

# Intravenous alpha-1 antitrypsin augmentation therapy: systematic review

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## ABSTRACT

We reviewed the benefits and harms of augmentation therapy with alpha-1 antitrypsin in patients with alpha-1 antitrypsin deficiency and lung disease.

We searched for randomised trials comparing augmentation therapy with placebo or no treatment in PubMed and ClinicalTrials (7 January 2010).

Two trials were included with a total 140 patients. The trials ran for two to three years. Mortality data were not reported. There was no information on harms in the first trial; in the second trial, serious adverse events were reported in ten of 38 patients in the drug group and in 18 of 39 patients in the placebo group. Annual number of exacerbations and quality of life were reported in the second trial and were similar in the two groups. The meta-analyses showed that forced expiratory volume in one second deteriorated a little more in the drug group than in the placebo group (difference -20 ml per year; 95% confidence interval -41 to 1;  $p = 0.06$ ). For carbon monoxide diffusion, the difference was -0.06 mmol/min./kPa per year (95% confidence interval -0.17 to 0.05;  $p = 0.31$ ). Lung density measured by computed tomography deteriorated a little less in the drug group than in the placebo group (difference 1.14 g/l; 95% confidence interval 0.14 to 2.14;  $p = 0.03$ ) over the total course of the trials.

Augmentation therapy with alpha-1 antitrypsin cannot be recommended in view of the lack of evidence of clinical benefit and the cost of treatment.

Alpha-1 antitrypsin deficiency is an inherited disorder that can cause lung or liver disease [1]. The prevalence of the genotype associated with severe alpha-1 antitrypsin deficiency is about one in 1,600 to 5,000 newborns [2, 3]. Alpha-1 antitrypsin helps to regulate protease activity and plays an important role in controlling inflammation and repair mechanisms in the body.

Smokers with hereditary alpha-1 antitrypsin deficiency have a particularly high risk of developing pulmonary emphysema, e.g. almost all smokers with the Z phenotype (PI\*ZZ, i.e. who are homozygotic for the deficiency) will develop emphysema in early adult life and their life expectancy is reduced [4, 5].

The major cause of morbidity and death in severe alpha-1 antitrypsin deficiency is chronic obstructive pul-

monary disease with pulmonary emphysema [6], and liver disease is the second most common complication [7]. The emphysema is mainly located in the lower lobes of the lung, whereas smokers with normal phenotype predominantly have upper lobe disease.

The first symptoms of lung disease usually appear between the ages of 20 and 50 years, and include shortness of breath following mild activity, reduced ability to exercise and wheezing. About 10-15% of those who have alpha-1 antitrypsin deficiency have liver damage. In rare cases, alpha-1 antitrypsin deficiency also causes a skin condition known as panniculitis, which is characterized by hardened skin with painful lumps or patches [1].

Preparations of alpha-1 antitrypsin are made from normal human plasma from blood donors. The drug is generally infused at a dose of 60 mg/kg intravenously every week and is available in some countries for replacement therapy in patients with symptomatic emphysema, although the effect has been poorly documented.

The mechanism behind the lung damage is believed to be well-understood. Alpha-1 antitrypsin inhibits protein-degrading enzymes and protects the pulmonary tissue against the destructive activity of elastase [8]. Elastase is released by neutrophils when they penetrate into the alveolar wall by chemotaxis induced by cigarette smoke. Replacement therapy with alpha-1 antitrypsin may therefore be beneficial.

## OBJECTIVES

We studied whether augmentation therapy with alpha-1 antitrypsin is effective in patients with alpha-1 antitrypsin deficiency and lung disease, and we also reviewed its harms.

## MATERIAL AND METHODS

We included randomised clinical trials in any language that compared augmentation therapy with alpha-1 antitrypsin with placebo or no intervention in patients with alpha-1 antitrypsin deficiency, with or without a diagnosis of chronic obstructive pulmonary disease. We did not include trials in newborns, as there is a separate Cochrane review on this age group [9], which showed that prophylactic administration of alpha-1 antitrypsin to preterm neonates did not reduce their risk of developing

## REVIEW ARTICLE

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Dan Med Bul 2010;57(9):A4175

chronic lung disease. Our primary outcomes were mortality and harms of the intervention. Secondary outcomes were: number of exacerbations, number of lung infections, number of hospital admissions, quality of life, forced expiratory volume in one second (FEV1), carbon monoxide diffusion and lung density measured by computed tomography (CT).

