Supplementary material - Edgar RG et al - International Journal of COPD March 2017

Treatment of lung disease in alpha-1 antitrypsin deficiency: a systematic review.

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Supplementary methods

Search strategies

The following terms were used in each database, for the time periods described.

Database: Ovid MEDLINE(R) 1946 to April Week 1 2015

Search Strategy:

1 alpha 1-Antitrypsin/
2 alpha-1 antitrypsin.ti,ab.
3 alpha 1 antitrypsin.ti,ab.
4 alpha1 antitrypsin.ti,ab.
5 alpha-1-at.ti,ab.
6 alpha-1-antitrypsin.ti,ab.
7 alpha one antitrypsin.ti,ab.
8 alpha one antitrypsin.ti,ab.
9 AAT.ti,ab.
10 A1AT.ti,ab.
11 AATD.ti,ab.
12 deficien$ or lack$.ti,ab.
13 alpha 1-Antitrypsin Deficiency/
14 or/1-10
15 12 and 14
16 11 or 13 or 15
17 limit 16 to humans

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 09, 2015

Search Strategy:

1 alpha-1 antitrypsin.ti,ab.
2 alpha 1 antitrypsin.ti,ab.
3 alpha1 antitrypsin.ti,ab.
4 alpha-1-at.ti,ab.
5 alpha-1-antitrypsin.ti,ab.
6 alpha one antitrypsin.ti,ab.
7 alpha one-antitrypsin.ti,ab.
8 alfa 1 antitrypsin.ti,ab.
9 AAT.ti,ab.
10 A1AT.ti,ab.
11 AATD.ti,ab.
12 deficien$ or lack$.ti,ab.
13 or/1-10
14 12 and 13
15 11 or 14

Database: Embase (Ovid) 1974 to 2015 April 09

Search Strategy:

1 alpha-1 antitrypsin.ti,ab.
2 alpha 1 antitrypsin.ti,ab.
3 alpha1 antitrypsin.ti,ab.
4 alpha-1-at.ti,ab.
5 alpha-1-antitrypsin.ti,ab.
6 alpha one antitrypsin.ti,ab.
7 alpha one-antitrypsin.ti,ab.
8 alfa 1 antitrypsin.ti,ab.
9 AAT.ti,ab.

10 A1AT.ti,ab.
11 or/1-10
12 deficien$. or lack$.ti,ab.
13 11 and 12
14 AATD.ti,ab.
15 exp alpha 1 antitrypsin deficiency/
16 13 or 14 or 15

Databases : Cochrane Library (Wiley) CENTRAL issue 3 of 12 2015, CDSR Issue 4 of 12 2015, HTA, EED and DARE Issue 1 of 4
Search date: 10/04/2015
Search strategy:
#1 "alpha-1 antitrypsin"
#2 "alpha 1 antitrypsin"
#3 "alpha1 antitrypsin"
#4 "alpha-1-at"
#5 "alpha-1-antitrypsin"
#6 "alpha one antitrypsin"
#7 "alpha one-antitrypsin"
#8 "alfa 1 antitrypsin"
#9 deficien* or lack*
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#11 #9 and #10
#12 AATD
#13 MeSH descriptor: [alpha 1-Antitrypsin Deficiency] explode all trees
#14 #11 or #12 or #13

Correspondence and clarification
E-mail correspondence with Professor A Dirksen (26/02/2016) in regards to:[1]

- Clarification for the method used for the physiological adjustment for CT lung density was confirmed to be the same as previous published work.[2]

E-mail correspondence with Professor A Dirksen (26/02/2016) in regards to:[2]

- Request for unpublished SGRQ raw summary data to enable meta-analysis. Data kindly supplied by Grifols.

E-mail contact with Professor K Chapman (24/02/2016) in regards to[3] including response from CSL Behring:

- Clarification of typographical error in Table 2 of published manuscript[3] for units of DLCO values should be mL/mmHG/min.
- Clarification of differences in data between ClinicalTrials.Gov and published manuscript for change in DLCO. Published manuscript included correct descriptive results and ClinicalTrials.Gov also includes ANCOVA analysis.
- Clarification for the method used for the physiological adjustment for CT lung density was confirmed to be the same as previous published work.[2]

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Custom bias assessment tool for non-randomised studies.

