Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease (Review)

Gøtzsche PC, Johansen HK

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Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.


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ABSTRACT

Background

Alpha-1 antitrypsin deficiency is an inherited disorder that can cause lung disease. People who smoke are more seriously affected and have a greater risk of dying from the disease.

Objectives

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

Search strategy

PubMed, the Cochrane Trials Register and ClinicalTrials.gov (7 January 2010), and the Cochrane Cystic Fibrosis & Genetic Disorders Group’s Trials Register (13 March 2009).

Selection criteria

Randomised trials of augmentation therapy with alpha-1 antitrypsin compared with placebo or no treatment.

Data collection and analysis

The two authors independently selected trials, extracted outcome data and assessed the risk of bias.

Main results

Two trials were included (total 140 patients) that ran for two to three years. All patients were ex- or never-smokers and had genetic variants that carried a very high risk of developing chronic obstructive pulmonary disease. Mortality data were not reported. There was no information on harms in the first trial; in the second trial, serious adverse events were reported to have occurred in 10 patients in the active group and in 18 patients in the placebo group. Annual number of exacerbations and quality of life were similar in the two groups; none of the trials reported on average number of lung infections or hospital admissions. Forced expiratory volume in one second deteriorated a little more in the active group than in the placebo group (difference was -20 ml per year; 95% confidence interval
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 CT scan deteriorated a little less in the active 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.

**Authors’ conclusions**

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

**PLAIN LANGUAGE SUMMARY**

**Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease**

Alpha-1 antitrypsin deficiency is an inherited disorder that can cause lung disease. It affects about 1 in 1600 to 5000 people. Those with lung disease suffer from shortness of breath, reduced ability to exercise and wheezing. People who smoke are more seriously affected and have a greater risk of dying from the disease. We reviewed the benefits and harms of treating patients who have the form of the disease that affects the lungs with alpha-1 antitrypsin extracted from human plasma. We found two randomised trials (total 140 patients) comparing this treatment with placebo for two to three years. All patients were ex-smokers or had never smoked but had the genetic problem that carried a high risk of developing lung problems. Neither trial reported on the number of lung infections, hospital admissions or death from the disease. The studies found no difference between the two groups in quality of life or in number of exacerbations of the disease. The lung function deteriorated slightly less measured by CT scan, but slightly more measured by forced expiratory volume in one second. Therapy with alpha-1 antitrypsin cannot be recommended, in view of the lack of evidence of clinical benefit and the high cost of treatment.

**BACKGROUND**

**Description of the condition**

Alpha-1 antitrypsin deficiency is an inherited disorder that can cause lung or liver disease (Genetics Home Reference 2007). The prevalence of the genotype associated with severe alpha-1 antitrypsin deficiency is about 1 in 1600 to 5000 newborns (O’Brien 1978; Sveger 1978). Alpha-1 antitrypsin helps to regulate protease activity. Proteases are enzymes, and enzymes need to be carefully regulated, otherwise they can attack and damage normal tissues.

Cigarette smokers often develop chronic obstructive pulmonary disease. A major constituent of the lung pathology is pulmonary emphysema, which is characterised by loss of lung tissue and enlarged alveolar spaces. 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 (Evald 1990; Hutchison 1988).

The major cause of morbidity and death in severe alpha-1 antitrypsin deficiency is COPD with pulmonary emphysema (Larsson 1978), and liver disease is the second most common complication (Sharp 1971). The emphysema is mainly located in the lower lobes of the lung, whereas smokers with normal phenotype have predominantly 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 to 15 per cent of people with 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 (Genetics Home Reference 2007).

**Description of the intervention**

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.

How the intervention might work

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 (Sveger 1976). Elastase is released by neutrophils when they penetrate into the alveolar wall by chemotaxis induced by cigarette smoke. Replacement therapy with alpha-1 antitrypsin might therefore be beneficial.

Why it is important to do this review

It is important to know whether treatment with alpha-1 antitrypsin is effective for lung disease.

