Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Managing Stable COPD
Alpha-1 antitrypsin replacement therapy
Index

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Dirksen, A., Dijkman, J. H., Madsen, F., Stoel, B., Hutchison, D. C. S., Ulrik, C. S., Skovgaard, L. T., Kok-Jensen, A., Rudolphus, A., Seersholm, N., Vrooman, H. A., Reiber, J. H. C., Hansen, N. C., Heckscher, T., Viskum, K., & Stolk, J. 1999, "A randomized clinical trial of alpha1-antitrypsin augmentation therapy", *American Journal of Respiratory & Critical Care Medicine*, vol. 160, no. 5 I, pp. 1468-1472.	1999	1249
The Alpha 1-Antitrypsin Deficiency Registry Study Group 1998, "Survival and FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin. ", *American Journal of Respiratory & Critical Care Medicine*, vol. 158, pp. 49-59. McElvaney, N., Stroller, J., & Buist, S. 1997, "Baseline Characteristics of Enrollees in the National Heart, Lung and Blood Institute Registry of Alpha 1-Antitrypsin Deficiency.", *Chest*, vol. 111, pp. 394-403. Alpha 1-Antitrypsin Deficiency Registry Study Group, Schluchter, M., Barker, A. F., Crystal, R. G.,	1998	1336 / 1354 / 1355

Robbins, R. A., Stocks, J. M., STOLLER, J., & Wu, M. C. 1994, "A registry of patients with severe deficiency of alpha 1-antitrypsin: design and methods.", *Chest.*, vol. 106, pp. 1223-1232.		
Seersholm, N., Wencker, M., Banik, N., Viskum, K., Dirksen, A., Kok, J. A., & Konietzko, N. 1997, "Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. [see comments]", *European Respiratory Journal*, vol. 10, pp. 2260-2263.	1997	1258

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N=	N=56 Duration & location=1991 to 1995 Danish population / 1993 to 1997 Dutch population.
Research Design	Randomised, parallel, double-blind, placebo controlled trial
Aim	To investigate whether α1-antitrypsin replacement therapy prevents the progression of pulmonary emphysema in patients with α1-antitrypsin deficiency.
Operational Definition	α1-antitrypsin deficiency of PI*ZZ phenotype (FEV1 between 30% and 80% of predicted)
Population	N=26 Danish / N=30 Dutch Moderate emphysema / Ex smokers (validated by 1/12 urinary cotinine throughout trial) Participants were stratified by age, FEV1 and nationality Danish population active / placebo N=13/13. Dutch population active / placebo N=15/15
Intervention	α1-antitrypsin 250mg/kg infusions at 4 wk intervals for at least 3 yrs
Comparison	Albumin 625 mg/kg infusions at 4 wk intervals for at least 3 yrs
Outcomes	Respiratory laboratory testing at baseline and every 3/12, 15 mins after nebulised Terbutaline 5mg, VC, FVC & FEV1

	Self administered spirometry performed morning and evening at home Yearly lung density computed tomography (CT) to assess the degree of emphysema
Characteristics	Male/female ratio differed between centres (Danish 14/12 whilst Dutch 20/10) Mean age – Danish 50yrs / Dutch 45yrs FEV1 – Danish 1,570 ml, 49% predicted / Dutch 1,660 ml, 47% predicted.
Results	Primary outcome: **FEV1** There were no significant differences between the α1-antitrypsin and comparison group for daily self-administered FEV1. α1-antitrypsin group showed an annual decline of 26.5 +/- 15.1 ml compared to the control group of 25.2 +/- +/- 22.0 ml, p=0.96 Secondary outcome: **Lung density** Loss of lung tissue measured by CT was 2.57 +/- 0.41 g/L/yr for placebo compared with 1.5 +/- 0.41 g/L/yr for α1-antitrypsin, equating to an annual loss of lung tissue by 1.07 g/L in comparison to the placebo group (p=0.07). The study authors state, "Power analysis showed that this protective effect would be significant in a similar trial with 130 pts" and that "lung density measurements by CT may facilitate future RCTs". There were no significant differences in the baseline and the time trend lung function variables for either group. No adverse outcomes were observed in either group.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1249

