Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial

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Summary

Background The efficacy of α1 proteinase inhibitor (A1PI) augmentation treatment for α1 antitrypsin deficiency has not been substantiated by a randomised, placebo-controlled trial. CT-measured lung density is a more sensitive measure of disease progression in α1 antitrypsin deficiency emphysema than spirometry is, so we aimed to assess the efficacy of augmentation treatment with this measure.

Methods The RAPID study was a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial of A1PI treatment in patients with α1 antitrypsin deficiency. We recruited eligible non-smokers (aged 18–65 years) in 28 international study centres in 13 countries if they had severe α1 antitrypsin deficiency (serum concentration <11 μM) with a forced expiratory volume in 1 s of 35–70% (predicted). We excluded patients if they had undergone, or were on the waiting list to undergo, lung transplantation, lobectomy, or lung volume-reduction surgery, or had selective IgA deficiency. We randomly assigned patients (1:1; done by Accovion) using a computerised pseudorandom number generator (block size of four) with centre stratification to receive A1PI intravenously 60 mg/kg per week or placebo for 24 months. All patients and study investigators (including those assessing outcomes) were unaware of treatment allocation throughout the study. Primary endpoints were CT lung density at total lung capacity (TLC) and functional residual capacity (FRC) combined, and the two separately, at 0, 3, 12, 21, and 24 months, analysed by modified intention to treat (patients needed at least one evaluable lung density measurement). This study is registered with ClinicalTrials.gov, number NCT00261833. A 2-year open-label extension study was also completed (NCT00670007).

Findings Between March 1, 2006, and Nov 3, 2010, we randomly allocated 93 (52%) patients A1PI and 87 (48%) placebo, analysing 92 in the A1PI group and 85 in the placebo group. The annual rate of lung density loss at TLC and FRC combined did not differ between groups (A1PI –1·50 g/L per year [SE 0·22]; placebo –2·12 g/L per year [0·24]; difference 0·62 g/L per year [95% CI –0·02 to 1·26], p=0·06). However, the annual rate of lung density loss at TLC alone was significantly less in patients in the A1PI group (–1·45 g/L per year [SE 0·23]) than in the placebo group (–2·19 g/L per year [0·25]; difference 0·74 g/L per year [95% CI 0·06–1·42], p=0·03), but was not at FRC alone (A1PI –1·54 g/L per year [0·24]; placebo –2·02 g/L per year [0·26]; difference 0·48 g/L per year [–0·22 to 1·18], p=0·18). Treatment-emergent adverse events were similar between groups, with 1298 occurring in 92 (99%) patients in the A1PI group and 1068 occuring in 86 (99%) in the placebo group. 71 severe treatment-emergent adverse events occurred in 25 (27%) patients in the A1PI group and 58 occurred in 27 (31%) in the placebo group. One treatment-emergent adverse event leading to withdrawal from the study occurred in one patient (1%) in the A1PI group and ten occurred in four (5%) in the placebo group. One death occurred in the A1PI group (respiratory failure) and three occurred in the placebo group (sepsis, pneumonia, and metastatic breast cancer).

Interpretation Measurement of lung density with CT at TLC alone provides evidence that purified A1PI augmentation slows progression of emphysema, a finding that could not be substantiated by lung density measurement at FRC alone or by the two measurements combined. These findings should prompt consideration of augmentation treatment to preserve lung parenchyma in individuals with emphysema secondary to severe α1 antitrypsin deficiency.

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Introduction

Severe deficiency of α1 antitrypsin, first described by Laurell and Eriksson[1] in 1963, is associated with a strong tendency for development of emphysema, often, but not always, panlobular in character and basal in distribution. This emphysema is thought to be the result of inadequate neutralisation of naturally occurring proteases, such as neutrophil elastase, by α1 proteinase inhibitor (A1PI), which normally serves as a protease inhibitor.[2] A1PI, purified from pooled human plasma and given as an intravenous infusion once a week at a dose of 60 mg/kg, increases and maintains A1PI serum concentrations at more than the accepted protective threshold of 11 μM while producing measurable increases in the antielastase activity of the epithelial lining fluid of the lung.[3]

No randomised, placebo-controlled clinical trial has been able to substantiate that progression of emphysema is slowed by A1PI augmentation treatment as shown by established disease variables such as forced expiratory volume in 1 s (FEV_1). Such trials were not regarded as feasible when augmentation treatment was first developed.[4,5] Changes in FEV_1 take place slowly for many years, even in a rapidly progressive disease setting, so that several hundred patients would need to be randomised to augmentation treatment or placebo for 5 years to establish the effect of augmentation treatment on emphysema.[4,5] In a rare disease setting, to do such a trial was not thought possible on the basis of several considerations—not just the absence of a sufficiently large population of identified patients available for study, but also the high costs of such a study and ethical concerns raised by extended treatment with placebo. Since the introduction of augmentation treatment for clinical use in the USA, Germany, Canada, and other nations, findings from observational and cohort studies have shown that the rate of FEV_1 loss is slower in individuals who receive augmentation treatment than in those who do not.[6–8] The largest of these observational studies, the National Institutes of Health registry study,[9] showed that augmentation treatment was associated with reduced mortality in the most severely obstructed patients. However, such non-randomised findings can be confounded by other factors, such as differences in socioeconomic status and health-care-seeking behaviour between groups.

