmentation therapy was conducted by Barker et al.[32] in 1997. These investigators administered 120 mg/kg of purified pooled human AAT (Prolastin®) to 23 *PI*ZZ* patients. Each patient received ten infusions. Surprisingly, and in contrast to the studies cited earlier, nadir serum AAT levels were not maintained above the 11 μmol/L (80 mg/dL) protective threshold over the complete 14-day dose administration interval. On average, serum levels exceeded the protective threshold for 7 days of the 14-day dose administration interval. Furthermore, the ELF levels and the neutrophil elastase neutralising effects were low and correlated poorly with serum levels. Finally, $FEV_1$ showed no change over the 20-week follow-up period.

Data on biochemical efficacy are also available on a second pooled human plasma AAT product, Aralast™. In contrast to Prolastin®, which is puri-

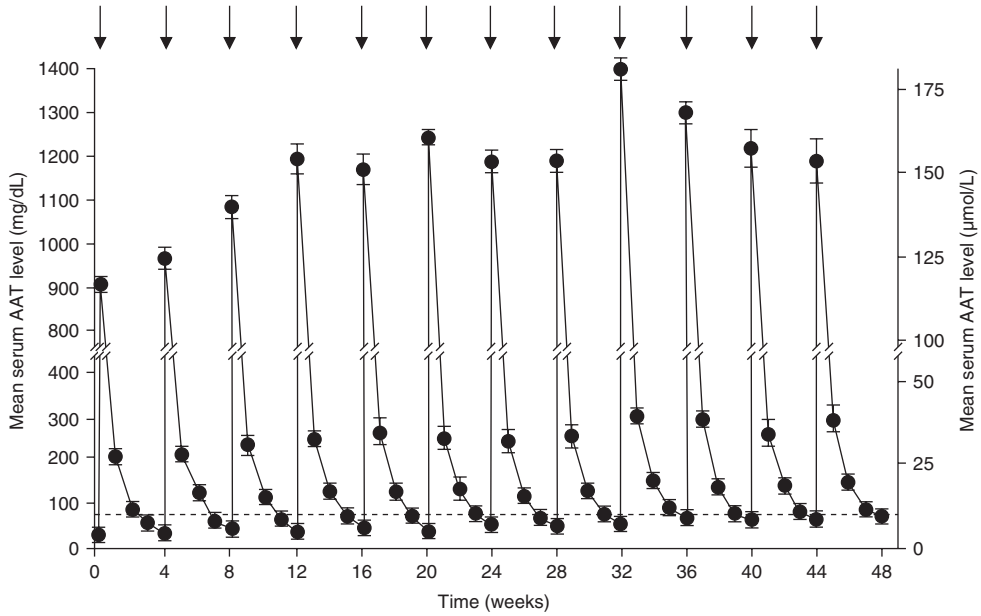


**Fig. 3.** Mean ± standard error of mean serum levels of $\alpha_1$-antitrypsin (AAT) following monthly intravenous infusions of 250 mg/kg of purified pooled human AAT. Peaks reflect serum levels 30 minutes post-infusion, and troughs represent levels at 28 days, just prior to the next infusion. The dashed line represents the epidemiologically established protective threshold. The left ordinate (mg/dL) represents the mass concentrations based on the commercial standard while the right ordinate (μmol/L) represents the molar concentrations based on the true laboratory standard (reproduced from Hubbard et al.,[6] with permission).

fied by pasteurisation, Aralast™ is purified by nanofiltration and solvent detergent techniques. The sole available clinical study is a randomised, double-blind controlled trial conducted in four centres to evaluate the bioequivalence of Aralast™ (called Respitin™ at the time of the study), to the comparator, Prolastin®.[7] A total of 28 patients were enrolled and 26 completed the study protocol, with half allocated to each group. After the initial 12-week, double-blind, random administration of Aralast™ and Prolastin®, an open-label follow-up was conducted during which all 26 study subjects received 60 mg/kg weekly infusions of Aralast™ from weeks 12 through 24. Overall, the study demonstrated bioequivalence of the two preparations. Specifically, the trough serum AAT levels between weeks 8 and 11 were similar between the two preparations, with an Aralast™ **:** Prolastin® ratio of 0.905 ($p = 0.026$) and the slope of the change in trough serum AAT level between weeks 12 and 24 at −0.003, well below the −0.1 slope criterion proposed (figure 4 and figure 5). Also, levels of urinary desmosine (a product of elastin breakdown) were similar in the two groups. Serum half-life estimates of Aralast™ and Prolastin® were determined by pharmacokinetic studies conducted in the first week of drug administration and were 5.7 and 5.0 days,