OBJECTIVES

To review the benefits and harms of augmentation therapy with intravenous alpha-1 antitrypsin in patients with alpha-1 antitrypsin deficiency. We restricted the review to trials in lung disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials in any language, published or unpublished.

Types of participants

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 (Shah 2001).

Types of interventions

Experimental intervention: augmentation therapy with alpha-1 antitrypsin.
Control intervention: Placebo or no intervention.

Types of outcome measures

Primary outcomes

1. Mortality
2. Forced expiratory volume in one second (FEV₁)
3. Harms of the intervention

Secondary outcomes

1. Number of exacerbations as defined in the trial report
2. Number of lung infections
3. Number of hospital admissions
4. Quality of life
5. Carbon monoxide diffusion
6. Lung density measured by CT scan

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Group’s Inborn Errors of Metabolism Trials Register using the terms: antitrypsin, “proteinase inhibitor”, Prolastin, Aralast, Zemaira or Trypsolone. The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of The Cochrane Library), quarterly searches of MEDLINE and the prospective handsearching of one journal – Journal of Inherited Metabolic Disease. Unpublished work was identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis & Genetic Disorders Review Group module. Date of last search of the register: 13 March 2009; term: “alpha 1-antitrypsin deficiency”.

We searched PubMed, limited to randomised trials (Appendix 1), the Cochrane Trials Register (Clinical Trials) (Appendix 2) and ClinicalTrials.gov (Appendix 3), with no restrictions for publication year. Date of last searches: 7 January 2010.

Searching other resources

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

Data collection and analysis

For each step below, we resolved disagreements by discussion.
Selection of studies
Two authors independently selected the trials to be included in the review.

Data extraction and management
Two authors independently extracted outcome data; one author extracted descriptive data that were checked by the other author.

Assessment of risk of bias in included studies
Two authors independently 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.

Measures of treatment effect
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 outcomes, we preferred end of treatment values when available rather than change from baseline values, as baseline recordings are not always available in clinical trials, and as investigators are inclined to show baseline differences and adjust for them when this procedure favours the experimental treatment (Gøtzsche 2006a). For continuous data and for average numbers of exacerbations, infections and hospital admissions per patient, we used the mean difference or standardised mean difference, as appropriate, but abstained from doing a meta-analysis if the distribution of the data was non-Gaussian. For time-to-event data, we preferred to use the hazard ratio, but accepted the risk ratio if that was the only statistic available. We present data with 95% confidence intervals.

Dealing with missing data
When trial reports provided insufficient information of potential significance for the results, we contacted the corresponding author.

Assessment of heterogeneity
We assessed heterogeneity statistically and also used I² as a guide to its magnitude (Higgins 2003) (I² goes from zero to 100%).

Assessment of reporting biases
We attempted to assess selective reporting of outcomes within trials, and publication bias related to non-publication of whole trials. If there will be enough trials in future updates of this review, we will look for funnel plots asymmetry.

Data synthesis
We used a fixed-effect model for meta-analysis, unless there was heterogeneity (P < 0.10) or other good reasons for using a random-effects model, e.g. if the interventions were of a very different nature.

Subgroup analysis and investigation of heterogeneity
The reasons for any heterogeneity were explored, e.g. by comparing the characteristics of participants, interventions and outcomes in the included trials. We did not plan any subgroup analyses.

Sensitivity analysis
If possible, we would have performed a sensitivity analysis where only trials with low risk of bias for allocation concealment and blinding were included (Wood 2008).

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of ongoing studies.

Results of the search
We retrieved 144 records on PubMed and 357 in the Cochrane Central Register of Controlled Trials and went through all the records. We identified two placebo controlled randomised trials that were eligible for the review and found a third, ongoing trial on ClinicalTrials.gov that planned to include 180 patients and which will record mortality (NCT00261833 2006).