Author / Title / Reference / Yr	The Alpha 1-Antitrypsin Deficiency Registry Study Group 1998, "Survival and FEV1 decline in individuals with severe deficiency of alpha 1-antitrypsin. ", *American Journal of Respiratory & Critical Care Medicine*, vol. 158, pp. 49-59. Ref ID: 1336 McElvaney, N., Stroller, J., & Buist, S. 1997, "Baseline Characteristics of Enrollees in the National Heart, Lung and Blood Institute Registry of Alpha 1-Antitrypsin Deficiency.", *Chest*, vol. 111, pp. 394-403. Ref ID: 1354 Alpha 1-Antitrypsin Deficiency Registry Study Group, Schluchter, M., Barker, A. F., Crystal, R. G., Robbins, R. A., Stocks, J. M., Stoller, J., & Wu, M. C. 1994, "A registry of patients with severe deficiency of alpha 1-antitrypsin: design and methods.", *Chest.*, vol. 106, pp. 1223-1232. Ref ID: 1355
N=	N=1,129. Location=37 clinical centres. Geographic site=USA & Canada. Duration=From March 1989 through October 1992. Follow up over a 44-month period, continued through to April 1996.
Research Design	Prospective, longitudinal natural history study. Cohort Design (Exposed vs non exposed to augmentation therapy)

Aim	The National Heart, Lung and Blood Institute and the National Institutes of Health initiated a registry of people with of α1-antitrypsin deficiency in order to define the natural history and clinical course of the disorder.
Operational Definition	Serum α1-antitrypsin levels 11umol.L confirmed by a Central Phenotyping Laboratory OR A ZZ or ZNull genotype identified by genomic DNA analysis.
Population	Patients with severe deficiency of alpha-1-antitrypsin
Augmentation Therapy	Classification Patients were classified as always, partly, or never receiving α1-antitrypsin therapy. Classification of these subjective categories is provided. Augmentation Therapy Use Among the 1,129 participants enrolled in the study, 34% of patients never received augmentation therapy, 35% always received therapy and 32% were partly receiving therapy. 20% patients were receiving α1-antitrypsin therapy at enrolment in the Registry Within 3 months of enrolling, this percentage increased to 46%. 58% of patients receiving therapy were those with FEV1 <30% predicted. 54% of patients with FEV1 between 30% and 49% predicted were also receiving augmentation therapy within 3/12 of enrolment. Infusion Regimes 53% of patients received augmentation therapy once weekly by infusion 23% received therapy by monthly infusions 24% received intravenous therapy every 2 or 3 weeks
Outcomes	Followed for 3.5 to 7 years with spirometry measurements every 6 to 12 months.
Characteristics	Average age 46 +/- 10 years / 72% symptomatic / 99% white / 56% male / 20% never-smokers, 72% ex smokers and 8% current smokers / 79% family history of lung disease / 25% family history of liver disease
Results	Mortality 5-year mortality was 19% (95% CI: 16 to 21%) Age and baseline FEV1 % predicted were significant predictors of mortality (N=1,048, multivariate analyses >6 months after enrolling). Patients receiving augmentation therapy had decreased mortality (RR 0.64, 95% CI: 0.43 to 0.94, p=0.02) compared to those not receiving therapy. In those participants with initial FEV1 <50% predicted, mortality was significantly higher (p<0.001) for patients who never as opposed to sometimes or always received augmentation therapy. Use of augmentation therapy was associated with lower mortality in the subgroup with initial FEV1 values of 35 to 49% predicted (ATS Stage II) (RR 0.21, 95% CI 0.09 to 0.50, p<0.001)