Study Identifying Number:		**Yes**	**No**	**Unclear**	**Final Risk**
Selection	Definition of source information.				
	Clear comparability of groups evident.				
	Indication of time period of data collection documented.				
	Appropriate adjustment for confounding made and detailed.				
Performance	Clear fidelity of the interventions recorded.				
	Clear inclusion exclusion criteria outlining quality of the information regarding who received defined intervention.				
	Evidence of blinding (where appropriate) of participants and healthcare providers.				
Detection	Unbiased and correct assessment of outcome.				
	Assessment of outcome blinded to assessors.				
	A priori outcomes identified and assessed				
Attrition	Completeness of sample evident with adequate explanation for attrition.				
	A priori follow-up period adhered to and complete data accounted for.				
Reporting	Clear reporting of a priori outcomes with clarification of missing data.				
	No evidence of publication biases.				
	No evidence of selective reporting of results.				

Notes:

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Supplementary results

Supplementary table 1: Characteristics of included studies

In the interest of brevity only inclusion criteria has been included in the table.

Placebo Controlled RCTs of augmentation

Author Year	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Outcomes
Dirksen 1999[1]	PiZZ phenotype; moderate to severe emphysema; FEV1 30% - 80% of predicted.	N= 58 Recruited from both the Danish and Dutch AATD Registries Mean FEV1% predicted (SD): Int: 50·0 (15·9) Cont: 46·2 (11·9)	AAT Augmentation(n=28) 250mg/kg body weight intravenously infused every 4 weeks. Minimum treatment duration of 3 years.	Placebo (n=28) Human albumin in an isotonic solution 625mg/kg body weight infused every 4 weeks. Minimum treatment duration of 3 years.	Lung Function - FEV1, SVC, KCO, DLCO and patient-administered serial spirometry - no differences between treatment groups Lung density - Annual rate of decrease in lung density measured by CT scan. Treatment significantly slowed lung density decline. Study underpowered for this outcome.
Dirksen 2009[2]	AAT -serum concentrations <11μM; ≥18yrs; ≥1 exacerbation in past 2 years; post bronchodilator FEV1% ≥25% and ≤80% with FEV1/FVC ratio ≤0·70; Normal Spirometry could be included if KCO was ≤80%; Weight 42kg-92kg;	N=82 77 randomised across 3 sites in Denmark, Sweden and the UK. Mean Age (yrs.) (SD): Int: 54·7 (8·4) Cont: 55·3 (9·8) Sex (male) n (%): Int: 25 (65·8) Cont: 16 (41·0) Mean FEV1% predicted (SD): Int: 46·3 (19·6) Cont: 46·6 (21·0)	AAT Augmentation (n= 35) Prolastin: 60mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Placebo (n= 32) 2% human albumin infused weekly. 2 year treatment. Additional optional 6 month open label extension study.	Lung Density – Trend for rate of lung density slower in treatment not significant. Pulmonary Exacerbations – No difference in patient reported exacerbation frequency. Post hoc analysis showed proportionally fewer 'severe' exacerbations in active treatment group. Lung Function - FEV1, DLCO and KCO all demonstrated no significant differences between treatment groups. Mortality-Nil Quality of life – SGRQ no differences in groups Adverse events – Safe and well tolerated.
Chapman 2015[3]	Aged 18-65years; emphysema 2o AATD; serum AAT ≤11μM; FEV1 35-70% predicted.	N=180 180 randomised across 28 sites in 13 countries. Mean Age (yrs.) (SD): Int: 53·8 (6·9) Cont: 52·4 (7·8) Sex (male) n (%): Int: 48 (51·6) Cont: 50 (57·5) Mean FEV1% predicted (SD): Int: 47·4 (12·1) Cont: 47·2 (11·1)	AAT Augmentation (n=93) Zemaira: 60mg/kg/week Investigational product: AAT60mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 2 year open label extension study in non-US countries.	Placebo (n=87) Lyophilized preparation 60mg/kg body weight intravenously infused weekly. 2 year treatment. Additional optional 2 year open label extension study in non-US countries.	Adverse events – Safe and well tolerated. Lung density - Annual rate of decrease in lung density measured by CT scan. Treatment group significantly slowed lung density decline. Mortality – 1death in treatment group, 3 deaths in control group. Pulmonary exacerbations - time to first exacerbation, rate, duration and severity of exacerbations. No differences Lung Function - FEV1, FEV1/FVC, FVC, DLCO no significant or clinical differences. Quality of Life – SGRQ showed no significant or clinical differences.