Included studies
Both trials had recruited patients with genetic variants that carry a very high risk of developing chronic obstructive pulmonary disease (Silverman 2009). The first trial, which was supported by public funds, enrolled 58 patients from Denmark and The Netherlands (Dirksen 1999). The patients were ex-smokers with alpha-1 antitrypsin deficiency of PI*ZZ genotype and had moderate emphysema (FEV₁ between 30% and 80% of predicted). They were treated for at least three years with four-weekly infusions of alpha-1 antitrypsin (250 mg/kg) (brand name not stated) 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. CT scans were also made.
The second trial, registered in ClinicalTrials.gov as NCT00263887, the EXACTLE trial, was financed by Talecris Biotherapeutics, Inc., and had co-authors from the company (Dirksen 2009). The patients were either 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-months extension) with weekly infusions of 60 mg/kg alpha-1 antitrypsin (Prolastin) or 2% albumin as placebo. The primary effect measure was lung density measured by CT scans (although this was considered an exploratory outcome), while lung function measures and other outcomes were regarded as secondary.

Excluded studies
None.

Risk of bias in included studies
See details in the table Characteristics of included studies. In this table, 'Yes' means low risk of bias, 'No' means high risk of bias, and 'Unclear' means that the risk of bias could not be assessed. There were some limitations in the trials, but they were not serious, and overall, the risk of bias was at an acceptable level.

Allocation
The randomisation method in the first trial (Dirksen 1999) was minimization. The procedure was not described, and it was not possible to judge whether it had led to comparable groups, as patient characteristics at baseline were shown 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 scan values (Dirksen 1999). In the second trial (Dirksen 2009), the sequence generation was adequate whereas it was not clear whether there was allocation concealment. There were more males in the active group than in the placebo group, but this could be a chance finding, as the two groups were comparable for other baseline characteristics (Dirksen 2009).

Blinding
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 (Dirksen 1999). The second trial was effectively blinded (Dirksen 2009).

Incomplete outcome data
Outcome data were not available for 2 of the 58 patients in the first trial who dropped out because they resumed smoking (Dirksen 1999), and it was not described to which groups they were randomised. In the second trial, 82 patients were described as enrolled, but only 77 as randomised. Three of the 77 patients withdrew from the active group and seven from the placebo group; data from the CT scans were included from 71 patients, but change from baseline was only available for 67 patients after 2 years, and 34 patients after 2.5 years (Dirksen 2009). We therefore used CT scan data after 2 years.

Selective reporting
We found no signs of selective reporting for the first trial (Dirksen 1999), apart from the fact that the table of baseline values did not give data for the two randomised groups, but from the two countries that were included in the trial. The trial registration for the second trial noted that mortality would be recorded, but this was not reported (Dirksen 2009). Furthermore, the trial report only addressed CT scan measurements, exacerbations and quality of life (Dirksen 2009). For lung function measurements, the report states that "Values for FEV$_1$, DLCO and KCO 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)". We find it inappropriate to not give data on the FEV$_1$ finding in the main report and to dismiss the results by saying that no significant difference was found, particularly because FEV$_1$ is the accepted method that not only is described as the 'gold standard' in the report (Dirksen 2009) but also showed a trend towards a harmful effect of the drug, whereas the CT scan measurements were described as 'exploratory', both when the trial was registered and in the trial report.

Other potential sources of bias
There was no information about possible conflicts of interest in the original report of the first trial (Dirksen 1999). The final version of the 2009 published paper contained a link to “Statement of Interest”, due to a misprint in the journal the published link did not work; however, the statement of interest is available on the European Respiratory Society website (http://erj.ersjournals.com/misc/statements33.dtl#D) (Dirksen 2009). According to other publications, it seems that the first author of both trial reports may have had much influence on the manuscript (Goetzsch 2006b).
Another indication of possible commercial influence may be the fact that the trade name was preferred for the generic name in the trial report.

**Effects of interventions**

End of treatment data were not available, and we therefore used changes from baseline. We did not detect heterogeneity in any of the analyses ($I^2 = 0$).

**Primary outcomes**

1. **Mortality**
   
   Mortality data were not reported in either trial (Dirksen 1999; Dirksen 2009).