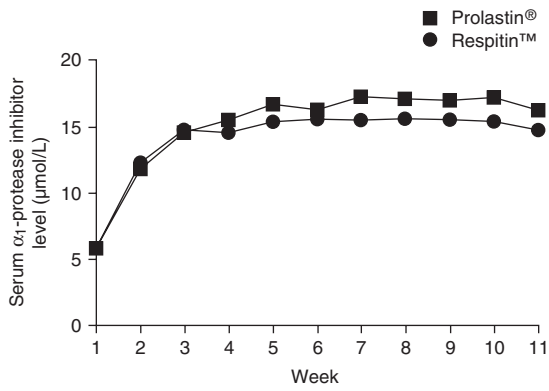


**Fig. 4.** Comparison of the serum $\alpha_1$-protease inhibitor levels following the intravenous administration of 60 mg/kg of active Respitin™ (n = 13) or Prolastin® (n = 13) over an 11-week period (reproduced from Stoller et al.,[7] with permission).

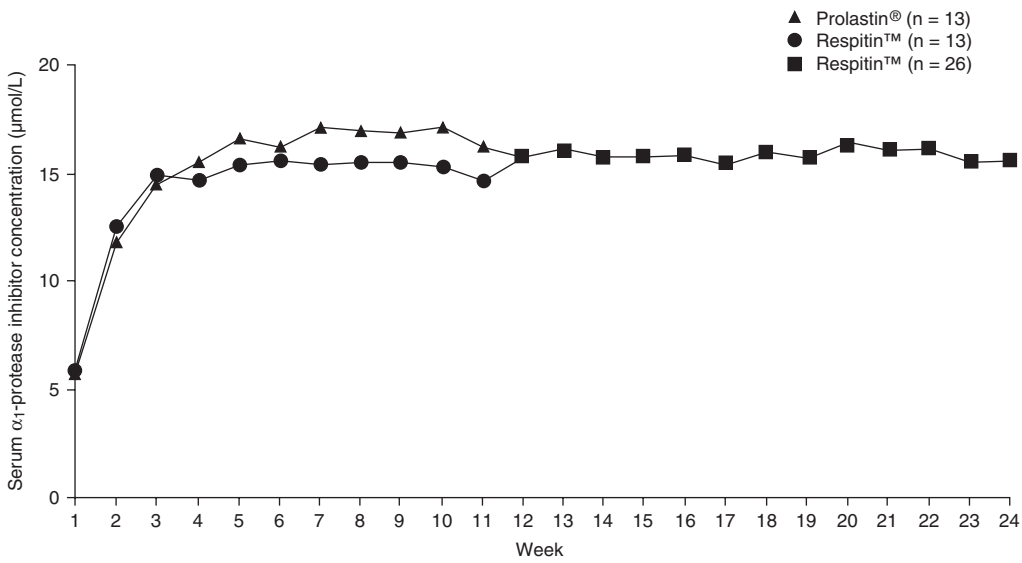


**Fig. 5.** Display of the serum $\alpha_1$-protease inhibitor levels comparing the intravenous augmentation with 60 mg/kg of active Respitin™ (n = 13) or Prolastin® (n = 13) during weeks 1–11, and weeks 12–24 during which all subjects received active Respitin™ (n = 26) [reproduced from Stoller et al.,[7] with permission).

respectively. More importantly, analysis of adverse effects and potential for antibody formation were similar between the two preparations and no serious adverse events were recorded with Aralast™ use. Overall, on the basis of this biochemical equivalence of Aralast™ to Prolastin®, Aralast™ received US FDA approval in December 2002. The third available pooled human plasma AAT preparation, Zemaira™, was approved by the US FDA on 8 July 2003. We are unaware of published studies regarding its biochemical and clinical profiles.

Overall, available studies satisfy criteria for the biochemical efficacy of intravenous AAT augmentation therapy with pooled human plasma AAT and have contributed to approval for their use by the US FDA. Other countries in which Prolastin® has received regulatory agency approval include Spain, Germany and Italy.