Investigators have sought more sensitive treatment endpoints than FEV_1 that would make possible a definitive randomised, placebo-controlled trial in fewer patients for less time. One such outcome measure is lung density as quantified by CT. In the setting of emphysema related to α1 antitrypsin deficiency, CT lung density seems to better show lung destruction and thus disease severity than do traditional measurements of lung function. CT lung density, for example, is a better predictor of mortality in α1 antitrypsin deficiency emphysema than FEV_1 is.[10] In 1999, Dirksen and colleagues[11] examined both FEV_1 and CT lung density endpoints in a randomised, placebo-controlled trial of augmentation treatment, reporting slower rates of lung density loss in patients given augmentation treatment than in those given placebo, although the difference was not significant. In a pilot study of new CT methods, Dirksen and colleagues[12] reported similar findings. Although the data from these two trials have been pooled to show a highly significant preservation of lung density with augmentation treatment,[13] no single, randomised, placebo-controlled trial has been definitive with respect to this endpoint. For this reason, we undertook the RAPID trial to assess the effect on CT lung density of intravenous A1PI augmentation treatment compared with intravenous placebo in patients with emphysema secondary to severe deficiency of α1 antitrypsin.

Methods

Patients and study design

In this multicentre, double-blind, randomised, parallel-group, placebo-controlled trial, we recruited men and women aged 18–65 years with emphysema secondary to α1 antitrypsin deficiency (with a serum A1PI concentration of ≤11 μM) and an FEV_1 of 35–70% of the predicted normal value from 28 study centres in 13 countries. We excluded potential participants if they had smoked tobacco within 6 months before recruitment; had undergone or were on the waiting list to undergo lung transplantation, lobectomy, or lung volume-reduction surgery; or had selective IgA deficiency. We did not allow concurrent augmentation treatment. All patients provided written informed consent and we obtained approval from local institutional review boards.

Randomisation and masking

We randomly allocated patients (1:1; done by Accovion, Marburg, Germany) who completed a screening period of 1–4 weeks treatment with A1PI or matching placebo. A randomisation list containing the assignment of patient number to treatment group (A1PI or placebo) was generated by a computerised pseudorandom number generator. We stratified patients by centre. Masked study treatments were supplied to each site in blocks of four containing sequential patient numbers. After a patient met all qualifications for study participation, we assigned them the next available patient number and the appropriate study treatment was dispensed to give to the patient. To achieve treatment concealment, A1PI and placebo were packaged identically as lyophilised preparations and individual packages were identified only by patient number. Study drug material was suspended in sterile water for injection and placed in an intravenous bag that was covered with an opaque sleeve by a designated study nurse or pharmacist who did not interact with the patients. Clinical trial associates monitored compliance with the masking procedure throughout the trial.

All patients and study investigators were unaware of treatment allocation throughout the study, including those assessing outcomes. The randomisation codes remained sealed until after data collection and cleaning, and completion of a masked analysis. The data safety monitoring board was unmasked.

Procedures

Patients randomly allocated A1PI received intravenous A1PI (Zemaira; CSL Behring, PA, USA) 60 mg/kg per week for 24 months. In non-US centres, patients completing the double-blind portion (in both the A1PI and placebo groups) of the protocol were eligible to receive open-label augmentation treatment with A1PI 60 mg/kg per week for a further 2 years (non-US patients were enrolled because of unavailability of A1PI treatment in non-US countries).

We did spiral CT scans at total lung capacity (TLC) and functional residual capacity (FRC).[14] We transformed lung density, measured in Hounsfield units, to g/L, and applied a physiological volume correction to 15th percentile CT lung density (PD15), as described previously.[12] We stored CT scan electronic files on CDs in the DICOM-3.0 format, and identified them by patient and visit number per investigational site before sending them by courier to the CT core laboratory for analysis (BioClinica, Leiden, Netherlands), which used the PulmoCMS software package (Medis Specials, Leiden, Netherlands).

Outcomes

The primary outcome variable was annual rate of decrease in lung density calculated from the shift of the 15th percentile of lung density measured by CT[12] at baseline, 3, 12, 21, and 24 months. Although previous studies have focused exclusively on lung density at TLC, at the request of the regulatory authorities, the primary outcome was a combined assessment of CT lung density (PD15 values) summing density values calculated at both TLC and FRC. Further primary outcomes were separate measurements of PD15 density measures at FRC and TLC alone. Secondary endpoints, measured at ten clinic visits scheduled at intervals through the trial, were the number of exacerbations as defined by the Anthonisen criteria,[15] exacerbation duration and severity, FEV_1, single-breath diffusion capacity, baseline and achieved A1PI concentrations (functional and antigenic assays), incremental shuttle walk test results, health status established with the St George's Respiratory Questionnaire (for which high scores represent increased disability), body-mass index, mortality, and safety.

We deemed any untoward medical event occurring during the trial as an adverse event, and they were assessed by the investigators as being not related, possibly related, probably related, or related to the trial treatment, and classified as mild, moderate, or severe. We deemed adverse events resulting in death, judged life-threatening, or resulting in admission to hospital serious adverse events.

Statistical analysis

We calculated the sample size using findings from a previous randomised, controlled trial by Dirksen and colleagues,[11] in which the treatment effect—the difference in the rate of lung density decline between the treatment group and placebo—of 1·07 g/L per year had a common SD of 2·17 g/L per year. After accounting for a dropout proportion of 25%, we calculated that 180 patients recruited and randomly assigned evenly to the two groups would provide at least 80% power against a two-sided α of 0·05.