2. **Forced expiratory volume in one second (FEV₁)**
   
   When data from both studies are combined, FEV₁ deteriorated a little more in the active group than in the placebo group; the difference was -20 ml per year (95% confidence interval -41 to 1; $p = 0.06$) (Analysis 1.1).

3. **Harms of the intervention**
   
   There was no information on harms in the first trial (Dirksen 1999). In the second trial, serious adverse events were reported to have occurred in 10 patients in the active group and in 18 patients in the placebo group (Dirksen 2009). 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.

**Secondary outcomes**

1. **Number of exacerbations**
   
   Annual number of exacerbations was reported in the second trial, and was 2.6 in the active group and 2.2 in the placebo group ($p = 0.27$) (Dirksen 2009).

2. **Number of lung infections**
   
   Number of infections was not an outcome measure for either trial (Dirksen 1999; Dirksen 2009).

3. **Number of hospital admissions**
   
   None of the trials reported on mean number of hospital admissions (Dirksen 1999; Dirksen 2009).

4. **Quality of life**
   
   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 score at baseline of 44 (Dirksen 2009).

5. **Carbon monoxide diffusion**
   
   For carbon monoxide diffusion, the difference between the active and placebo groups from both studies was -0.06 mmol/min/kPa per year, i.e. deteriorated slightly more in the active group (95% confidence interval -0.17 to 0.05; $p = 0.31$) (Analysis 1.2).

6. **Lung density measured by CT scan**
   
   Lung density measured by CT scan was analysed in four different ways in the second trial in an exploratory fashion (Dirksen 2009). We therefore used the average of the four estimates, but it would make virtually no difference if we had chosen any of them, as they were very similar. When data from both studies were combined, lung density deteriorated a little less in the active group than in the placebo group; the statistically significant difference was 1.14 g/l (95% confidence interval 0.14 to 2.14; $p = 0.03$) (over the total course of the trial and not as annual change, as for FEV₁).

**DISCUSSION**

**Summary of main results**

The two trials were small and only measured surrogate outcomes (FEV₁, carbon monoxide diffusion and CT scans), apart from quality of life in the second trial, and that was not affected by the drug (Dirksen 2009). Even for the surrogates, there was no convincing evidence of a beneficial effect of alpha-1 antitrypsin. Measured as FEV₁, lung function appeared to decline faster with active treatment than with placebo, mean difference -19.92 (95% CI -40.86 to 1.02); whereas the CT scans of lung density suggested the opposite, that active treatment might decrease the loss of lung tissue, mean difference 1.14 (95% CI 0.14 to 2.14). The confidence intervals were wide, and since the effects appear contradictory and of uncertain clinical significance, the results are difficult to interpret. In both cases, one of the boundaries was close to no effect, although it included zero for FEV₁. In both trials, the CT scans showed considerable lung density loss, consistent...
with emphysema progression, in both the active and comparator groups.

**Overall completeness and applicability of evidence**

The harms were not well elucidated in the trials. In clinical use, serious reactions have been described in 1% of the patients in the form of dyspnoea, deterioration of serious heart failure and serious allergic reactions (Chen 2007). A report on 747 patients mentions 720 reactions in 174 patients, 72% of which were moderate and 9% serious (Heresi 2008).

**Quality of the evidence**

The crucial question for this very expensive treatment, which can amount up to 70,000 Euros annually for each patient (Chen 2007), or far more, $150,000, in USA (Silverman 2009), is whether it decreases mortality. However, there were no data on mortality in either trial. According to the Cochrane Handbook for Systematic Reviews, primary outcomes should be essential for decision-making and should usually have an emphasis on patient-important outcomes. This is why we decided that FEV$_1$ and lung density measured by CT scan should be secondary outcomes in the protocol we published for our review, in much the same way as one would consider temperature and thorax X-ray secondary outcomes in a review of an antibiotic for pneumonia. Others may think differently, but they would need to take into consideration that it is a highly bias-prone process to change the status of an outcome and make a secondary outcome a primary one after having seen the data. According to a request from the Editor, FEV$_1$ has changed status from being a secondary outcome to being a primary outcome.

