

## opinions/hypotheses

# Augmentation Therapy Reduces Frequency of Lung Infections in Antitrypsin Deficiency\*

## A New Hypothesis With Supporting Data

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**Study objectives:** To propose an hypothesis that antiprotease augmentation therapy reduces the incidence of lung infections in  $\alpha_1$ -antitrypsin (AAT)-deficient patients, and to present supporting data.

**Design:** The proposed concept is based on a survey taken via the Internet of patients receiving augmentation therapy for 1 to 10 years compared to similar patients not receiving such therapy.

**Setting:** A questionnaire was submitted to patients with a ZZ phenotype for AAT deficiency to determine whether those receiving antitrypsin augmentation therapy were aware of any personal benefit, and whether the therapy had an effect on the frequency of lung infections.

**Patients:** Ninety-six adult patients receiving human  $\alpha_1$ -proteinase inhibitor ( $\alpha_1$ -PI) responded, as did 47 similar patients not receiving augmentation therapy.

**Results:** Seventy-four of 89 patients who had received  $\alpha_1$ -PI infusions for > 1 year believed that they had definitely benefited from such therapy. Fifty-six of the 74 patients claiming a benefit attributed this to a reduction in the number of lung infections since starting therapy with  $\alpha_1$ -PI infusions. Before starting  $\alpha_1$ -PI, the majority of patients had three to five infections per year, dropping to zero to one infection per year during  $\alpha_1$ -PI therapy ( $p < 0.001$ ).

**Conclusions:** Replacement therapy for AAT deficiency-associated emphysema appears to be associated with a marked reduction in the frequency and severity of lung infections. This association must be evaluated further in future, more rigid, prospective studies of AAT augmentation therapy. Findings support the hypothesis that antiprotease therapy with  $\alpha_1$ -PI reduces the incidence of lung infections in addition to slowing the deterioration of lung function and causing a reduction in mortality. (CHEST 2000; 118:1480-1485)

**Key words:** antitrypsin; augmentation therapy; emphysema; infections;  $\alpha_1$ -proteinase inhibitor

**Abbreviations:** AAT =  $\alpha_1$ -antitrypsin;  $\alpha_1$ -PI = human  $\alpha_1$ -proteinase inhibitor

The discovery of  $\alpha_1$ -antitrypsin (AAT) deficiency in 1963 has led to an understanding of the mechanism whereby lung damage takes place in the pathogenesis of pulmonary emphysema. A genetic deficiency of this blood protein is strongly associated with a predisposition to the development of emphysema and, in some instances, to chronic bronchitis or bronchiectasis.<sup>1</sup> The association of lung

disease with the severe deficiency state (*ie*, homozygous ZZ phenotype) is widely accepted, and an association with the intermediate deficiency state (*ie*, heterozygous MZ phenotype) is now receiving wider acceptance, especially when it is present in cigarette smokers.<sup>2-4</sup> Even though the severe deficiency has been reported in only 2 to 8% of emphysema patients,<sup>2,3</sup> and the intermediate deficiency has been reported in 8 to 18% of such patients, the same mechanism for lung damage involving proteolytic enzymes is now believed to take place in essentially all patients with pulmonary emphysema.

Knowledge of this enzymatic pathway for the development of pulmonary emphysema has led to a

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potential therapy utilizing antitrypsin augmentation via the infusion of human  $\alpha_1$ -proteinase inhibitor ( $\alpha_1$ -PI; Prolastin; Bayer Pharmaceuticals; West Haven, CT) extracted from human blood plasma.<sup>5-7</sup> Such therapy was devised and approved with the knowledge that the infusions were safe and would raise the blood level of AAT to at least that usually found in heterozygotes for the genetic defect (commercial standard,  $> 80$  mg/dL) with a transient increase to a high level of approximately 400 mg/dL and an associated increase of AAT in fluid of the lung epithelial lining. A blind study to confirm the clinical benefit of replacement therapy was not undertaken by the developers of augmentation therapy, because it would have been exceedingly costly and difficult. However, beginning in 1988, a National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of  $\alpha_1$ -Antitrypsin was set up for those patients receiving  $\alpha_1$ -PI infusions as well as for untreated AAT-deficient patients; this was not a randomized study. These patients had been followed up by the registry for 3.5 to 7 years with spirometry measurements every 6 to 12 months<sup>8</sup> when an evaluation revealed that subjects receiving augmentation therapy had a decreased mortality rate compared to those not receiving therapy. In addition, subjects with a mean FEV<sub>1</sub> of 35 to 49% of predicted showed an FEV<sub>1</sub> decline that was significantly slower for subjects receiving augmentation therapy than for those not receiving such therapy.