We applied a mixed-effect model to the primary endpoint using SAS PROC MIXED. In this model, the value of adjusted PD15 measured at baseline, 3, 12, 21, and 24 months was the dependent variable. An indicator of whether the value of adjusted PD15 was measured at TLC or FRC, country, time elapsed since randomisation date, treatment, and treatment-by-time interaction were fixed effects of independent variables. Patient and patient-by-time interaction (ie—annual rate of decrease at an individual level) were random coefficients. We calculated percentage reduction in the rate of lung density decrease relative to placebo for all three lung density outcome measures. We analysed the primary and secondary endpoints for both the modified intention-to-treat population, excluding patients for whom no lung density measurements were available, and the per-protocol population, excluding patients with a major protocol violation.

We did a planned interim descriptive analysis of the patients in the extension study when at least 50% of them had at least two valid CT lung density measurements at different timepoints and repeated this analysis at the request of the regulatory authorities when approximately 75% of patients met this criterion. Using data from the

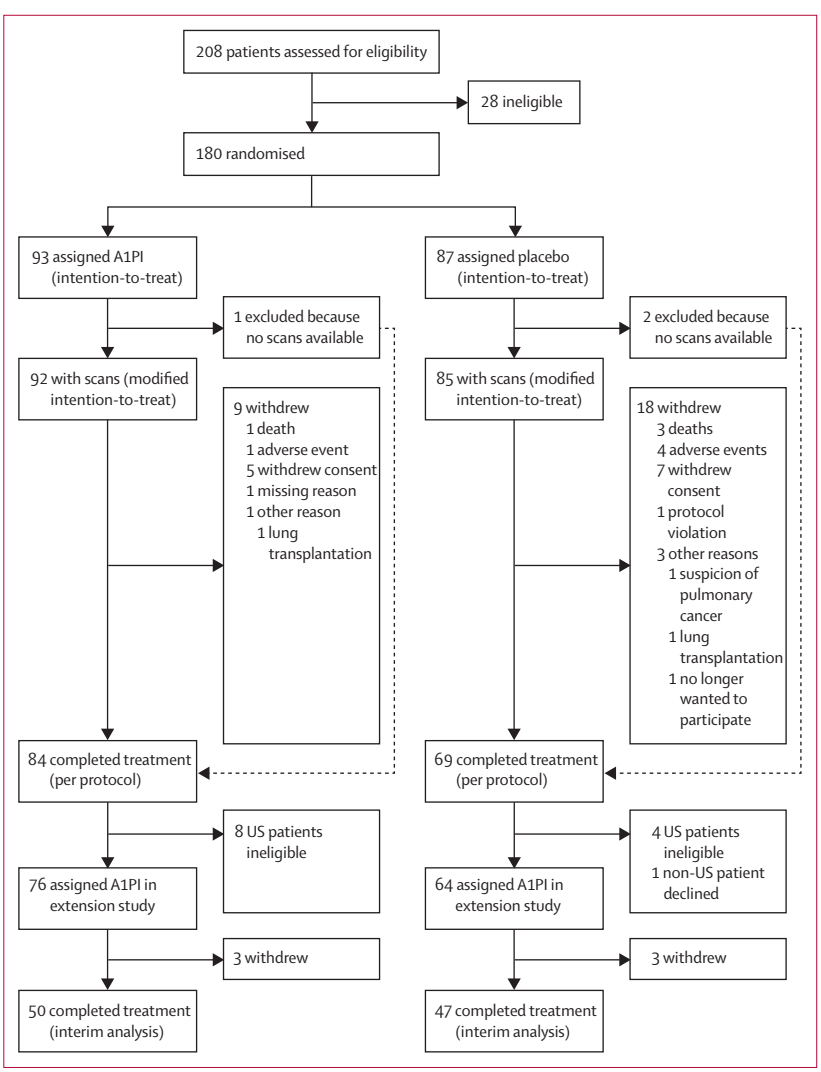


Figure 1: **Trial profile**
A1PI=α1 proteinase inhibitor.

double-blind portion of this trial, we also did a post-hoc stepwise regression analysis to establish factors that affected trough serum concentration of A1PI achieved and the relation between concentration achieved and efficacy.

A data safety monitoring board (consisting of a statistician and clinician independent of the funder and study) monitored the study for safety on the basis of adverse events and possible occurrence of anti-A1PI serum antibodies.

This study is registered with ClinicalTrials.gov, number NCT00261833 (extension study NCT00670007).

	A1PI (n=93)	Placebo (n=87)
Mean age (years)	53·8 (6·9)	52·4 (7·8)
Sex		
Male	48 (52%)	50 (57%)
Female	45 (48%)	37 (43%)
Race		
White	93 (100%)	87 (100%)
FEV_1 predicted (%)	47·4% (12·1)	47·2% (11·1)
Baseline antigenic A1PI serum concentration (μM)	6·38 (4·62)	5·94 (2·42)
Baseline CT lung density (g/L)		
TLC	45·5 (15·8)	48·9 (15·5)
FRC	47·6 (15·7)	50·7 (15·0)
Combined	46·6 (15·6)	49·8 (15·1)

Data are n (%) or mean (SD). A1PI=α1 proteinase inhibitor. FEV_1=forced expiratory volume in 1 s. TLC=total lung capacity. FRC=functional residual capacity.