### 4.2 Clinical Efficacy

Regarding clinical efficacy, the primary outcome measures in available studies of intravenous AAT augmentation therapy range broadly and include the rate of $FEV_1$ decline, mortality rate, change in the frequency of infections, change in lung density on chest CT, as well as change in several inflammatory and degradation markers. As recently reviewed[33] and presented in table II, seven studies have addressed the clinical efficacy of intravenous AAT augmentation therapy.

The first such study by Seersholm et al.[34] was an observational cohort with concurrent controls that examined the rate of $FEV_1$ decline. Specifically, the study compared the rate of $FEV_1$ decline in 97 Danish ex-smokers with severe AAT deficiency not receiving AAT augmentation therapy to that of 198 German ex-smokers receiving weekly infusions of AAT 60 mg/kg. Overall, the rate of $FEV_1$ decline in the treated group was significantly lower than in the control group (−53 vs −75mL, $p = 0.02$). *Post hoc* analysis by strata of $FEV_1$ percentage predicted (i.e. <30%, 31–65% and >65% predicted) showed that a significant slowing in $FEV_1$ decline among augmentation therapy recipients was observed only in the subset with $FEV_1$ 31–65% predicted (−62 vs −83mL, $p = 0.04$).

In 1998, the National Heart, Lung, and Blood Institute Registry for Individuals with Severe Deficiency of AAT[35] reported results in the largest

**Table II.** Available studies on clinical efficacy of $\alpha_1$-antitrypsin augmentation therapy (reproduced from Stoller and Aboussouan,[33] with permission from the BMJ Publishing Group)

| Study (year) | Design | Outcome measures | Main results |
|---|---|---|---|
| Seersholm et al.[34] (1997) | Observational cohort, concurrent controls | $FEV_1$ decline | In patients with $FEV_1$ 31–65% of predicted, augmentation slowed the decline of $FEV_1$ by 21 mL/year |
| NHLBI Registry[35] (1998) | Observational cohort, concurrent controls | $FEV_1$ decline and survival | In patients with $FEV_1$ 35–49% of predicted, augmentation slowed the decline of $FEV_1$ by 27 mL/year. Risk ratio for death with augmentation was 0.64 compared with non-recipients |
| Dirksen et al.[31] (1999) | Randomised controlled trial | $FEV_1$ decline lung density (by CT) | Loss of lung tissue was 2.6 g/L/year with placebo and 1.5 g/L/year with augmentation |
| Gottlieb et al.[36] (2000) | Descriptive | Urinary desmosine | Augmentation did not reduce the rate of elastin degradation |
| Lieberman[37] (2000) | Observational (web-based survey) | Frequency of lung infections | The number of lung infections per year decreased from 3–5 pre-augmentation to 0–1 post-augmentation |
| Wencker et al.[38] (2001) | Observational (before-after therapy) | $FEV_1$ decline | Rates of $FEV_1$ decline pre- and post-augmentation were 49.2 vs 34.2 mL/year, respectively |
| Stockley et al.[39] (2002) | Descriptive | Sputum inflammatory markers | Augmentation reduced sputum leukotriene B4 |

**$FEV_1$** = forced expiratory volume in 1 second; **NHLBI** = National Heart, Lung, and Blood Institute.

cohort of individuals in whom augmentation therapy was evaluated. Specifically, of 1129 enrolees, the 747 who ever received augmentation therapy showed a decreased mortality rate compared with non-recipients (relative risk 0.64, $p = 0.02$). Predictors of an accelerated decline of $FEV_1$ included male gender, age 30–44 years, current smoking, $FEV_1$ between 35% and 79% of predicted and bronchodilator responsiveness. Although the rate of $FEV_1$ decline was not statistically different between augmentation therapy recipients and the non-recipients overall, subgroup analysis showed that $FEV_1$ decline slowed significantly (by 27 mL/year, $p = 0.03$) in augmentation therapy recipients with ATS stage II COPD ($FEV_1$ 35–49% of predicted). As amply pointed out by the investigators, the results of this observational study require cautious interpretation in the context that confounding baseline differences between the treatment and non-treatment groups (e.g. socioeconomic status, etc.) could contribute to differences in outcomes between the groups.

In 1999, Dirksen et al.[31] conducted the only randomised, double-blind, placebo-controlled trial to date of AAT augmentation therapy. In this study, 56 patients with the *PI**ZZ phenotype were randomly allocated to two groups, the first of which received 250 mg/kg of AAT augmentation therapy at 4-weekly intervals over at least 3 years, while the other group received monthly placebo (albumin) infusions. Although no difference in the rate of $FEV_1$ decline was observed between augmentation and placebo recipients, a trend toward slower loss of lung tissue (by CT scan) in augmentation therapy recipients was evident ($p = 0.07$).