The major concept behind augmentation therapy for AAT deficiency has been that a rise in the level of AAT in blood and tissues would protect the lung from continued destruction by blood and tissue proteases (*ie*, primarily leukocyte elastase). The observed reductions in mortality and in FEV<sub>1</sub> decline reported by the registry suggest that this may indeed be taking place. Neither the National Heart, Lung, and Blood Institute Registry, nor other similar studies in Denmark and Germany,<sup>9,10</sup> ever focused in on the possibility that augmentation therapy might have an effect on the incidence of lung infections.

I now present a new hypothesis regarding antitrypsin augmentation therapy; the concept is that such therapy reduces the incidence of lung infections in antitrypsin-deficient patients receiving infusions of  $\alpha_1$ -PI. This hypothesis was developed when a few so-called "Alphas" (*ie*, patients with a ZZ phenotype) participating in the  $\alpha_1$  Internet List reported that they experienced a reduction in the number and severity of respiratory infections since starting augmentation therapy with  $\alpha_1$ -PI. I was familiar with the literature suggesting that  $\alpha_1$ -antitrypsin had an immunosuppressive action,<sup>11</sup> that trypsin inhibitors had been shown to have an antibiotic action,<sup>12</sup> and that antiproteases were effective in

the treatment of HIV infections.<sup>13</sup> It is also well-known that AAT normally is an "acute-phase reactive" protein the blood level of which increases during infections or other inflammatory, estrogenic, or neoplastic states. Therefore, I postulated that a rise of antiprotease levels in blood may play an important role in resistance to infection in AAT-deficient subjects.

To further investigate this hypothesis, a questionnaire was prepared that was directed toward subjects with a ZZ phenotype receiving augmentation therapy with  $\alpha_1$ -PI, and another questionnaire was prepared for those subjects with the same phenotype who were not receiving augmentation therapy. In this report, I will present the following data that were obtained from these questionnaires: (1) the percentage of patients receiving  $\alpha_1$ -PI who feel that they have benefited from therapy; (2) the impressions of these patients as to how they benefited; and (3) the frequency of respiratory infections per year before starting replacement therapy and since starting such therapy compared to a group of similar patients who never received  $\alpha_1$ -PI infusions. The findings of these surveys suggest that a reduction in the frequency of respiratory infection may be a major effect of augmentation therapy with  $\alpha_1$ -PI for AAT deficiency-related emphysema. This was not a survey of the general AAT-deficient population but, rather, was a survey only of patients enrolled in an international Internet support group. There is a possibility that the sampling method may have introduced biases into the conclusions. However, few of the patients involved in the study were actually aware of the interest in a potential effect of  $\alpha_1$ -PI on the frequency of lung infections, and the questionnaire contained many unrelated questions dealing with other types of health problems associated with AAT deficiency.

## MATERIALS AND METHODS

### *Patients*

Patients were recruited through announcements on the  $\alpha_1$  Internet List. The appropriate questionnaires were made available to all participants on the list and were then returned by the responders by private e-mail to one person who sorted the replies and forwarded them to Dr. Lieberman for evaluation.

### *Questionnaires*

The questionnaires prepared for ZZ patients who were participants on the  $\alpha_1$  Internet List included information on sex, age, and age when patients had received a diagnosis of AAT, as well as on smoking history. For those receiving  $\alpha_1$ -PI infusions, the year of starting such infusions and the frequency of the infusions was elicited. Key questions dealt with the frequency per year of

respiratory infections before starting  $\alpha_1$ -PI therapy and since starting  $\alpha_1$ -PI therapy, whether the subject felt that he or she had benefited from receiving augmentation therapy, and the reasons for their conclusions. (Patients defined lung infections as increased cough and sputum production, usually with a change of sputum color, oftentimes with fever, and usually requiring antibiotics and, possibly, hospitalization.)