Table 1: **Baseline demographic and clinical characteristics (intention-to-treat patients)**

See Online for appendix

Role of the funding source

The funder had a role in oversight and management of data collection. JME, LH, and ZY, who are employees of the funder, participated in data analysis, data interpretation, and writing of the report. Both placebo and A1PI treatments were provided by the funder. The funder paid Accovion to do the randomisation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2006, and Nov 3, 2010, we screened 208 patients, randomly assigning 180 to active treatment (93 [52%] patients) or placebo (87 [48%] patients), completing data collection on Sept 26, 2012 (figure 1, table 1). Of these 180 patients, 168 (93%) were ZZ genotype; the remainder were other variants with α1 antitrypsin serum concentrations of less than 11 μM. 16 (9%) patients had previously received augmentation treatment, but none within 3 months before randomisation. Assessable lung density data for at least two timepoints were available for 92 patients in the A1PI group and 85 in the placebo group. Fewer patients receiving augmentation treatment (nine [10%]) withdrew from the trial prematurely than did those receiving placebo (18 [21%]; p=0·04). For both the modified intention-to-treat and per-protocol populations, active and placebo groups were well matched. The characteristics of the patients who continued into the open-label extension study were similar to those of the overall population in this trial (appendix).

	A1PI (n=93)		Placebo (n=87)		A1PI *vs* placebo
	Baseline	24 months	Baseline	24 months	Least-square mean difference
Spirometry					
Predicted FEV_1 (%)	47·4% (12·1)	−3·1% (10·7)	47·2% (11·1)	−2·3% (13·1)	−2·26%* (p=0·21)
D_{LCO} (mL/mm Hg per min; %)	13·6% (5·3)	−2·2% (18·2)	15·0% (5·6)	−1·5% (19·5)	−1·31%* (p=0·64)
SGRQ score					
Total	44·3 (17·1)	1·4 (11·1)	42·4 (18·0)	2·2 (11·7)	−0·19* (p=0·91)
Symptoms	46·5 (22·7)	−1·4 (16·7)	44·1 (24·8)	2·0 (20·1)	−1·11* (p=0·67)
Activity	62·1 (18·6)	1·7 (12·4)	60·1 (21·4)	2·6 (13·5)	−0·16* (p=0·94)
Impact	33·6 (18·4)	2·1 (14·8)	31·4 (17·6)	1·8 (12·5)	0·74* (p=0·72)
Shuttle walk distance (m)	424·5 (183·0)	10·8 (139·8)	435·1 (199·7)	16·1 (101·6)	−13·09* (p=0·48)
A1PI concentration (μM)					
Antigenic	6·38 (4·62)	10·12 (3·52)	5·94 (2·42)	−0·07 (1·32)	10·05† (p=0·02)
Functional	2·88 (3·65)	7·30 (2·50)	2·30 (1·34)	0·12 (0·96)	7·18† (p=0·02)
Exacerbations‡					
Annual number	..	1·70 (1·51–1·89)	..	1·42 (1·23–1·61)	1·26§ (0·92–1·74)
Relative duration (days)	..	13·8 (15·0)	..	10·8 (11·6)	0·56 (p=0·18)

Data are mean (SD) or n (95% CI), unless otherwise stated. A1PI=α1 proteinase inhibitor. FEV_1=forced expiratory volume in 1 s. D_{LCO}=diffusion capacity. SGRQ=St George's Respiratory Questionnaire. *Adjusted for country, treatment group, and baseline values. †Based on a post-hoc analysis and are the results from t tests. ‡Exacerbations occurring in the first 2 years. §Presented as an adjusted risk ratio from a negative binomial regression model in which country and treatment were fixed effects, and adjustment was made for treatment duration.

Table 2: **Summary of other efficacy variables (intention-to-treat patients)**

When measured at TLC and FRC combined, the absolute difference in lung density between the augmentation treatment group and placebo group was 0·62 g/L per year (95% CI –0·02 to 1·26, p=0·06; A1PI –1·50 g/L per year [SE 0·22]; placebo –2·12 g/L per year [0·24]), corresponding to a relative reduction of 29% (0·93–76·4), but the difference was not significant. At TLC alone, mean annual rate of lung density loss was significantly lower in the augmentation treatment group (–1·45 g/L per year [SE 0·23]) than in the placebo group (–2·19 g/L per year [0·25]; p=0·03), with an absolute difference of 0·74 g/L per year (95% CI 0·06–1·42), corresponding to a relative reduction of 34% (2·2–84·5) in favour of augmentation treatment. However, the difference was also not significant at FRC alone: 0·48 g/L per year (95% CI –0·22 to 1·18, p=0·18; A1PI –1·54 g/L per year [SE 0·24] *vs* placebo –2·02 g/L per year [0·26]). SDs for unadjusted PD15 values were lower at TLC (A1PI 2·23; placebo 2·38) than at FRC (A1PI 2·31, placebo 2·73; TLC and FRC combined: A1PI 2·11; placebo 2·20).

One (1%) patient in the active treatment group died during the trial (respiratory failure) and three (3%) died in the placebo group (sepsis, pneumonia, and metastatic breast cancer). Secondary outcome variables are shown in table 2 and did not differ significantly between the two groups, except for A1PI concentration. Reported adverse events of treatment were similar between active and placebo groups, with 1298 treatment-emergent adverse events occurring in 92 (99%) patients in the A1PI group and 1068 events occurring in 86 (99%) patients in the placebo group (table 3). 71 severe treatment-emergent adverse events occurred in 25 (27%) patients in the A1PI group and 58 events occurred in 27 (31%) patients in the placebo group (table 4). One treatment-emergent adverse event leading to withdrawal from the study occurred in one patient (1%) in the A1PI group and ten events occurred in four (5%) patients in the placebo group. The time to first Anthonisen exacerbation did not differ between groups (appendix). However, a post-hoc per-protocol analysis done in the overall study population showed that lung density correlated significantly with pulmonary function and clinical variables at baseline and study completion. For example, at study end (24 months), the Pearson correlation coefficients were low to moderate: 0·31 (p<0·001) for predicted FEV_1, 0·44 (p<0·001) for diffusion capacity, 0·26 (p=0·002) for incremental shuttle walk test, and –0·22 (p=0·02) for St George's Respiratory Questionnaire total score.