We searched PubMed (limited to randomised trials) and the Cochrane Trials Register (Clinical Trials) using the terms: antitrypsin, "proteinase inhibitor", Prolastin, Aralast, Zemaira or Trypsone. We also searched for ongoing trials on ClinicalTrials with the term "antitrypsin and placebo" (date of last searches: 7 January 2010).

We accepted letters, abstracts and unpublished trials in an attempt to reduce the impact of selective reporting of trials and outcomes.

The two authors independently extracted outcome data and assessed the risk of bias. In particular, we recorded generation of the randomisation sequence, concealment of treatment allocation, any blinding, and exclusions of patients from the analysis. One author extracted descriptive data that were checked by the other author. Disagreements were resolved by discussion.

We sought data on all randomised patients, i.e. including patients the investigators might have excluded because of poor compliance, ineligibility or loss to follow-up (intention-to-treat analysis).

For dichotomous data, we used the risk ratio. For continuous data and for average numbers of events, we used the mean difference or standardised mean difference, as appropriate. We present data with 95% confidence intervals.

We used a fixed-effect model for meta-analysis [10]. We assessed heterogeneity statistically and also used  $I^2$  as a guide to its magnitude [11].

## RESULTS

We identified two placebo-controlled randomised trials that were eligible for the review [12, 13] and a third ongoing trial that plans to include 180 patients [14].

Both trials had recruited patients with genetic variants that carry a very high risk of developing chronic obstructive pulmonary disease [15]. The first trial, which was supported by public funds, enrolled 58 patients from Denmark and the Netherlands [12]. The patients were ex-smokers with alpha-1 antitrypsin deficiency of the PI\*ZZ genotype who had moderate emphysema (FEV1 between 30% and 80% of the predicted values). They were treated for at least three years with four weekly infusions of alpha-1 antitrypsin (250 mg/kg) or albumin (625 mg/kg) as placebo. The primary effect measure was FEV1, and it was noted in the trial report that the deterioration in the emphysema would be assessed as FEV1 and carbon monoxide diffusion.

The second trial, the EXACTLE trial, was financed by Talecris Biotherapeutics, Inc., and had co-authors from the company [13]. The patients were ex- or never-smokers and had similar characteristics as those in the first trial; they either had the ZZ genotype or the PI\*Z phenotype. The trial enrolled 82 patients from Copenhagen, Malmö and Birmingham (UK) who were treated for two years (with an optional six-month extension) with weekly infusions of 60 mg/kg alpha-1 antitrypsin or 2% albumin as placebo. The primary effect measure was lung density measured by CT (although this was considered an exploratory outcome), while lung function measures and other outcomes were regarded as secondary.

## RISK OF BIAS IN INCLUDED STUDIES

The randomisation method in the first trial was minimization [12]. The procedure was not described, and it was not possible to judge whether it had led to comparable groups, as a table in the paper compared patient characteristics at baseline for the two countries and not for the two randomised groups. Another table showed that the groups were comparable at baseline for lung function measurements and CT values.

In the second trial, patients were randomised in blocks of four for each city; the block size was not disclosed to the study sites [13]. A computer-generated random code was used to produce randomisation envelopes that were issued to the unblinded pharmacist or designee at each study centre and which were to be kept confidential. The randomisation envelopes were sent to the pharmacist with the study medication. The clinical site pharmacy personnel who prepared the study medication were not blinded. There were more males in the active group than in the placebo group ( $p = 0.02$ ), but this could be a chance finding, as the two groups were comparable for other baseline characteristics.

Both trials were double-blind and placebo-controlled, but the blinding procedure was not described in the first trial, and it is not clear whether the attempted blinding was effective [12]. In the second trial, it was ensured that all patients received the same total volume per kg body weight of study medication with no visible difference in the external aspect between the drugs, as variation in colour by lot was masked by using opaque sleeves. Throughout the course of the second trial, individual treatment assignments were unknown to the clinicians, the monitors, the CT facility, and the sponsor's data management, clinical and biostatistical teams [13].

Outcome data were not available for two of the 58 patients in the first trial who dropped out because they resumed smoking, and it was not described to which groups they were randomised [12]. According to the description of the second trial, 82 patients were enrolled, but only 77 randomised. Three of the 77 patients with-

drew from the active group and seven from the placebo group; data from the CTs were included from 71 patients, but data on change from baseline was only available for 67 patients after two years, and for 34 patients after 2.5 years [13]. We therefore used CT data after two years. Data after end of treatment were not available, and we therefore used changes from baseline.

### SELECTIVE REPORTING AND CONFLICTS OF INTEREST

We found no signs of selective reporting for the first trial, apart from the fact that the table of baseline values did not give data for the two randomised groups [12]. We also noted that no serious adverse events were reported in the first trial, in contrast to 28 in the second.