Several additional observational studies have more recently addressed the clinical efficacy of augmentation therapy. For example, Gottlieb et al.[36] showed that urine desmosine, a product of elastin breakdown, did not change after beginning augmentation therapy in 12 individuals.

In another observational study, Lieberman[37] conducted a web-based survey of the frequency of patient-reported lung infections in AAT augmentation therapy recipients versus non-recipients. In analysing responses from 143 *PI**ZZ patients (96 receiving augmentation therapy and 47 not receiving therapy) regarding the subjective benefits and the incidence of lung infections, Lieberman reported that patients receiving augmentation therapy noted significantly fewer lung infections ($p < 0.001$). Al-

so, the percentage of non-recipient patients who reported experiencing more than two infections per year was significantly higher than the frequency in AAT augmentation therapy recipients (55% vs 18%, $p < 0.001$).

More recently, Wencker et al.[38] retrospectively assessed the rate of decline of $FEV_1$ in patients before versus after starting AAT augmentation therapy. Ninety-six patients with severe AAT deficiency (serum level <35% of normal) and moderate airflow obstruction (mean $FEV_1$ 41% of predicted) showed a reduced rate of $FEV_1$ decline on augmentation therapy compared with baseline (−34.2 vs −49.2mL, $p = 0.019$). Subgroup analysis showed that the greatest slowing in the rate of $FEV_1$ decline on augmentation therapy occurred in subjects with baseline $FEV_1$ >65% of predicted (−49 vs −123mL, $p = 0.045$), as well as in those patients whose $FEV_1$ fell below 65% prior to starting augmentation therapy.

Finally, Stockley et al.[39] measured markers of neutrophilic inflammation including IL-8, myeloperoxidase, elastase and leukotriene B4 (LTB4) and AAT serum levels in individuals receiving augmentation therapy. In showing a reduction in sputum elastase activity ($p < 0.002$) and LTB4 levels ($p < 0.02$), the results supported the clinical efficacy of AAT augmentation therapy.

Overall, notwithstanding the lack of definitive evidence from a randomised controlled trial, the weight of evidence supports the clinical efficacy of intravenous AAT augmentation therapy, at least in selected groups. On this basis, available standards documents from the Canadian Thoracic Society[29,40] and from the ATS and the ERS[4] endorse selected use of AAT augmentation therapy. Specifically, in the recent ATS/ERS standards document, the executive summary states: "The Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency. Evidence that augmentation therapy confers benefit (e.g. slowed rate of $FEV_1$ decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g. $FEV_1$ 35–60% of predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (e.g. $FEV_1$ ≤35% of predicted) or mild (e.g. $FEV_1$ ≥50–60% predicted) airflow obstruction are less clear".[4] Because active smoking both increases the elastase burden to the lungs and may partially inactivate infused AAT, some clinicians recommend offering augmentation therapy only to confirmed current nonsmokers.[40]

## 5. Adverse Effects of AAT Augmentation Therapy

Adverse effects of intravenous infusion of purified pooled human plasma AAT have been evaluated in two large observational studies. The first study was conducted by Wencker et al.[41] in 1998 and described 124 adverse events in 65 patients (out of a total of 443 patients followed-up). The majority of these adverse effects were mild and self-limited, including nausea and vomiting (21 [4.7%]), urticaria (18 [4.1%]), fever/chills (17 [3.8%]), dyspnea (13 [3%]) and fatigue (7 [1.6%]). Only five adverse events (four anaphylactic and one congestive heart failure) prompted an intervention and three patients had to discontinue intravenous augmentation therapy because of recurrent post-infusion fever and chills. Importantly, there were no reports of viral transmission (HIV or hepatitis) or deaths.