Trough serum A1PI concentrations achieved during active treatment during the double-blind portion of the trial tended to be higher in patients of higher bodyweight and higher pretreatment serum A1PI concentrations (data not shown). A post-hoc pharmacometric analysis showed that annual rate of lung density loss was inversely proportional to the trough serum A1PI concentrations achieved, with no evidence of a plateau during the measured range (p=0·03; figure 2).

The terminal event for progressive emphysema is either lung transplantation or death, which occurred in five patients. Average lung density at study exit for these patients was less than 19·0 g/L (95% CI 3·5–29·5), and at baseline for enrolled patients (n=180) was 47·1 g/L (23·0–76·1). With these two lung density values and the rates of annual lung density decrease at TLC in the two groups, the time to terminal respiratory function can be extrapolated. In the augmentation treatment group, we estimated time to terminal respiratory failure to be 18·1 years (12·2–30·1); for patients receiving placebo, the estimate was 12·3 years (8·1–19·9).

Annual rate of lung density decrease during both the double-blind and open-label portions of the trial is shown in figure 3 for all patients who had completed the open-label extension at the time of the second interim analysis. The rate of lung density loss was greater in patients who were taking placebo during the double-blind portion of the trial than in those given A1PI, but slowed to parallel that of patients who had received active treatment throughout in the extension study.

	A1PI (n=93)		Placebo (n=87)	
	Patients	Events	Patients	Events
Any TEAE	92 (99%)	1298 (7·58)	86 (99%)	1068 (7·23)
Infections and infestations	77 (83%)	334 (1·95)	76 (87%)	369 (2·50)
Bronchitis	12 (13%)	26 (0·15)	11 (13%)	16 (0·11)
Influenza	14 (15%)	14 (0·08)	10 (11%)	12 (0·08)
Nasopharyngitis	30 (32%)	53 (0·31)	26 (30%)	58 (0·39)
Pneumonia	11 (12%)	15 (0·09)	12 (14%)	25 (0·17)
Sinusitis	12 (13%)	17 (0·10)	10 (11%)	18 (0·12)
Upper respiratory	14 (15%)	26 (0·15)	14 (16%)	25 (0·17)
Lower respiratory	18 (19%)	88 (0·51)	17 (20%)	72 (0·49)
Viral*	3 (3%)	5 (0·03)	4 (5%)	6 (0·04)
Respiratory disorders	63 (68%)	249 (1·45)	49 (56%)	127 (0·86)
Chronic obstructive pulmonary disease	30 (32%)	107 (0·63)	20 (23%)	53 (0·36)
Cough	20 (22%)	31 (0·18)	7 (8%)	7 (0·05)
Dyspnoea	17 (18%)	29 (0·17)	10 (11%)	11 (0·07)
Oropharyngeal pain	22 (24%)	36 (0·21)	10 (11%)	13 (0·09)
Gastrointestinal disorders	46 (49%)	104 (0·61)	47 (54%)	92 (0·62)
Nausea	15 (16%)	23 (0·13)	8 (9%)	11 (0·07)
General and administration site disorders	48 (52%)	144 (0·84)	42 (48%)	101 (0·68)
Condition aggravated	20 (22%)	62 (0·36)	14 (16%)	41 (0·28)
Fatigue	8 (9%)	14 (0·08)	10 (11%)	12 (0·08)
Pyrexia	13 (14%)	15 (0·09)	6 (7%)	8 (0·05)
Nervous system	46 (49%)	194 (1·13)	43 (49%)	134 (0·91)
Headache	37 (40%)	98 (0·57)	33 (38%)	105 (0·71)
Musculoskeletal and connective tissue disorders	35 (38%)	68 (0·40)	37 (43%)	75 (0·51)
Back pain	12 (13%)	12 (0·07)	10 (11%)	12 (0·08)