**Potential biases in the review process**

It is difficult to know whether other studies exist that have not been published, but it is reasonable to assume that any such studies would not be likely to change the results of the review in a positive direction.

**Agreements and disagreements with other studies or reviews**

A Canadian health technology assessment report concluded that there was no evidence showing health improvement in patients receiving augmentation therapy with alfa-1 antitrypsin (Chen 2007). 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 mentioned the results of the CT scans and not those for the lung function measurements (Stockley 2008). The authors of a recent review (Silverman 2009) had substantial conflicts of interest related to companies selling alfa-1 antitrypsin. They advised that augmentation therapy should be considered in patients with alfa-1 antitrypsin deficiency “although compelling evidence of benefit is lacking from randomized trials”. They furthermore note that the guidelines of the American Thoracic Society and the European Respiratory Society recommend augmentation therapy for patients with airflow obstruction related to alfa-1 antitrypsin deficiency. In our opinion, these recommendations are not reasonable. The drug has not shown any clinical benefit, it is extremely costly, and it has important adverse effects. A recent meta-analysis found a positive effect of alfa-1 antitrypsin on FEV$_1$ but it included historically controlled before-after studies (Chapman 2009).

**Authors’ Conclusions**

**Implications for practice**

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

**Implications for research**

Further studies with surrogate markers cannot be recommended, if the aim is to elucidate whether or not augmentation therapy with alpha-1 antitrypsin has a relevant clinical effect. Studies should be large enough to detect a possible effect on mortality.

**Acknowledgements**

We thank Prof. Asger Dirksen for comments on our protocol for this review.
References to studies included in this review

Dirksen 1999 [published data only]

Dirksen 2009 [published data only]

References to ongoing studies

NCT00261833 2006 [unpublished data only]

Additional references

Alpha-1 Foundation 2008

Chapman 2009

Chen 2007

CLS Behring 2008

Evald 1990

Genetics Home Reference 2007

Gutzsche 2006a

Gutzsche 2006b

Heresi 2008

Higgins 2003

Hutchison 1988

Larsson 1978

O’Brien 1978

Seersholm 2007

Shah 2001
Sharp 1971

Silverman 2009

Stockley 2008

Sveger 1976

Sveger 1978

Wood 2008

* Indicates the major publication for the study.
### Characteristics of included studies  
**[ordered by study ID]**

**Dirksen 1999**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind, placebo-controlled.</th>
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<tbody>
<tr>
<td>Participants</td>
<td>58 ex-smokers from Denmark and the Netherlands with alpha-1 antitrypsin deficiency of PI*ZZ phenotype and moderate emphysema (FEV$_1$ between 30% and 80% of predicted).</td>
</tr>
</tbody>
</table>
| Interventions | Treated for at least 3 years.  
Experimental: 4-weekly infusions of alpha-1 antitrypsin (250 mg/kg).  
Placebo: 4-weekly infusions of albumin (625 mg/kg). |
| Outcomes | Primary: FEV$_1$.  
Secondary: carbon monoxide diffusion, patient-administered serial spirometry (PASS) at home, forced vital capacity (FVC), VC, lung density with CT scan. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>“Patients were stratified by age, level of FEV$_1$, and nationality and randomized by the minimization method”. Randomisation procedure was not described.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>No details given.</td>
</tr>
</tbody>
</table>
| Blinding? All outcomes | Yes | Described as double-blind and placebo controlled.  
No information on method. |
| Incomplete outcome data addressed? All outcomes | No | Data and group assignment not available for 2 patients who dropped out. |
| Free of selective reporting? | Yes | The table of baseline values did not give data for the two randomised groups, but from the two countries that were included in the trial. |
| Free of other bias? | No | No information about possible conflicts of interest, but according to other publications, the first author had financial conflicts of interest. |
Dirksen 2009

