



TITLE: Alpha1-Proteinase Inhibitor Therapy for Alpha1-Antitrypsin Deficiency: A Review of the Clinical Evidence

DATE: 30 August 2010

CONTEXT AND POLICY ISSUES:

The proteinase inhibitor, alpha-1 antitrypsin (AAT) is predominantly produced in the liver¹ and helps to regulate proteases². Proteases are enzymes which must be carefully regulated, otherwise they can attack and damage normal tissue.² One of the main physiological functions of AAT is the inhibition of neutrophil elastase, an enzyme which has a high potential to destroy lung matrix components.¹

Alpha-1 antitrypsin deficiency is an inherited disease affecting the lung and liver.² In this disease the balance between proteases and antiproteases is disturbed.¹ The majority of the released proteases remain active and slowly proceed to destroy lung matrix components, alveolar structures, and blood vessels. Within a few decades, the progressive destruction results in chronic obstructive bronchitis and lung emphysema.¹ There are some patients with AAT that will not have symptoms nor will they have significant lung function impairment. These individuals with AAT deficiency will only be detected through family screening.³

Treatment of the lung symptoms in patients with AAT deficiency consists of the standard treatment for chronic obstructive pulmonary disease (COPD).⁴ The classes of drugs that are used to treat COPD are: anticholinergic bronchodilators, beta-agonist bronchodilators and inhaled corticosteroids.⁵ Because their mechanisms of action differ, these drugs can be used in combination to control symptoms.⁵ In advanced stages of AAT deficiency, lung transplantation may be necessary.¹

Intravenous augmentation therapy, which consists of the infusion of purified pooled human plasma AAT is now available for the treatment of AAT deficiency. This treatment aims to raise and maintain serum AAT levels above the putative threshold value of 11 $\mu\text{mol/L}$.⁶ In controlled trials the evidence for health benefits from augmentation therapy are inconclusive but outcomes reported in observational studies suggest that there is a benefit in patients with severe AAT deficiency and moderate airflow obstruction.⁷ Therefore, augmentation therapy has been

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approved for patients with AAT deficiency with FEV1 (forced expiratory volume in one second) measures of greater than 30% predicted. A regional health authority has been asked to approve augmentation therapy for a patient with FEV1 of less than 30% predicted. They require information for this policy decision about the use of alpha1-proteinase inhibitor therapy for patients with AAT deficiency with a FEV1 <30% predicted.

RESEARCH QUESTION:

1. What is the current clinical evidence to support the use of alpha1-proteinase inhibitor therapy for patients with alpha-1 antitrypsin deficiency and a FEV1 less than 30% predicted?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including: OVID Medline, Medline In-Process & Other Non-Indexed Citations and Embase; PubMed (for non-Medline records); Wiley's The Cochrane Library (Issue 3, 2010); University of York Centre for Reviews and Dissemination (CRD) databases; EuroScan; international health technology agencies; and a focused Internet search. The search was limited to English language articles published between January 2005 and July 14, 2010. Filters were applied to limit the retrieval to clinical or observational studies, meta-analyses, systematic reviews, or health technology assessments (HTA).

Two reviewers (KG and KC) independently reviewed the titles and abstracts of all the literature identified from the search using specific criteria (Appendix 1). All citations meeting the criteria or for those citations where there was uncertainty or disagreement between reviewers were retrieved for full text review. The literature search identified 459 potential articles and 26 articles underwent full text screening (Appendix 2).

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. No additional evidence was identified.

SUMMARY OF FINDINGS:

Of these 26 articles, one systematic review and meta-analysis that reported results for individuals with FEV1 <30% predicted was identified.⁸

There were an additional five studies (one HTA,⁷ one systematic review and meta-analysis,² three RCTs⁹⁻¹¹) which had the potential to enroll patients with FEV1 <30% predicted but did not report the results for this group separately. One of the RCTs¹¹ was included in the systematic review² and is not summarized individually in this rapid response. A second RCT¹⁰ reported the same results as Dirksen et al.¹¹ and a third RCT⁹ was a bioequivalence study so both were excluded leaving one HTA⁷ and one systematic review.² There were no relevant observational studies identified.