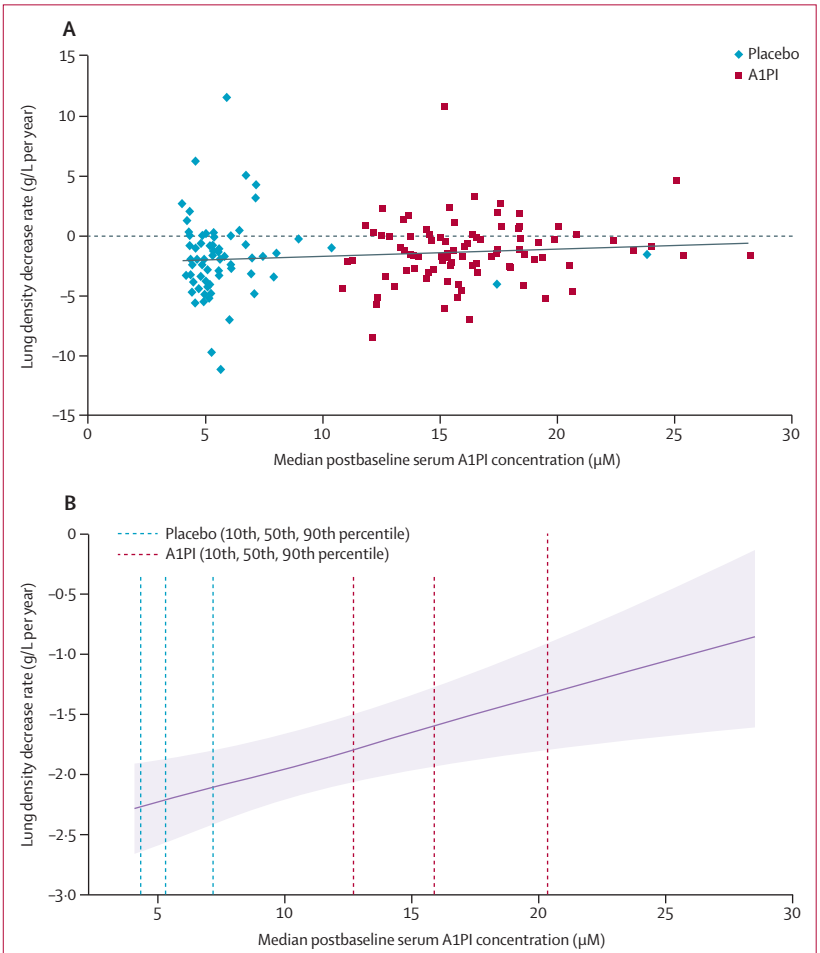
Data are n (%) or n (annualised incidence rate). The annualised incidence rate is based on exposures of 171·14 A1PI subject years and 147·75 placebo patient years. Each patient could have more than one adverse event. A1PI=α1 proteinase inhibitor. TEAE=treatment-emergent adverse event. *Experienced by less than 10% of patients in either treatment group.

Table 3: **Reported TEAEs and exposure-adjusted incidence rates organised by selected system organ classifications and preferred terms experienced by at least 10% of patients in either treatment group (safety population)**

	A1PI (n=93)		Placebo (n=87)	
	Patients	Events	Patients	Events
Any TEAE	92 (99%)	1298 (7·58)	86 (99%)	1068* (7·23)
Mild	13 (14%)	780 (4·56)	16 (18%)	666 (4·51)
Moderate	54 (58%)	447 (2·61)	43 (49%)	343 (2·32)
Severe	25 (27%)	71 (0·41)	27 (31%)	58 (0·39)
Any related TEAE	21 (23%)	91 (0·53)	21 (24%)	50 (0·34)
Any TEAE within 24 h	78 (84%)	373 (2·18)	78 (90%)	328 (2·22)
Any related TEAE within 24 h	15 (16%)	51 (0·30)	18 (21%)	35 (0·24)
Any AR†	86 (92%)	702 (4·10)	83 (95%)	560 (3·79)
Occurring within 72 h	85 (91%)	677 (3·96)	83 (95%)	549 (3·72)
Related	21 (23%)	91 (0·53)	21 (24%)	50 (0·34)
Any serious TEAE	28 (30%)	57 (0·33)	28 (32%)	45 (0·30)
Any related serious TEAE	1 (1%)	1 (0·01)	1 (1%)	1 (0·01)
Any TEAE leading to withdrawal from study	1 (1%)	1 (0·01)	4 (5%)	10 (0·07)
Any related TEAE leading to withdrawal from study	1 (1%)	1 (0·01)	1 (1%)	4 (0·03)

Data are n (%) or n (annualised incidence rate). The annualised incidence rate is based on exposures of 171·14 A1PI patient years and 147·75 placebo patient years. Each patient could have more than one adverse event. A patient with more than one TEAE was counted in the severity category associated with the most severe TEAE. TEAE=treatment-emergent adverse event. AR=adverse reaction. *One TEAE (panic attack) was not classified by severity. †ARs could occur both within 72 h and be related to treatment.

Table 4: **Reported TEAEs and exposure-adjusted incidence rates organised by severity (safety population)**



Discussion

Although the primary statistical endpoint of PD15 lung density at TLC and FRC combined was non-significant (along with the primary endpoint of FRC alone), this finding can be accounted for by the fact that measurement error for unadjusted PD15 is highest for CT scans obtained at lowest lung volumes (eg, FRC) and lowest for those acquired at highest volumes (eg, TLC).[16] The combination of CT data obtained at TLC and FRC results in a measurement error intermediate to that at either TLC alone or FRC alone. CT lung density measurement at TLC alone (a primary endpoint) did show a significant difference between the rate of lung parenchymal loss in patients with α1 antitrypsin deficiency emphysema who received infusions of purified A1PI and those who did not—about a third slower in those that received A1PI than in those who did not. Data from this trial substantiates previous reports[16,17] that CT density measured at TLC has smaller variation than does that measured at FRC, and thus CT data acquired at TLC are deemed more reliable than those acquired at FRC. These findings are consistent with the understood biological mechanisms of α1 antitrypsin protein and the reported results of observational and cohort studies[7–9] showing reduced rates of FEV_1 decrease and mortality with augmentation treatment (panel). Moreover, our estimates of lung density decrease are consistent with those reported for treated and untreated patients in previous studies using CT densitometry.[11,12] The rate of lung density decrease in this trial was similar to that noted in a randomised controlled trial by Dirksen and colleagues[12] (0·86 g/L per year [95% CI −0·08 to 1·78]). In another randomised controlled trial with some methodological differences,[11] the rate was 1·07 g/L per year (SE 0·58).