	FEV1 Mean FEV1 decline was 54ml/yr with more rapid decline in males, aged 30 to 40 yrs, current smokers, FEV1 35 to 79% predicted and those who ever had a bronchodilator response. (N=927 patients with two+ FEV1 measurements >1 yr apart). Among all patients, there was no significant difference in FEV1 decline between augmentation therapy groups. Among patients with a mean FEV1 35 to 49% predicted, FEV1 decline was significantly slower for patients receiving augmentation therapy compared to those who were not (mean difference 27ml/yr, 95% CI: 3 to 51 ml/yr, p=0.03).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	11b
NCC CC ID	1336 / 1354 / 1355

Author / Title / Reference / Yr	Seersholm, N., Wencker, M., Banik, N., Viskum, K., Dirksen, A., Kok, J. A., & Konietzko, N. 1997, "Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. [see comments]", *European Respiratory Journal*, vol. 10, pp. 2260-2263. Ref ID: 1258
N=	N=295 Location=two geographical populations. Geographic site= Danish and German.
Research Design	Cohort study.
Aim	To compare the decline in FEV1 between Danish patients who had never received augmentation therapy and German patients treated with weekly infusion of α1- antitrypsin.
Operational Definition	Not provided
Population	N=97 Danish people with α1- antitrypsin deficiency N=198 German people with α1- antitrypsin deficiency
Intervention	German patients with α1- antitrypsin deficiency and weekly infusions of α1- antitrypsin 60-mg/kg. Duration not stated.
Comparison	Danish patients with α1- antitrypsin deficiency and no augmentation therapy
Outcomes	Decline in FEV1 German population: Lung function measures were carried out prior to commencing augmentation therapy, 1 wk after the start of the study, 3 and 6 months post commencement and then 6 monthly for the treated group. Danish population: Two-spirometry measurements at least 1 yr apart.
Characteristics	**German population (treated):** PiZZ phenotype / ex smokers / received augmentation therapy for at least 1 year / spirometry was performed by specially trained staff as per European recommendations / FEV1 <65% pred / post bronchodilator FEV1. Initial FEV1 % predicted was significantly

	lower at baseline in the treated group compared with the Danish untreated population (FEV1 % pred 37 vs 42 respectively). There were also significantly more males in the German treated population at baseline compared to the untreated group (72 vs 57% respectively). There average follow up time was 3 yrs in the German group and 6 yrs in the Danish group. Average age at entry 46 yrs. **Danish population (untreated):** α1-antitrypsin Pi type was determined by in some cases (numbers not provided) by laboratory phenotyping, however, where this had not been performed the patients were "assumed to have phenotype PiZZ or PiZ0 if α1 antitrypsin serum level was less than 12 umol/L". Spirometry was performed by referring physician or chest clinic according to European recommendations. Not stated whether post bronchodilator FEV1 measured. FEV1 % pred at inclusion not documented. Ex smokers. See above for demographic differences between the two groups. Average age 45 yrs at entry.
Results	FEV1 There was a significant difference between the two groups of 22ml/yr (p=0.02). **Treated group** – Annual declines of 53ml/yr (95% CI, 48 to 58 ml/yr) **Untreated group** – Annual declines of 75 ml/yr (95% CI, 63 to 87 ml/yr) To explore whether the FEV1 differences between the two groups were due to the initial baseline differences between the groups, the impact of variables such as gender, follow up time and initial FEV1% were analysed. Neither gender nor follow up time had any influence on FEV1. Stratification by initial FEV1 % predicted showed a significant effect of the treatment in the group of α1 antitrypsin deficient patients in the augmentation treated only in the group of patients with an initial FEV1% pred of 31 to 65%. In this group FEV1 was reduced by 21ml/yr (p=0.04). Treated group FEV1 % pred 62ml/yr vs 83ml/yr in the untreated group.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	11b
NCC CC ID	1258