Similar questions were asked of ZZ patients who were not receiving augmentation therapy, but questions dealing with  $\alpha_1$ -PI usage were eliminated. A question was included as to why the patient was not receiving augmentation therapy.

#### Informed Consent

Informed consent was implied through the voluntary response and submission by each participant of a completed questionnaire. The potential use of the tabulated information in a publication was expressed in the original request for volunteers that had been viewed by all participants.

#### Statistical Analysis

A statistical comparison of the frequency of lung infections was made by  $\chi^2$  test between the untreated ZZ subjects (group II) and the treated subjects (group I) before and during  $\alpha_1$ -PI therapy.  $\chi^2$  analysis employed a two-column and two-row setup, dividing the two groups into those with less than two lung infections per year and those with two or more infections per year. The choice of two lung infections per year as the dividing point for comparison was based on the obvious change in distribution of lung infections per year resulting from  $\alpha_1$ -PI use (Fig 1). Statistical calculations using three lung infections for the separation of these groups gave similar  $\chi^2$  results.

## RESULTS

Questionnaires were filled out and submitted by 96 adult patients with homozygous ZZ AAT defi-

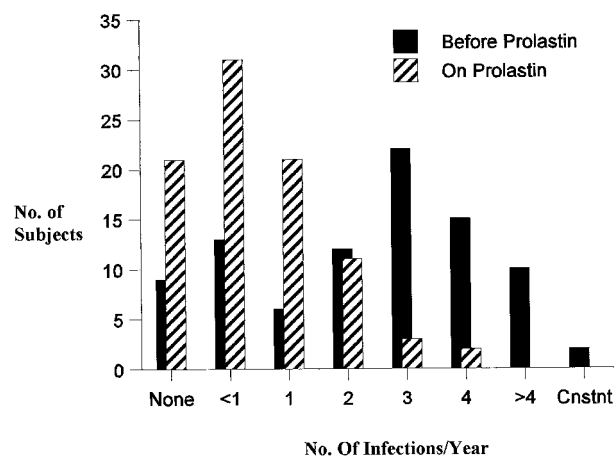


FIGURE 1. The effect of augmentation therapy with  $\alpha_1$ -PI (Prolastin) on the number of respiratory infections experienced by AAT-deficient patients (ZZ phenotype). The distribution of lung infections per year is shown for patients prior to starting  $\alpha_1$ -PI augmentation therapy and since starting  $\alpha_1$ -PI therapy. All ZZ phenotype patients receiving  $\alpha_1$ -PI, whether they benefited or not, are shown (group I) ( $n = 89$ ).

ciency (this includes one patient of SZ phenotype) who were receiving  $\alpha_1$ -PI replacement therapy (group I). This group included 50 men and 46 women. The age range for men was 36 to 67 years (median age, 50 years), and the age range for women was 33 to 72 years (median age, 53 years). The age range at which a diagnosis of AAT deficiency was made for men was 28 to 66 years (median, 40 years), and the age range for women was 31 to 65 years (median, 42 years).

All of the 50 men in group I had been moderate to heavy smokers who quit smoking soon after developing lung symptoms. Of the 46 women in this group, 43 had been smokers and 3 had never smoked. One of the women who had never smoked submitted that she had lived in an environment with heavy exposure to second-hand smoke.

A second group included 47 adult ZZ patients not receiving  $\alpha_1$ -PI (group II); 24 were men (age range, 37 to 70 years; median age, 55 years) and 23 were women (including one woman with SZ phenotype) [age range, 33 to 67 years; median age, 45 years].