Health technology assessments

Patients with AAT deficiency and potential FEV1 <30%

Chen et al.⁷ conducted a rapid HTA to determine the clinical effectiveness (improved health outcomes, improved intermediate outcomes and reduced harm) of augmentation therapy for patients with AAT deficiency with or without a diagnosis of COPD. A systematic search for clinical evidence on alpha1-proteinase inhibitor therapies for AAT deficiency was performed in multiple bibliographic databases, with additional grey literature searching. Study inclusion was limited to English language studies of any design, including randomized controlled trials (RCTs), cohort studies, case-control studies, and case series. Case reports and review articles were excluded. Both the Jadad scale and the Newcastle-Ottawa Scale (NOS) were used to assess the quality of the included randomized controlled trials (RCTs) and cohort studies, respectively. The authors did not attempt to pool data because the data were unsuitable.

One relevant RCT and four cohort studies evaluating the clinical effectiveness of augmentation therapy were identified. The RCT and three of the four cohort studies were of good quality, as determined by review authors' formal quality assessment. Characteristics of all five studies are summarized in Table 1 (reproduced from Chen et al.⁷). Details on individual study outcome measures and results can be found in Appendix 3.

Table 1: Characteristics of Studies Included in Chen et al. ⁷				
Included Studies	Design	Quality*	Participants' Characteristics	Intervention and Comparator
Dirksen et al. ¹²	RCT	4 out of 5 (Jadad); unclear concealment	26 Danish and 30 Dutch ex-smokers, with moderate to severe emphysema; mean age 50.4±1.64 years for Danish pts, 45.1±1.17 for Dutch pts; FEV1 1,570/mL and 49.4±2.75% pred for Danish pts, 1,660/mL and 47.1±2.58% pred; 14 males and 12 females in Denmark, 20 males and 10 females in the Netherlands; 2 dropouts (both Dutch, resumed smoking); pts from AAT registries	tx=α1-PI infusion every 4 weeks, 250 mg/kg; control=albumin infusion every 4 weeks, 625 mg/kg; tx duration ≥3 years
Seersholm et al. ¹³	Cohort study, R	selection: 3 of 4; comparability: 2 of 2; outcome: 1 of 3 (NOS)	tx=198 German pts, mean age 46±8 years, 142 males, 56 females, Ex-smokers (abstained for ≥3 months); initial FEV1(% pred) 37±14% (patients from WATL database); non-tx=97 Danish pts, mean age 45±10 years,	tx=weekly Prolastin, 60 mg/kg, duration ≥1 year, follow-up 3.2±1.6 years; non-tx=followup 5.8±3.4 years

Table 1: Characteristics of Studies Included in Chen et al.⁷

Included Studies	Design	Quality*	Participants' Characteristics	Intervention and Comparator
			55 males, 42 females, ex-smokers (abstained for ≥3 months), initial FEV1(% pred) 42±10% (patients from Danish α1-Antitrypsin Deficiency Register)	
Chapman et al. ¹⁴	Cohort study, R	selection: 3 of 4; comparability: 2 of 2; outcome: 2 of 3 (NOS)	63 pts, 67% male, 33%, female. FEV1(% pred) ≥50%=28%, FEV1(% pred) 30% to 49%=48%, FEV1(% pred) <30%=24%; tx=21 pts, mean age 50.1±10.1 years; matched control (age, sex, and smoking)=42 pts, mean age 49.3±11.5 years, FEV1(% pred) ≥50%=41%, FEV1(% pred) 30% to 49%=33%, FEV1(% pred) <30%=26% (patients from Canadian AIR Registry)	dosage not indicated, tx duration= 4.4 years, median observation period was 5.6 years
Lieberman ¹⁵	Cohort study, R (pts recruited and surveyed through Internet)	selection: 3 of 4; comparability: 0 of 2; outcome: 1 of 3 (NOS)	tx=96 pts receiving Prolastin, 50 men (all ex-smokers, median age 50 years), 46 women (43 ex-smokers, 3 non-smokers, median age 53 years), 89 pts used for data analysis; control group 47 pts, 12 non-smokers, 24 men (median age 55 years), 23 women (median age 45 years); significant difference between numbers of non-smokers in the 2 groups	various dose frequencies, total dose of Prolastin had been adjusted accordingly to equal 60 mg/kg as weekly dose
AATD Registry Study Group ¹⁶	Cohort study, R	selection: 4 of 4; comparability: 2 of 2; outcome: 3 of 3 (NOS)	total pts=1,129, 1,048 pts used for survival analysis, 927 pts used for FEV1 decline analysis; 30% never, 42% always, and 28% partly received Prolastin; mean age 46±11 years, 55% male, 71% ex-smokers, 21.4% non-smokers, 8.1% current smokers, baseline FEV1(% pred) 49±30%, baseline FEV1 1,748 mL;	dosing frequency varied (inter- and intra-variation); mean length of follow-up (only included survivors) 57±17 months