The second observational study conducted by Stoller et al.[42] reported 720 adverse events with AAT augmentation therapy in 174 patients (out of a total of 747 patients followed-up). The most common symptoms reported were headache (339 [47.1%]), dizziness (121 [16.8%]), nausea (64 [8.9%]), dyspnea (61 [8.5%]), chills (54 [7.5%]) and fever (53 [7.4%]). Using a severity-based classification scheme, 63 (8.8%) of adverse events were deemed severe, 521 (72.4%) moderate and 136 (18.9%) mild. On the basis of a consequence-based scheme that classified events by whether they led to an emergency room (ER) visit or hospitalisation, a physician's visit and/or medication administration, or augmentation therapy discontinuation, a minority of reactions (172 [23.8%]) elicited a response. Only

12 (1.7%) resulted in an ER visit or hospitalisation and 8 (1.1%) resulted in the discontinuation of augmentation therapy. The rate of adverse events associated with varying dosage frequencies (i.e. weekly, fortnightly, monthly, etc.) was found to be higher among patients receiving weekly infusions (0.03 events per patient-month) than among those treated with other frequencies. Still, the absolute rate of adverse events was very low (i.e. two events over 5 years of therapy).

## 6. Cost Effectiveness of Intravenous AAT Augmentation Therapy

In the current climate of rising healthcare costs, cost effectiveness and affordability of medications have become important determinants of whether medications should and will be used. In the case of intravenous augmentation therapy with pooled human plasma AAT, Stoller et al.[42] reported that 30% of severely AAT-deficient individuals not receiving intravenous augmentation therapy cited financial constraints as the main impediment to use.

The costs of AAT augmentation therapy have been estimated to be $US54 765 per year (2001 value).[43] As summarised in table III, further analysis of cost effectiveness of intravenous augmentation has been undertaken in three available studies.[43-45] The most recent estimates suggest that, while current augmentation therapy does not satisfy conventional criteria for cost effectiveness, continued current use is recommended by its being the only currently available specific therapy for severe AAT deficiency.

## 7. Conclusion

Intravenous AAT augmentation therapy remains the only US FDA-approved treatment option for patients with severe AAT deficiency. New and evolving approaches,[47] including administration of recombinant-produced AAT, delivery by inhalation,

**Table III.** Comparison of cost-effectiveness studies of intravenous augmentation therapy for patients with $\alpha_1$-antitrypsin deficiency

| Study | Estimate of cost effectiveness | Comments |
|---|---|---|
| Hay and Robin[44] | Life expectancy is based on the study by Larsson[46]<br>Outcome efficacy is hypothetical with estimates over a wide range<br>Outcome index is CLYS<br>Healthiness weight is set at 75% of normal | First cost-effectiveness study<br>At 30% efficacy, the CLYS ranged between $US50 000 and $US128 000 (1990 value)<br>Cost found comparable to other medical interventions<br>Differences in cost and QOL between health states were not considered<br>Predicted a greater increase in life expectancy and a lower CLYS to active smokers<br>Cost of augmentation estimated at $US30 000/year (1990 value) |
| Alkins and O'Malley[45] (NHLBI Registry) | Life expectancy is based on DEALE<br>Outcome efficacy is estimated to be 55% based on NHLBI Registry data<br>Outcome index is ICYLS<br>Healthiness weight is not included | DEALE assumes a constant death rate<br>At 55% efficacy, the ICYLS for patients with $FEV_1$ <50% is estimated at $US13 971<br>The study does not account for changes in QOL between disease states<br>The expense of treatment for COPD besides augmentation therapy is not taken into account<br>Cost of augmentation estimated at $US51 940/year (1998 value)<br>Assumed that augmentation would be used for 5 years, but spread cost over the entire expected benefit interval of 18 years |
| Gildea et al.[43] (NHLBI Registry) | Life expectancy is based on a Markov analytical model<br>Outcome efficacy is based on NHLBI registry data<br>Outcome indices are QALY and ICER<br>Healthiness weight is based on COPD stage and varies between 93% and 26% of normal | ICER for lifetime therapy per QALY gained is estimated at $US312 511 (2001 value)<br>Study includes the cost of therapy for COPD other than augmentation<br>Cost of augmentation estimated at $US54 765 (2001 values) |

**CLYS** = cost per life-year saved; **COPD** = chronic obstructive pulmonary disease; **DEALE** = declining exponential approximation of life expectancy; **$FEV_1$** = forced expiratory volume in 1 second; **NHLBI** = National Heart, Lung, and Blood Institute; **ICER** = incremental cost-effectiveness ratio; **ICYLS** = incremental cost per year of life saved; **QALY** = quality-adjusted life-year; **QOL** = quality of life.

small molecule neutrophil elastase inhibitors and gene therapy, offer promising prospects for treating individuals with severe AAT deficiency.

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