The report on the second trial only addressed CT measurements, exacerbations and quality of life [13]. For lung function measurements, the report stated that "Values for FEV1, DL<sub>co</sub> and K<sub>co</sub> decreased slightly in both treatment groups during the study but, since these measures were less sensitive than CT, no significant differences were found between the groups (see online supplement for details)". The report was published online on 5 February 2009, and at that time and during the next couple of months, we found no additional material on the journal's website. It cannot have been because of lack of space that the important data on FEV1 were omitted, as the main text in the trial report amounted to 4,357 words. Furthermore, it is inappropriate to dismiss the FEV1 findings by saying that no significant difference was found, particularly because FEV1 is the accepted method. Thus, it was described as the "gold standard" in the report, and it also showed a trend towards a harmful effect of the drug. In contrast, the CT measurements were described as "exploratory", both when the trial was registered (ClinicalTrials Identifier: NCT00263887) and in the trial report [13]. Finally, an earlier version of the manuscript for this trial that we received from its primary author did contain the FEV1 data.

### EFFECTS OF ALPHA-1 ANTITRYPSIN

We did not detect heterogeneity in any of the analyses

( $I^2 = 0$ ). Mortality data were not reported in either of the two trials. There was no information on harms in the first trial [12], which is surprising. In the second trial, serious adverse events were reported to have occurred in ten drug group patients and in 18 placebo group patients [13]. Most of these events were unlikely to have any relation to the drugs, e.g. breast cancer, osteoarthritis and pulmonary embolism were reported among patients receiving placebo.

The annual number of exacerbations was reported in the second trial: 2.6 in the drug group and 2.2 in the placebo group ( $p = 0.27$ ) [13]. Neither trial reported the mean number of lung infections or hospital admissions. Quality of life was reported in the second trial as St. George's Respiratory Questionnaire, and it deteriorated by 1.5 and 2.4, respectively ( $p = 0.70$ ), which are very small changes from an average baseline score of 44 [13]. FEV1 deteriorated slightly more in the active group than in the placebo group; the difference was -20 ml per year (95% confidence interval -41 to 1;  $p = 0.06$ , **Figure 1**). For carbon monoxide diffusion, the difference was -0.06 mmol/min./kPa per year (95% confidence interval -0.17 to 0.05;  $p = 0.31$ , **Figure 2**). Lung density measured by CT scan was analysed in four different ways in the second trial in an exploratory fashion [13]. We therefore used the average of the four estimates, but it would have made virtually no difference which measurements had been chosen, as they were very similar. Lung density deteriorated slightly less in the active group than in the placebo group; the difference was 1.14 g/l (95% confidence interval 0.14 to 2.14;  $p = 0.03$ , **Figure 3**) (but this was over the total course of the trials, i.e. several years, and not an annual change, as for FEV1).

### DISCUSSION

The two trials were small and only measured surrogate outcomes, apart from quality of life in the second trial [13]. Even for the surrogates, there was no convincing evidence of a beneficial effect of alpha-1 antitrypsin. Measured as FEV1, lung function declined more quickly with active treatment than with placebo ( $p = 0.06$ ;

 **FIGURE 1**

Change from baseline in forced expiratory volume in the first second, ml.

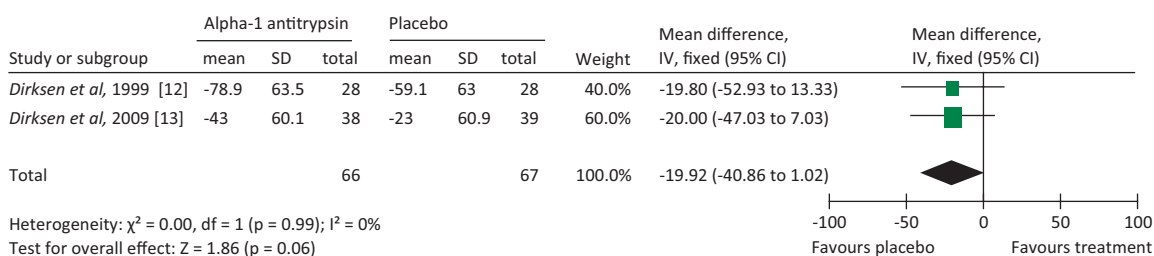


FIGURE 2

Change from baseline in carbon monoxide diffusion, mmol/min./kPa.