Table 1: Characteristics of Studies Included in Chen et al.⁷

Included Studies	Design	Quality*	Participants' Characteristics	Intervention and Comparator
			excluded 202 pts with <2 FEV1 readings, this group had more severe airflow obstruction at baseline; pts from NHLBI Registry.	

*Quality of RCT assessed with Jadad scale and adequacy of allocation concealment; quality of cohort study assessed with NOS; WATL=Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen; NHLBI=National Heart, Lung, and Blood Institute; tx=treatment; R=retrospective; pt=patient; NOS=Newcastle-Ottawa Scale; RR=relative risk; P=prospective; IV=intravenous; pred=predicted; NR=not reported.

Review authors concluded that in RCTs, when compared with usual care, alpha1-proteinase inhibitor augmentation therapy has not demonstrated a decrease in lung function impairment in patients with AAT deficiency and COPD. However, based on the available observational studies, authors concluded that AAT augmentation therapy is suggestive of benefit for moderate airflow obstruction (FEV1 between 30% and 65% predicted).

Limitations of this HTA report include the limited number of relevant studies available, and that the majority of the evidence came from nonrandomized studies. Additionally, because this was a rapid review, it was not necessarily as comprehensive as a full HTA or systematic review might have been.

Systematic reviews and meta-analyses

Patients with AAT deficiency and FEV1 <30%

Chapman et al.⁸ conducted a systematic literature review to test the hypothesis that augmentation therapy slows the accelerated decline in lung function, as measured by FEV1, among patients with AAT deficiency. No formal quality assessment scale was used. Studies were included that compared augmentation therapy with a control group and reported long-term (> 1 year) FEV1 follow-up data. They identified one relevant RCT, three non-randomized parallel group comparisons and one before-during therapy comparison. One of the non-randomized parallel group comparison studies and the before-during therapy comparison study enrolled patients with AAT deficiency for post-marketing drug surveillance while the RCT and the remaining two non-randomized parallel group comparisons studies enrolled patients from AAT patient registries. There was a total of 924 patients receiving augmentation therapy (454 patients had FEV1 <30% predicted, 398 patients had FEV1 > 30-65% of predicted and 43 patients had FEV1 >65% predicted) compared to 681 control patients (180 patients had FEV1 <30% predicted, 263 patients had FEV1 30%-65% of predicted and 173 patients had FEV1 >65% predicted). After pooling FEV1 data across all categories, the authors report that augmentation therapy was associated with a 23% slower decline in FEV1 (absolute difference of 13.4 mL/year; 95% CI; 1.5, 25.3). The duration of patient participation in the pooled studies ranged from 1 to 8.5 years. The protective effect of augmentation therapy was primarily attributable to the subset of patients with baseline FEV1 of 30% to 65% predicted. Statistically significant effects on lung function could not be demonstrated in the subsets with baseline FEV1 <30% (absolute difference of 1.8 mL/year; 95% CI; -7.0, 10.5) or >65% (absolute difference of 3.5mL/year; 95% CI; -49.0, 55.9) of predicted. The authors concluded that the results of their meta-analysis lent validity to the proposal that augmentation therapy can reduce lung function

decline in patients with AAT deficiency, and that those with moderate obstruction would be most likely to benefit.

Limitations of this meta-analysis include the limited number of studies from which data was drawn, and the generally increased risk of bias due to the fact that of the five studies included, only one was an RCT and the other four were nonrandomized. Additionally, the RCT had a small sample size of 56, which could limit the statistical power of results. The dosing and scheduling of infusions were not uniform across the five studies and also varied within studies. They ranged from weekly infusions (the most common scheduling) to every four weeks. These factors may limit the generalizability of these results.