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Other AAT augmentation studies

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Outcomes
Weber 1987[4] Uncontrolled Observational	PiZZ AATD, clinical evidence of progressive emphysema, non-smoking.	N= 10 Three centre study in Germany with average pre inclusion follow up of 2·5 years. Of the completers: Mean Age (yrs.) (SD): Int: 48 (5) Sex (male) n (%): Int: 7 (70)	AAT Augmentation (n=10) AAT Augmentation: AAT 60mg/kg body weight intravenously infused weekly. Up to 18 months treatment.		Biochemical – achieved a-priori serum AAT trough levels. Adverse Events – Safe and well tolerated Lung Function – No Change in lung function
Wewers 1987[5] Controlled Observational	PiZZ AATD, Clinical evidence of destructive lung disease.	N=30 Single centre recruitment from National Heart, Lung and Blood Institute (NHLBI), USA. Mean Age (yrs.) (SEM): Int: 46 (2) Cont: 28 (3) Sex (male) n (%): Int: 18 (85·7) Cont: 6 (66·7) Mean FEV1% predicted (SEM): Int: 37 (3) Cont: n/a	AAT Augmentation (n= 21) AAT Augmentation: AAT 60mg/kg body weight intravenously infused weekly. Up to 6 months treatment.	Control = 9 No intervention participants with PiMM phenotype, normal levels of AAT	Lung Function – No changes in lung function observed over the 6 months. Adverse Events – No severe adverse reactions observed. Only 4 "important" adverse events Biochemical – Biochemical efficacy in raising Serum and fluid in the epithelial lining of the lungs AAT trough levels($p<0·0001$), Serum and fluid in the epithelial lining of the lungs anti-neutrophil elastase($p<0·0001$).
Schmidt 1988[6] Uncontrolled Observational	AATD PiZZ phenotype with COPD	N= 20 Recruited from 3 sites in Germany. Mean Age (yrs.) (SD): 46·6 (7·6) Sex (male) n (%): 15 (75) Mean FEV1 L(SD) n=17: 1·1(0·32)	AAT Augmentation (n= 20) AAT (Cutter Biological of Miles Inc., Berkeley, California) 60mg/kg body weight intravenously infused weekly. Up to 6 months treatment.		Adverse Events – Well tolerated and safe. Biochemical – Effective at augmenting circulating serum AAT.
Barker 1994[7] Uncontrolled Observational/ Retrospective chart review.	AATD PiZZ phenotype.	N= 14 Recruited from NHLBI National AAT Registry USA. Mean Age (yrs.) (SD): 50 (6·16) Sex (male) n (%): 10 (71·4) Mean FEV1 L (SD): 1·11 (n/a)	AAT Augmentation (n=14) Prolastin 60mg/kg body weight intravenously infused every 4 weeks. 48 months		Adverse Events – Similar safety profile to previously reported data. Lung Function –No statistical differences before and after treatment
Miravitlles 1994[8] Uncontrolled Observational	Plasma AATD <35% of normal, PiZZ PiNullNull or PiZNull, non smoker, aged 18-75, clinical/radiological evidence of Emphysema and compatible PFT's(FEV1<80% and/or RV>140% of predicted).	N= 13 Recruited from single centre in Italy . Of the completers: Mean Age (yrs.) (SD): 46·6 (9·4) Sex (male) n (%): 6 (46·1) Mean FEV1% predicted (SD):	AAT Augmentation (n= 13) Prolastin 60mg/kg body weight intravenously infused every week for four weeks then 240mg/kg body weight intravenously infused every four weeks. Minimum treatment duration of		Adverse Events – Safe and well tolerated. Biochemical – 3 of 16 participants did not achieve a 'protective' level of AAT. Lung Function – Insufficient data for statistical analysis.