Of the 47 subjects in group II, 12 had never smoked. Despite not smoking, one of the subjects was receiving 2 L/min of oxygen for emphysema, one subject had chronic bronchitis, one subject had had bronchiectasis since childhood, and nine subjects were asymptomatic of any lung disease. Asymptomatic ZZ subjects discovered their involvement during family studies in which another member of the family had a lung problem. None of the smokers in this group II was asymptomatic; one person is on the waiting list for a lung transplant.

There was a significant difference between group I and group II ( $\chi^2$  test) in the number of nonsmokers that each group contained ( $\chi^2 = 15$ ;  $p < 0.001$ ). This difference did not appear to affect the results of this study since it was primarily due to the increased number of nonsmokers in group II, and if it caused any bias, it would have lessened the significance of the reduced number of lung infections in group I (*ie*, patients receiving  $\alpha_1$ -PI therapy).

Of the estimated 300 members of the Alpha Internet List with a ZZ phenotype, 143 (48%) responded by filling out a questionnaire. Three hundred is only an estimate of the total number of members on the list with ZZ phenotypes, since there are some members who remain registered but have become inactive and have ceased to participate actively, as well as a growing number of patients undergoing lung transplantation, which would remove them from this type of study. There is also considerable turnover in membership due to deaths, resignations, and new members. Control of the list is in the hands of volunteers, so there is no continuing attempt to classify the membership.

### Group I: Effects of $\alpha_1$ -PI Infusions

The frequency of  $\alpha_1$ -PI infusions differed among patients receiving such therapy. Fifty-four were receiving weekly infusions, 35 were receiving biweekly infusions, and 7 were receiving monthly infusions. Their total dose of  $\alpha_1$ -PI had been adjusted accordingly to equal 60 mg/kg as a weekly dose.

Seven patients had been receiving  $\alpha_1$ -PI for < 1 year; their opinions regarding the benefit they had received from therapy were omitted from the evaluations in the belief that their involvement with therapy was too brief to allow meaningful replies. The extent of  $\alpha_1$ -PI therapy for the remaining 89 patients ranged between 1 and 10 years.

Seventy-four of 89 patients (83.1%) who had received  $\alpha_1$ -PI infusions for > 1 year believed that they had definitely benefited. Twelve did not know whether they had benefited, and 3 believed that they had not received benefit. Fifty-six of the 74 patients who claimed benefit from replacement therapy attributed this to the fact that the yearly number of lung infections had dropped during therapy (Fig 1). Since starting  $\alpha_1$ -PI therapy, the number of patients with zero to one infection per year rose from 27 to 73 patients, and the percentage having two or more infections per year dropped from 64.6 to 18% ( $p < 0.001$ ;  $\chi^2$ ; Table 1). Many believed that they recovered from head colds and flu more rapidly without developing an overwhelming lung infection as had happened prior to starting  $\alpha_1$ -PI therapy. Most of those not claiming a benefit because of a reduced number of lung infections had no infections to begin with.

Since a questionnaire survey of patients is by nature subjective, it was of interest to read the actual statements made by patients supporting their opinion about the effectiveness of  $\alpha_1$ -PI. The majority of

the statements referred to the reduction in the number of infections, such as the following: "Fewer infections, general health better"; or "Less lung infections and less phlegm production"; or "Rate of infection dropped"; or "No lung infections since  $\alpha_1$ -PI."

### Group II: ZZ Not Receiving $\alpha_1$ -PI

**Frequency of Lung Infections:** The number of lung infections per year for this group (never  $\alpha_1$ -PI group; Fig 2) resembled that seen for the ZZ patients in group I prior to starting  $\alpha_1$ -PI therapy, except for a somewhat larger proportion with zero to one infection per year in group II. In group II, 21 subjects (43%) had zero to one infection per year, whereas in group I, 28 subjects (32%) had zero to one infection per year prior to starting  $\alpha_1$ -PI therapy.

**Statistical Analysis:** A statistical comparison of the two groups of patients (group II [never  $\alpha_1$ -PI] vs group I [while receiving  $\alpha_1$ -PI]), comparing less than two infections per year to two or more infections per year, showed a significant difference ( $p < 0.001$ ;  $\chi^2 = 18.854$ ). The use of less than three infections per year vs three or more infections per year gave a somewhat lower  $\chi^2$  of 13.570 although still significant ( $p < 0.001$ ). There was no significant difference between group II and the pre- $\alpha_1$ -PI data of group I ( $\chi^2 = 2.635$ ; the difference was not significant).