Patients with AAT deficiency and potential FEV1 <30%

Gøtzsche and Johansen² conducted a systematic literature search to identify RCTs (published and unpublished) which compared augmentation therapy to placebo or no treatment in non-newborn AAT deficiency patients with or without COPD. No formal quality assessment scale was used, though they reported independently assessing the risk of bias. They identified two trials (n=140 participants in total, FEV1 change results only available for 133) conducted by the same authors, 10 years apart (and the oldest article was the RCT included in the Chen et al.⁷ review). They pooled results for the two trials and reported there was no difference in the annual lung function deterioration, as measured by FEV1, between the active treatment and placebo (albumin infusions). The difference was -19.92 mL/year (95% CI: -40.86, 1.02; p=0.06). The duration of patient participation in the pooled RCTs ranged from 2 to 3 years. A secondary outcome, which was an exploratory measure utilized in both trials, was lung density measured by CT scan. The lung density deteriorated less in the augmentation group as compared to the placebo group with a difference of 1.14 g/L (95% CI: 0.14, 2.14; p=0.03 over the total course of the trial, not annual change). The authors did not recommend augmentation therapy for AAT deficiency due to the conflicting results between outcomes reported in the RCTs (no difference in FEV1 measures, but small difference in lung density).

The limitations of this meta-analysis are again the number of studies and the sample sizes. Also, given that pooled results were not separately presented for patients with a baseline FEV1 measure of <30%, it is unclear whether this patient population was represented in the pooled population and therefore study results cannot necessarily be generalized to a patient population of FEV1 <30%.

Limitations

In total one HTA and two systematic reviews with meta-analyses were identified that assessed the use of alpha1-proteinase inhibitor therapy for patients with AAT deficiency, but not all reports provided data specific to patients with FEV1 <30%. Further, the three included reports had a number of limitations as previously outlined in their summaries which should be considered when interpreting the findings.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

One systematic review⁸ was identified that reported pooled outcomes from three non-randomized parallel group comparisons and one before-during therapy comparison for patients with AAT deficiency and FEV1 <30% predicted receiving augmentation therapy. The authors also pooled data from one RCT and these four nonrandomized studies, and found that there was a slowing of lung function deterioration with augmentation therapy in the subgroup of patients with baseline FEV1 30%-65% predicted but that the effect in the subgroup with baseline FEV1 <30% predicted was not significant.

The other two reviews (one HTA and one systematic review) included enrolled patients with AAT deficiency and FEV1 <30% but did not report the results of the trial for this subgroup separately. Both the rapid HTA⁷ and the systematic review² concluded, based upon the RCT evidence using a FEV1 outcome, that augmentation does not slow the rate of lung function decline compared to control infusions of albumin. Chen et al.⁷ included nonrandomized cohort studies in their review and based upon this evidence they concluded that augmentation therapy is suggestive of a benefit for patients with AAT deficiency and moderate airflow obstruction (FEV1 30% - 65% predicted). Two of the cohort studies included in Chen et al.⁷ did report FEV1 outcome results for the group of patients with FEV1 <30% predicted and the authors concluded that augmentation therapy is not beneficial for this group of patients, which is similar to the conclusions drawn by Chapman et al.⁸

The evidence is insufficient to support a policy decision about funding augmentation treatment for all patients with AAT deficiency and FEV1 <30% predicted. Given the negative impact that this degree of airflow obstruction (i.e., FEV1 <30% predicted) can have on quality of life, it is important that combination therapy with inhaled agents is first optimized, prior to treatment with other agents where there is limited evidence to support their efficacy in this subgroup.

PREPARED BY:

Health Technology Inquiry Service

Email: htis@cadth.ca

Tel: 1-866-898-8439

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APPENDIX 1: Title and Abstract Screening Criteria for Alpha1-Proteinase Inhibitor Therapy