Our analyses provide two further arguments to suggest that augmentation treatment has a disease-modifying effect in patients with α1 antitrypsin deficiency emphysema. First, although our study was not designed to study the effect of different treatment doses across the range of post-treatment serum concentrations achieved with active and placebo treatment, the effect of treatment was dose-related such that patients with the highest trough serum concentrations tended to have the slowest annual rates of lung density loss. Second, our analysis of the open-label treatment extension makes an artifactual effect of augmentation treatment unlikely. If deposition of exogenous protein in the epithelial lining fluid of the lung could lead to lung density overestimation by CT techniques, we would expect delayed introduction of augmentation treatment to patients previously given placebo to return their estimated lung density to that of

Figure 2: **Rates of lung density decrease at total lung capacity versus trough A1PI serum concentrations achieved**
(A) All datapoints for patients across the entire range of observed lung density decrease. (B) Response-exposure curve. Shaded area represents 90% CIs. A1PI=α1 proteinase inhibitor.

continuously treated patients. Instead, their rate of lung density loss slowed to match that of continuously augmented patients, but the density lost was not recovered.

Unsurprisingly, findings from our study did not show significant differences between active and placebo treatment in conventional pulmonary function and clinical endpoints; the study was not designed with sufficient power to detect such changes. Small numerical differences between groups in rate of FEV_1 change and exacerbations favouring placebo were non-significant, but could have been affected by the different withdrawal between groups. We believe that estimation of lung density with CT is not just a more sensitive outcome measure than those used conventionally, but is more appropriate for this patient population. In typical non-α1 antitrypsin-deficient chronic obstructive pulmonary disease, the degree of emphysema present on CT scans can be discordant with clinical severity, a finding that shows the heterogeneous nature of the disease.[17] By contrast, emphysema in individuals with α1 antitrypsin deficiency is more homogeneous than is chronic obstructive pulmonary disease. Estimates of lung density for this form of emphysema correlate well with conventional measures of lung function and disease outcome, but lung density estimates have greater sensitivity and prognostic value than do conventional measures.[10]

In a post-hoc analysis, we noted an inverse relation between α1 antitrypsin serum concentration achieved and clinical efficacy as measured by rate of lung density decrease. We did not note a plateau to this dose–response relation, raising the possibility that the dose of 60 mg/kg per week is not the optimum augmentation treatment dose for all patients. This possibility has been considered previously because the present dose of treatment was based on achievement of serum concentrations at the lower limit of the range seen in mildly deficient genotypes, individuals thought to have no increased risk of emphysema and now understood to have a high risk of Global Initiative on Obstructive Lung Disease Stage II chronic obstructive pulmonary disease (odds ratio of more than 1·2).[18–21] Authors of preliminary studies have noted that infusions of 120 mg/kg per week are well tolerated,[22] and efficacy studies have been planned (NCT01669421 and NCT01983241).

In a further post-hoc analysis, we estimated that patients receiving purified A1PI would be expected to take more time to reach terminal respiratory function (transplantation or death) when compared with those not receiving active treatment, and the results pointed to the potential clinical effect of a reduction of the rate of lung density decrease in patients with emphysema. However, the precise numbers should be interpreted with caution as they are based on a very small number of patients who reached terminal respiratory failure or death—further investigations are needed.

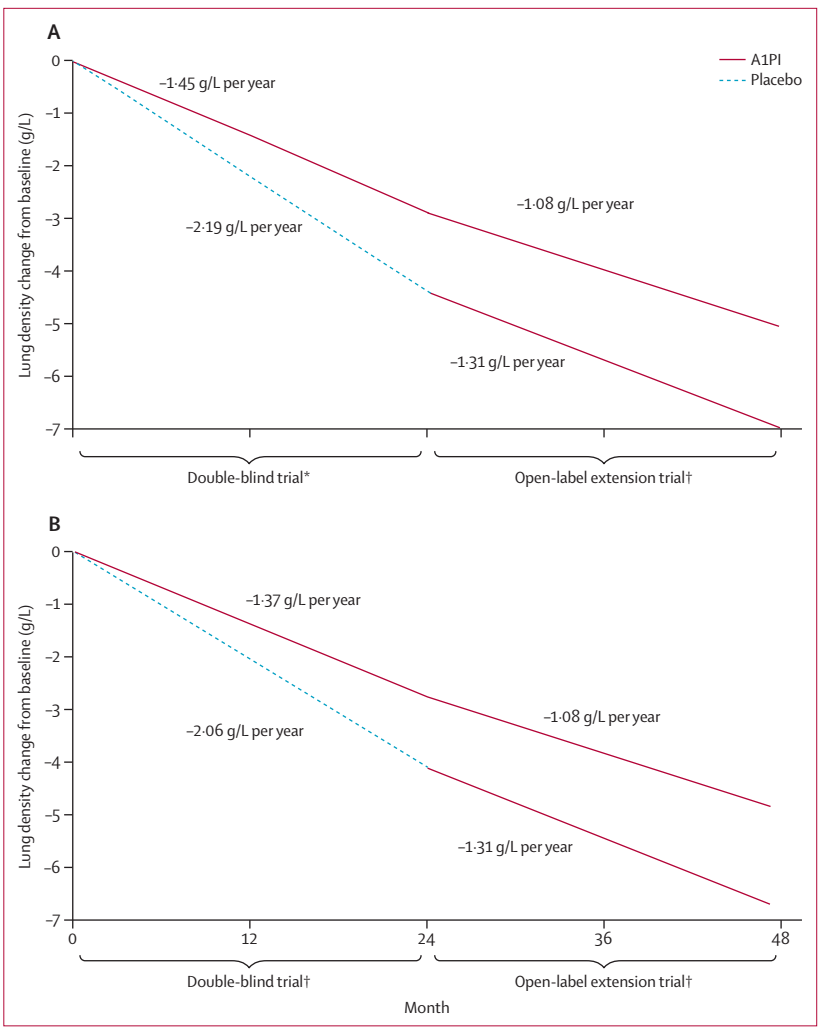


Figure 3: **Rates of lung density decrease at TLC during the double-blind and open-label portions of the trial in (A) all patients and (B) patients completing the open-label study only**
Values on graph are annual rates of decrease. A1PI=α1 proteinase inhibitor. *A1PI n=92; placebo n=85. †A1PI n=50; placebo n=47.