**Reasons for Not Using  $\alpha_1$ -PI:** The following is a summary of the reasons for not using  $\alpha_1$ -PI given by patients with ZZ phenotypes in group II:

1. It was not available in the patient's country: Australia, three patients; England, five patients; Sweden, one patient; Netherlands, one patient;

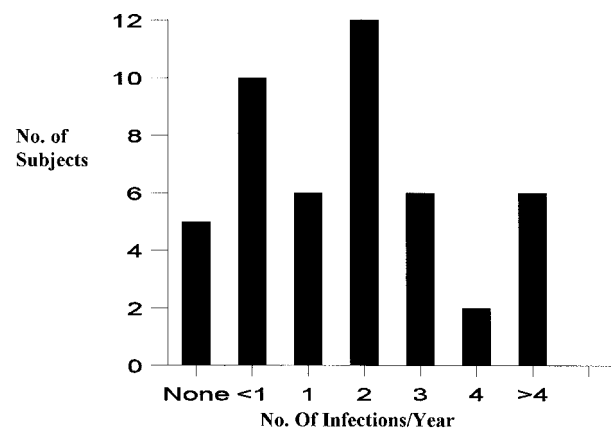
**Table 1—Number of Patients With Less Than Two, or Two or More, Lung Infections per Year in Groups I and II\***

Group†	Lung Infections, No./yr		
	< 2	≥ 2	Median
Group I			
Before $\alpha_1$ -PI	27	62 (64.6)	3–5
While receiving $\alpha_1$ -PI	73	16 (18)	0–1
Group II			
Never received $\alpha_1$ -PI‡	21	26 (55.3)	3–5

\*Data are presented as No. of patients (%).

† $p < 0.001$  for group I (before  $\alpha_1$ -PI) vs group I (receiving  $\alpha_1$ -PI), and group I (receiving  $\alpha_1$ -PI) vs group II. Comparison of group I (before  $\alpha_1$ -PI) vs group II was not significant.

‡Two patients in this group had started  $\alpha_1$ -PI therapy but stopped due to allergic reactions.



**FIGURE 2.** The distribution of lung infections per year is shown for AAT-deficient patients who are not receiving  $\alpha_1$ -PI augmentation therapy ( $n = 47$ ).

Denmark, one patient; Canada, three patients ( $\alpha_1$ -PI is available with private insurance in Canada); and New Zealand, one patient.

2. I do not want  $\alpha_1$ -PI, seven patients.
3. I am asymptomatic, five patients.
4. Cost and need for making financial arrangements, four patients.
5. In the process of arranging for use of  $\alpha_1$ -PI, three patients.
6. Not recommended by doctor, three patients.
7. Allergic to the  $\alpha_1$ -PI, two patients.
8. I have cirrhosis from AAT deficiency, one patient.
9. Not sure of its value, one patient.
10. Never heard of it, one patient.
11. Current shortage of  $\alpha_1$ -PI, two patients.

One patient received  $\alpha_1$ -PI for 3 years but developed a severe allergy to the preparation (*ie*, peppery metallic taste in mouth, skin rash on body, swelling of tongue, and rise in BP). These same symptoms resulted after four tries at infusing  $\alpha_1$ -PI. The patient says that she had fewer lung infections while receiving  $\alpha_1$ -PI, but cannot use it anymore because of the allergy. She now has approximately five infections per year.

## DISCUSSION

The results of studies conducted by means of a questionnaire survey directed to patients with AAT deficiency, who had ZZ phenotype and were participating in the  $\alpha_1$  Internet List, suggest that augmentation therapy with  $\alpha_1$ -PI is associated with a marked reduction in the frequency of lung infections in the majority of patients. Most patients reported a frequency of three to five infections per year before starting  $\alpha_1$ -PI therapy, which dropped to zero to one infection per year while receiving  $\alpha_1$ -PI. In two patients with a prior history of continuous lung infections,  $\alpha_1$ -PI therapy was associated with the complete absence of infection in one patient and with one to two infections per year in the second.