1. Does the patient population have alpha1-antitrypsin deficiency?

Yes No Don't know

2. Is the intervention under evaluation an alpha1-protease inhibitor?

Yes No Don't know

Include for full text screening if 1 and 2 are Yes or Don't know

APPENDIX 2: Full Text Screening Criteria for Alpha1-Proteinase Inhibitor Therapy

Author _____

Publication Year _____

Question	Response	
	Include	Exclude
1 Live HUMAN subjects or study participants	<input type="checkbox"/> Yes <input type="checkbox"/> Maybe <input type="checkbox"/> Can't decide	<input type="checkbox"/> No
2 What is the PATIENT GROUP in this article?	<input type="checkbox"/> Alpha1-Antitrypsin Deficiency with FEV1 < 30% <input type="checkbox"/> Can't decide	<input type="checkbox"/> Doesn't include patients with Alpha1-Antitrypsin Deficiency <input type="checkbox"/> FEV1 is not < 30%
3 What is the INTERVENTION?	<input type="checkbox"/> Prolastin <input type="checkbox"/> Zemaira <input type="checkbox"/> Aralast <input type="checkbox"/> Trypsone <input type="checkbox"/> Can't decide	<input type="checkbox"/> Not an anti-trypsin inhibitor
4 TYPE OF STUDY reported in this article	<input type="checkbox"/> HTA/Systematic review/Meta-analysis <input type="checkbox"/> Randomized Controlled Trials <input type="checkbox"/> Controlled clinical trials <input type="checkbox"/> All Observational Studies (including Case Control, Cross-Sectional, Case Report/Series, Surveys, etc.) <input type="checkbox"/> Can't decide	<input type="checkbox"/> Academic/Narrative Review, Comment, Consensus-based Guideline, Editorial, Letter, Note, Patient Handout, Study Design Description <input type="checkbox"/> Economic Evaluations
5. FINAL DECISION	<input type="checkbox"/> INCLUDE	<input type="checkbox"/> EXCLUDE

Reason for Exclusion: _____

REVIEWER: _____
 DATE _____ (ddmmmyyyy)

APPENDIX 3: Outcomes of Studies Included in Chen et al.⁷

Study	Outcome Measures and Results
Dirksen et al. ¹²	<p>patient-administered serial spirometry at home (mL/year, mean±SE): tx=26.5±15.1, control=25.2±22.0, p=0.96;</p> <p>decline of FEV1 measured at respiratory laboratory (mL/year, mean±SE): tx=78.9±12.0, control=59.1±11.9, p=0.25;</p> <p>15th percentile point of lung density distribution of whole lung by CT (g/L): tx=-1.50±0.41, control=-2.57±0.41, p=0.07;</p> <p>mean levels of serum AAT at 28 days after last infusion (µM): tx=8.8, control=6.2, p<0.001</p>
Seersholm et al. ¹³	<p>decline of FEV1 (mL/year, mean±SD) among German pts: 53.0±37.6 overall 24.2±23.6 for initial FEV1(% pred) <30% 61.8±25.3 for initial FEV1(% pred) 30% to 65% 162.0±28.7 for initial FEV1(% pred) >65%</p> <p>among Danish pts 74.5±59.6 overall p=0.02 30.9±36.3 for initial FEV1(% pred) <30% p=0.6; 82.8±49.3 for initial FEV1(% pred) 30% to 65%, p=0.04; 140.0±83.2 for initial FEV1(% pred) >65%, p=0.7</p>
Chapman et al. ¹⁴	<p>decline in FEV1 (mL/year, 95% CI) tx=29.9, control group=63.6 (40.3 to 86.9), difference=33.7 (6.2 to 61.3), p=0.019</p>
Lieberman ¹⁵	<p>number of lung infections per year: significant difference found between pre-tx and during-tx, p≤0.001; significant difference found between tx (after therapy) and control group, p≤0.001; no significant difference found between tx (before therapy) and control group</p>
AATD Registry Study Group ¹⁶	<p>mortality overall: pts receiving Prolastin versus those not receiving Prolastin (adjusted for gender and other significant predictors) RR=0.64, p=0.02;</p> <p>initial FEV1(% pred) 35% to 49%, lower for pts sometimes or always receiving Prolastin compared with those never receiving Prolastin RR=0.21, p≤0.001;</p> <p>initial FEV1(% pred) ≥50% or <35%, no significant different between groups RR=0.75, p=0.64;</p> <p>decline in FEV1 overall: pts receiving Prolastin did not significantly differ from those not receiving Prolastin, mean difference 4 mL/year, p=0.40;</p> <p>mean FEV1(% pred) of 35% to 49%, slower rate of decline observed for pts receiving Prolastin than for those not receiving Prolastin, mean difference 27 mL/year, p=0.03</p>

tx=treatment; SE=standard error; SD=standard deviation; pt=patient; pred=predicted; RR=relative risk