		26 (9·3)	3 years.		
Barker 1997[9] Uncontrolled Observational	AATD serum AAT levels of <50 mg/dL and PIZ genotype; airflow obstruction with an FEV1<75% of predicted; non/ex-smoker >1year; AAT augmentation therapy > 6 months prior to study entry.	N= 23 Patients referred from 4 states across the USA. Mean Age (yrs.) (SD): 51·1 (7·2) Sex (male) n (%): 18 (65·2) Mean FEV1 1 L(SD): 1·22 (0·56)	AAT Augmentation (n=23) Prolastin-C 120 mg/kg body weight every 2 weeks for a total of 9 infusions over a period of 16 weeks. A 10th infusion was administered at week 20, 4 weeks later. 20 month study duration.		Adverse Events - No patient required interruption or discontinuation of infusion. There were no other deaths or serious adverse events. Biochemical – No participants maintained AAT levels >80mg/dl >7 days. Lung Function - FEV1, FVC. No clinically or significant changes
Schwaiblmair 1997[10] Uncontrolled Observational.	AAT PiZZ, PiSZ phenotype; clinical evidence of destructive lung disease.	N= 20 Single centre recruitment in Germany. Mean Age (yrs.) (SD): 48·8 (1·8) Sex (male) n (%): 11 (55) Mean FEV1% predicted (SD): 41·7 (3·1)	AAT Augmentation (n= 20) AAT Augmentation: 60mg/kg once a week. Minimum treatment duration of 3 years.		Adverse Events – Safe and well tolerated. Biochemical – Mean Serum AAT adequately augmented. Lung Function - FEV1, FVC, TLCO, MEF50, RV, TLC at 12, 24 and 36 months. No changes
Seersholm 1997[11] Observational Controlled study.	PiZZ or AAT serum level <12 µmol·L; either FEV1 <65% predicted or annual decline in FEV1 >120mL; non/ex-smoking at enrolment; recipient of AAT augmentation therapy ≥1 yr.; ≥2 spirometries ≥1yr apart. performed during the treatment period; index cases; >25 yrs. of age at entry.	N= 295 Recruited from 25 centres across Germany and from the Danish AATD Registry Mean Age (yrs.) (SD): Int: 46 (8) Cont: 45 (10) Sex (male) n (%): Int: 142 (71·7) Cont: 55 (56·7) Mean FEV1% predicted (SD): Int: 37 (14) Cont: 42 (10)	AAT Augmentation (n= 198) Prolastin: infused weekly at 60 mg/kg body weight Mean follow up duration 3·2±1·6 years.	Control (n= 97) Normal clinical treatment with no AAT augmentation therapy Mean follow up duration 5·8±3·4 years.	Lung Function – 22ml/yr. Slower decline in FEV1in treatment group across all patients(p=0·02). No significant difference in change in FEV1 between the treated group and the untreated group among the patients with the lowest and the highest FEV1% pred. In patients with initial FEV1 of 31–65% predicted, significantly lower rate of decline in FEV1 among the treated patients (p= 0·04).
The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998[12] Observational Controlled study	>18 yr. of age; either AAT serum <11mMol or PiZZ genotype.	N= 1129 Patients from NHLBI AATD Registry USA. 1048 patients used in Survival analysis (no demographics) & 927 used for FEV1 slope analysis. Of the 927: Mean Age (yrs.) (SD): Int Grp 1: 46 (11) Int Grp 2: 47 (10) Cont: 43 (12) Sex (male) n (%): Int Grp 1: 227 (58·1) Int Grp 2: 206 (57·9) Cont: 187 (49·1) Mean FEV1% predicted (SD): Int Grp 1: 37 (18) Int Grp 2: 41 (21)	AAT Augmentation (n= 747 in two groups: 1)390 always received therapy, and 2)357 partly receiving therapy while in the Registry) Prolastin 60mg/kg body weight intravenously infused weekly. Up to 7 years follow up.	Control (n= 382) Normal care naive to AAT augmentation	Lung Function – Overall change in FEV1 was not significantly different between groups. Subgroup into GOLD disease severity by FEV1 decline is slowest in those receiving augmentation p=0·03. Survival – Across all patients no changes. Those with FEV1<50% saw significantly higher (p < 0·001) mortality in subjects who never as opposed to sometimes or always received augmentation therapy.