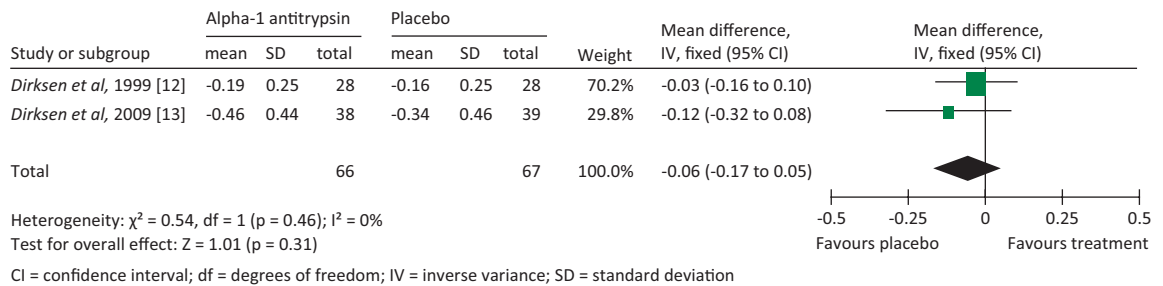
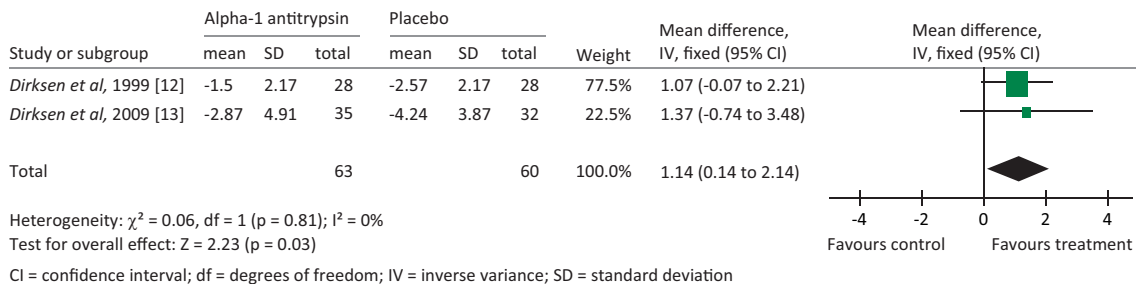


FIGURE 3

Change from baseline in computed tomography lung density, g/l.



whether  $p = 0.06$  or  $0.04$  is immaterial for this judgment). However, the CTs of lung density suggested the opposite, namely that active treatment may decrease loss of lung tissue ( $p = 0.03$ ). In both trials, the CTs showed considerable lung density loss, which was consistent with emphysemal progression. This was also the case in the actively treated group.

The harms were not well elucidated in the trials. In clinical use, serious reactions have been described in 1% of the patients where they took the form of dyspnoea, deterioration of serious heart failure and serious allergic reactions [16]. A report on 747 patients mentioned 720 reactions in 174 patients, 72% of which were moderate and 9% serious [17].

The crucial question for this very expensive treatment, which can amount to as much as 70,000 Euros annually for each patient [16] – and far more, \$150,000, in the USA [15] – is whether it decreases mortality. However, there were no data on mortality in either trial.

A Canadian health technology assessment report concluded that there was no evidence showing health improvement in patients receiving augmentation therapy with alpha-1 antitrypsin [16]. This report reviewed only results from the first trial. A meta-analysis of both trials was presented at a congress, but it represented selective reporting, as it only presented the results of the CTs and not those for lung function measurements [18].

A recent review is also problematic [15]. Its authors, who had substantial conflicts of interest related to companies selling alpha-1 antitrypsin, stated that augmentation therapy should be considered in patients with alpha-1 antitrypsin deficiency “although compelling evidence of benefit is lacking from randomized trials”. They furthermore noted that the guidelines of the American Thoracic Society and the European Respiratory Society recommend augmentation therapy for patients with airflow obstruction related to alpha-1 antitrypsin deficiency. In our opinion, such recommendations are irresponsible. The drug has not shown any clinical effect, it is extremely costly, and it has important adverse effects.

We conclude that augmentation therapy with alpha-1 antitrypsin cannot be recommended. Further studies with surrogate markers will not be helpful, if the aim is to elucidate whether or not augmentation therapy with alpha-1 antitrypsin has a relevant clinical effect. Future studies should be sufficiently large to detect an effect on mortality, if such an effect exists.

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**ACCEPTED:** 1 June 2010

**CONFLICTS OF INTEREST:** None

**ACKNOWLEDGEMENTS:** We thank professor Asger Dirksen for comments on our Cochrane protocol for this review. A similar Cochrane review was published in The Cochrane Library in July 2010.

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