The results of this study support the hypothesis that augmentation therapy with  $\alpha_1$ -PI reduces the incidence of lung infections in patients with AAT-related emphysema. It is possible that the reduction in the rate of infection is coincidental with other ancillary-care measures adopted in the treatment of pulmonary emphysema. However, it is unlikely that increased contact with a physician when receiving  $\alpha_1$ -PI infusions contributes to better health, since most patients either self-infuse their  $\alpha_1$ -PI or have a visiting nurse set up the infusions. The association of  $\alpha_1$ -PI administration and a reduced incidence of lung infections is so striking that I believe its possible

role in this therapy must be noted so that future, more rigid, prospective studies in this field will look for a reduction of infection rate as a potential benefit. This should be evaluated especially when infusion therapy with purified human AAT is compared to the inhaled form of the same or similar material. Will inhaled therapy offer the same protection against lung infections, or is a systemic mode of administration necessary for this effect? Cantin and Woods<sup>14</sup> have reported that aerosolized  $\alpha_1$ -PI suppresses bacterial proliferation in a rat model of chronic *Pseudomonas aeruginosa* lung infection. This supports the concept of an antibacterial effect from  $\alpha_1$ -PI and suggests that inhaled medication may be effective. Their study did not explore such action against other, more common, bacterial agents found in AAT-deficient patients.

The mechanism whereby AAT protects the patient against recurrent lung infections may involve both a direct antibacterial action of AAT and an anti-inflammatory, anti-immune response action of AAT. A deficiency of AAT also may thereby promote excessive inflammatory responses to minimal insults, and a predisposition to autoimmune diseases, as has been reported for rheumatoid arthritis, anterior uveitis, systemic lupus erythematosus, and asthma.<sup>15</sup>

Emphysema is not reversible, but a reduction in the number and severity of lung infections would contribute considerably to patient comfort and well-being, and would lead to a reduction of the load of intrapulmonary leukocyte elastase, which should reduce the rate of progression of the emphysematous process.

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## APPENDIX: QUESTIONNAIRE USED FOR GROUP I PATIENTS RECEIVING $\alpha_1$ -PI AUGMENTATION THERAPY

Questions for group II patients are the same as those for group I, except for questions dealing with  $\alpha_1$ -PI. The questions that were eliminated were Nos. 4, 5, 6, 11a, 11b, 11c, 12a, 12b, and 12c. Questions added were Nos. 11 and 12.

1. Sex
2. Age
3. Age when diagnosed AAT deficient
4. Date started on  $\alpha_1$ -PI
5. How often do you receive  $\alpha_1$ -PI infusion?
6. How do you receive the infusion (hospital, doctor's office, home, other)?

7. In addition to emphysema, do you have asthma?
8. Do you have allergies?
9. Do you have chronic bronchitis or bronchiectasis?
- 10a. Have you smoked cigarettes? Average No. of packs per day?
- 10b. Age when started smoking
- 10c. Age when quit smoking
11. For group I: How many lung infections do you average per year?
- 11a. Frequency of lung infections before starting  $\alpha_1$ -PI infusions (infections per year)
- 11b. Frequency of lung infections since starting  $\alpha_1$ -PI infusions (infections year)
- 11c. Have you had episodes of collapsed lung before and/or after starting  $\alpha_1$ -PI infusions?
12. For group II: reason for not utilizing  $\alpha_1$ -PI?
- 12a. Do you find that use of  $\alpha_1$ -PI has benefited you?
- 12b. If yes, in which way?
- 12c. Additional comments regarding use of  $\alpha_1$ -PI
- 13a. Are you still able to keep your job?
- 13b. Age when you had to stop working
- 14a. Have you applied for a lung transplant?
- 14b. Are you accepted for a lung transplant?
15. Are you on oxygen? Continuous? With exertion only? Hours per day?

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