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind, placebo-controlled.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>82 ex- or never-smokers from Copenhagen, Malmö and Birmingham (UK) with severe alpha-1 antitrypsin deficiency (serum concentration &lt;11 µM).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treated for 2 years (with an optional six months extension). Experimental: weekly infusions of alpha-1 antitrypsin (60 mg/kg). Placebo: weekly infusions of 2% albumin.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: lung density measured by CT scan. Secondary: FEV1, carbon monoxide diffusion, frequency of exacerbations, health status (St George's Respiratory Questionnaire).</td>
</tr>
</tbody>
</table>

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Patients were randomised in blocks of 4 for each city; the block size was not disclosed to the study sites. A computer-generated random code was used to produce randomisation envelopes.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Randomisation envelopes were issued to the unblinded pharmacist or designee at each study centre and were 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. It is not clear whether the envelopes were opaque and sealed.</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>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 trial, individual treatment assignments were unknown to the clinicians, the monitors, the CT scan facility, and the sponsor's data management, clinical and biostatistical teams.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear</td>
<td>82 patients enrolled, 77 randomised, 10 of which later withdrew; change from baseline for the CT scans only available for 67 patients after 2 years.</td>
</tr>
</tbody>
</table>
Free of selective reporting? No
Mortality was recorded but not reported. Values for FEV<sub>1</sub>, DL<sub>CO</sub> and K<sub>CO</sub> were not available in the trial report, only on the journal’s web site.

Free of other bias? No
Paper states: “This study was sponsored by Talecris Biotherapeutics, Inc (Research Triangle Park, NC 27709, USA) and was conducted between November 2003 and January 2007. Two of the authors of the manuscript (MW and CD) are employees of Talecris and participated in the design of the study, in the collection, analysis and interpretation of data (CD was the statistician for the study), in the writing of the manuscript and in the decision to submit the manuscript for publication. The article-processing charge would be sponsored by Talecris Biotherapeutics, Inc. Editorial assistance was provided by M. Kenig at PAREXEL and was supported by Talecris Biotherapeutics, Inc.”

**Characteristics of ongoing studies [ordered by study ID]**

**NCT00261833 2006**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>ClinicalTrials.gov identifier: NCT00261833</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Patients with emphysema due to alpha1-proteinase inhibitor deficiency</td>
</tr>
<tr>
<td>Interventions</td>
<td>Alpha1-proteinase inhibitor and placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality, lung density as measured by CT, Number, severity, and duration of exacerbations, lung function as measured by forced expiratory volume in 1 second (FEV&lt;sub&gt;1&lt;/sub&gt;) and lung diffusing capacity for carbon monoxide (DL&lt;sub&gt;CO&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Starting date</td>
<td>January 2006</td>
</tr>
<tr>
<td>Contact information</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td></td>
</tr>
</tbody>
</table>

DL_{CO}: carbon monoxide diffusing capacity  
FEV_{1}: forced expiratory volume at one second
## DATA AND ANALYSES

### Comparison 1. Alpha-1 antitrypsin versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FEV(_1), change (ml)</td>
<td>2</td>
<td>133</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-19.92 [-40.86, 1.02]</td>
</tr>
<tr>
<td>2 Carbon monoxide diffusion, change (mmol/min/kPa)</td>
<td>2</td>
<td>133</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.06 [-0.17, 0.05]</td>
</tr>
<tr>
<td>3 CT lung density, change (g/l)</td>
<td>2</td>
<td>123</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.14 [0.14, 2.14]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Alpha-1 antitrypsin versus placebo, Outcome 1 FEV\(_1\), change (ml).

**Review:** Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

**Comparison:** 1 Alpha-1 antitrypsin versus placebo

**Outcome:** 1 FEV\(_1\), change (ml)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alpha-1 antitrypsin N Mean(SD)</th>
<th>Placebo N Mean(SD)</th>
<th>Mean Difference IV/Fixed, 95% CI</th>
<th>Weight</th>
<th>Mean Difference IV/Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirksen 1999</td>
<td>28 -78.9 (63.5)</td>
<td>28 -59.1 (63)</td>
<td>-19.80 [-52.93, 13.33]</td>
<td>40.0 %</td>
<td>-19.80 [-52.93, 13.33]</td>
</tr>
<tr>
<td>Dirksen 2009</td>
<td>38 -43 (60.1)</td>
<td>39 -23 (60.9)</td>
<td>-20.00 [-47.03, 7.03]</td>
<td>60.0 %</td>
<td>-20.00 [-47.03, 7.03]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>66 -100 (60.1)</strong></td>
<td><strong>67 -50 (59.1)</strong></td>
<td><strong>100.0 %</strong> -19.92 [-40.86, 1.02]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi\(^2\) = 0.00, df = 1 (P = 0.99); I\(^2\) =0.0%