Some limitations to our study should be noted. First, although we have attempted to estimate the clinical effect of lung density changes on clinical outcomes with post-hoc analyses, our study does not allow us to establish the effect of lung density preservation on typical clinical outcomes of lung function, exacerbations, and survival. Second, although we have provided some evidence of efficacy of augmentation treatment at the currently recommended dose of 60 mg/kg per week, we have not established that this is the optimum dose. Third, we do not know whether preservation of lung density or structure is uniform across all severely deficient patients or stages of the disease. In non-α1 antitrypsin deficiency chronic obstructive pulmonary disease, for example, lung function changes occur more rapidly in mild than in severe disease.[23] Additionally, we do not know the duration of the protective effect with treatment continued beyond 4 years. Finally, the higher

Panel: Research in context

Systematic review

We searched PubMed up to April 24, 2015, for randomised, controlled trials of CT lung scanning to assess emphysema progression in patients with α1 antitrypsin deficiency who received intravenous α1 proteinase inhibitor (A1PI) augmentation treatment or control. We used the following search terms (with no language restrictions): "alpha-1 antitrypsin", "augmentation therapy", "computed tomography", and "randomized controlled trial". We identified two relevant randomised controlled trials. In 1999, Dirksen and colleagues[11] reported data from 56 ex-smokers with α1 antitrypsin deficiency (all PI*ZZ) and moderate emphysema who received monthly infusions of either intravenous A1PI or 2% human albumin for at least 3 years. No significant difference was noted between the two groups in terms of forced expiratory volume in 1 s, but a trend towards slower annual loss of lung density, as measured by CT densitometry, was apparent in the treated group. In a subsequent trial, Dirksen and colleagues[12] took lung CT measurements of 77 patients with α1 antitrypsin deficiency who received A1PI or 2% human albumin every week for 2–2·5 years, reporting a trend towards treatment benefit. Authors of a pooled analysis of these two randomised controlled trials[13] concluded that intravenous A1PI augmentation treatment significantly reduces the rate of CT-measured lung density decrease in patients with α1 antitrypsin deficiency-related emphysema.

Interpretation

Our data suggest that intravenous augmentation of serum α1 antitrypsin in individuals with α1 antitrypsin deficiency-related emphysema can slow loss of lung parenchyma as ascertained by CT-measured lung density at TLC, but this finding was not significant when measured at TLC and FRC combined, or FRC alone. In an exploratory post-hoc analysis, the finding was underscored by an apparent dose–response relation such that the higher the serum concentration achieved with infusion, the slower the resulting loss of lung density. This estimate was based on the small variation in serum concentrations seen after administration of the single standard recommended dose and raises the question of whether present dosing recommendations are the best possible. In a planned interim analysis of an open-label extension to the present randomised trial, we noted that delayed introduction of augmentation treatment slowed lung density loss, but lung parenchyma lost during the delay was not recovered. These findings should encourage early introduction of augmentation treatment in those with emphysema secondary to severe α1 antitrypsin deficiency and should stimulate further research into optimum dosing.

number of withdrawals in the patients given placebo than in those in the treatment group remains unexplained, but is concordant with the greater loss of lung density in this group and the relative insensitivity of conventional clinical variables to such deterioration. Differential withdrawal in other large trials of treatment in chronic obstructive pulmonary disease unrelated to α1 antitrypsin deficiency has been regarded as an indicator of treatment efficacy.[24]

Contributors

KRC, JGWB, EP, RAS, NS, JMS, and NGM were study investigators and planned the study, collected the data, reviewed the analyses, and wrote the report. KRC prepared the first draft of the report. NGM was the principal investigator. BCS, LH, ZY, and JME designed the study and analysed the data. All authors reviewed and approved the final version of the report.

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Declaration of interests

KRC has received compensation for consulting with AstraZeneca, Baxter, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Grifols, Kamada, Novartis, Nycomed, Roche, and Telacris; has done research funded by Amgen, AstraZeneca, Baxter, Boehringer Ingelheim, CSL Behring, Forest Labs, GlaxoSmithKline, Grifols, Novartis, Roche, and Takeda; and has participated in continuing medical education activities sponsored in whole or part by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Merck Frosst, Novartis, Pfizer, and Takeda. He is participating in research funded by the Canadian Institutes of Health Research operating grant entitled Canadian Cohort Obstructive Lung Disease. He holds the GlaxoSmithKline-Canadian Institutes of Health Research Chair in Respiratory Health Care Delivery at the University Health Network, ON, Canada. JGWB has received research funding from CSL Behring and consulted with Baxter. EP has received research funding for this study from CSL Behring. RAS reports grants and personal fees from CSL Behring during this study, other grants and personal fees from CSL Behring and Grifols, personal fees from Baxter, and non-financial support from the Alpha-1 Project (venture philanthropy) outside of the submitted work, and is employed by AlphaNet, a not-for-profit organisation providing disease management services for patients with α1 antitrypsin deficiency. All other authors declare no competing interests.

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