Test for overall effect: Z = 1.86 (P = 0.062)
## Analysis 1.2. Comparison 1 Alpha-1 antitrypsin versus placebo, Outcome 2 Carbon monoxide diffusion, change (mmol/min/kPa).

**Review:** Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

**Comparison:** 1 Alpha-1 antitrypsin versus placebo

**Outcome:** 2 Carbon monoxide diffusion, change (mmol/min/kPa)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alpha-1 antitrypsin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>N/Fixed</td>
<td>95% CI</td>
</tr>
<tr>
<td>Dirksen 1999</td>
<td>28</td>
<td>-0.19 (0.25)</td>
<td>28</td>
<td>-0.16 (0.25)</td>
<td>70.2 %</td>
</tr>
<tr>
<td>Dirksen 2009</td>
<td>38</td>
<td>-0.46 (0.44)</td>
<td>39</td>
<td>-0.34 (0.46)</td>
<td>29.8 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>66</td>
<td>67</td>
<td></td>
<td>100.0 %</td>
<td>-0.06 [ -0.17, 0.05 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

## Analysis 1.3. Comparison 1 Alpha-1 antitrypsin versus placebo, Outcome 3 CT lung density, change (g/l).

**Review:** Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

**Comparison:** 1 Alpha-1 antitrypsin versus placebo

**Outcome:** 3 CT lung density, change (g/l)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alpha-1 antitrypsin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>N/Fixed</td>
<td>95% CI</td>
</tr>
<tr>
<td>Dirksen 1999</td>
<td>28</td>
<td>-1.5 (2.17)</td>
<td>28</td>
<td>-2.57 (2.17)</td>
<td>77.5 %</td>
</tr>
<tr>
<td>Dirksen 2009</td>
<td>35</td>
<td>-2.87 (4.91)</td>
<td>32</td>
<td>-4.24 (3.87)</td>
<td>22.5 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>60</td>
<td></td>
<td>100.0 %</td>
<td>1.14 [ 0.14, 2.14 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0.0%

Test for overall effect: Z = 2.23 (P = 0.026)
APPENDICES

Appendix 1. Search strategy for PubMed (all years)

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>antitrypsin OR “proteinase inhibitor” OR Prolastin OR Aralast OR Zemaira OR Trypsone</td>
</tr>
</tbody>
</table>

Appendix 2. Search strategy for Clinical Trials Database on The Cochrane Library (all years)

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>antitrypsin OR “proteinase inhibitor” OR Prolastin OR Aralast OR Zemaira OR Trypsone</td>
</tr>
</tbody>
</table>

Appendix 3. Search strategy for clinicaltrials.gov (all years)

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>antitrypsin AND placebo</td>
</tr>
</tbody>
</table>

HISTORY
Protocol first published: Issue 2, 2009
Review first published: Issue 7, 2010

CONTRIBUTIONS OF AUTHORS
PCG wrote the first draft of the protocol and of the review and did the statistical analyses, HKJ participated in data extraction and provided comments.
DECLARATIONS OF INTEREST

We have no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- The Nordic Cochrane Centre, Denmark.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned to include head-to-head trials where both groups had received alpha-1 antitrypsin, e.g. in different doses or regimens, but abstained from this, as such trials have little interest as long as it has not been shown that augmentation therapy with alpha-1 antitrypsin has any clinical value compared with placebo or no treatment.

Prof Dirksen was listed as a co-author on the protocol but stepped down from that role for the full review.

According to a request from the Editor, FEV1 has changed status from being a secondary outcome to being a primary outcome.