		Cont: 74 (35)			
Wencker 1998[13] Uncontrolled Observational	>18 yrs.; AATD; FEV1<65% predicted, or annual decline of FEV1>120 mL; non/ex-smoker >3 months prior to the first infusion.	N= 443 Patients from 25 centres throughout Germany. Mean Age (yrs.) (SD): 47 (9) Sex (male) n (%): 292 (65·9) Mean FEV1% predicted (SD): Exsmokers:35·5 (14·8) Non-Smokers: 42·2 (18·2) Of 287 patients included in FEV1 Longitudinal follow up: Mean Age (yrs.) (SD): 46 (9) Sex (male) n (%): 187 () Mean FEV1% predicted (SD): 36·3 (15·2)	AAT Augmentation (n= 443) Prolastin 60mg/kg body weight intravenously infused weekly. Registry study and treatment duration varied.		Lung Function - FEV1 decline showed no differences. Subgroup analysis observed those with FEV1<30% predicted had a significantly slower rate of decline of FEV1 than those with FEV1>30% . Adverse Events – Safe and well tolerated.
Wencker 2001[14] Observational Controlled study	AATD serum levels , 35% of normal regardless of phenotype; FEV1≤65% predicted or decline in FEV1 of . 120 mL/yr.; non-smokers or ex-smokers >3 months.	N= 96 Data taken from the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenkrankungen (WATL) Germany. Baseline demographics: Mean Age (yrs.) (SD): Int: 44·3 (8·6) Sex (male) n (%): Int: 62 (64·6) Mean FEV1% predicted (SD): Int: 41·0 (17·3)	AAT Augmentation (n= 96) Prolastin: 60mg/kg body weight intravenously infused weekly. Mean follow-up after start of augmentation was 50·2 (30·2) months.	Control (n=96) Control group was the same cohort with data taken from at least the year prior to commencement of treatment. Mean follow-up before augmentation was 47·5 (28·1) months.	Lung Function - FEV1 declined significantly slower (p=0·019) after starting therapy - 34·3±29·7(SD)mL/yr. than prior to therapy with AAT augmentation -49·2± 60·8 mL/yr.
Stoller 2002[15] RCT	AATD serum levels <11 mol/L; airflow obstruction, post-bronchodilator FEV1 30-80% of predicted or an FEV1/FVC of <0·70, if FEV1>80%; DLCO <70%; emphysema on CT scan; non-smoking ≥6 months; >18 years; adequate contraception.	N= 28 Multi-centre study in USA. Mean Age (yrs.) (SD): Int: 45 (11) Cont: 49 (7) Sex (male) n (%): Int: 10 (71·4) Cont: 11 (78·6) Mean FEV1% predicted (SD): Int: 48 (18) Cont: 46 (15)	AAT Augmentation (n= 14) Respitin: 60mg/kg body weight intravenously infused weekly. Respitin for 10 weeks, after which all subjects received Respitin at the same dose for a total study duration of up to 2 years.	Control (n=14) Prolastin: 60mg/kg body weight intravenously infused weekly. Prolastin for 10 weeks, after which all subjects received Respitin at the same dose for a total study duration of up to 2 years.	Adverse Events – No differences, safe and well tolerated. Biochemical – Biochemically effective and comparable with control. Lung Function - FEV1, FVC, DLCO No Changes observed.
Stoller 2003[16] Observational Controlled study	Age >18 years; serum AAT level 11 mol/L; or a ZZ or Znull phenotype;	N= 1129 Patients were from the NHLBI AATD Registry USA. Mean Age (yrs.) (SD): 47 (9) Sex (male) n (%): 292 (65·9) Subgroups - always (Grp1), partly (Grp2) or	AAT Augmentation (n= 747 in two groups 1) 390 always received therapy, and 2) 357 were partly receiving therapy while in the Registry) AAT60mg/kg body weight intravenously infused weekly. Follow up 3·5-7 years.	Control (n=382) Normal care naive to AAT augmentation	Adverse events – Participants receiving weekly infusions reported a higher rate and severity of AE's than those treated every 2 to 3 weeks (p=0·020 and p=0·003) or monthly (p=0·001 and p=0·014). But compared to literature safe and well tolerated

		never (Grp3) receiving AAT therapy: Mean Age (yrs.) (SD): Grp 1: 48 (9) Grp 2: 47 (10) Grp 3: 45 (12) Sex (male) n (%): Grp 1: 226 (58) Grp 2: 204 (57) Grp 3: 197 (52) Mean FEV1% predicted (SD): Grp 1: 37 (18) Grp 2: 37 (21) Grp 3: 65 (37)			
Stocks 2006[17] RCT	18-70 years; males & post-menopausal females or non-pregnant, non-lactating females using reliable contraceptive; AATD serum AAT <11 µM and genotypes: PiZZ, PiZ null, or PiNullNull; CT evidence of emphysema; plus ≥1 of the following: chest X-ray evidence of lung destruction, FEV1≤80% , FEV1 decline of ≥35 mL/year or FEV1≥18% of predicted; no AAT augmentation ≥4 weeks prior to screening visit.	N= 44 Recruited from both the Danish and Dutch AATD Registries Mean Age (yrs.) (SD): Int: 50(7) Cont: 56(9) Sex (male) n (%): Int: 21(70%) Cont: 7(50%) Mean FEV1% predicted (SD): Int: 48·0(22·2) Cont: 45·2 (16·7)	AAT Augmentation (n= 30) Zemira: 60mg/kg body weight intravenously infused weekly. 24 weeks treatment	Control (n= 14) Prolastin: 60mg/kg body weight intravenously infused weekly for 10 weeks. Then crossed over to receive Zemira for a further 14 weeks treatment.	Adverse events – Comparatively safe and well tolerated. 1 death in the placebo group. Biochemical – Not inferior to control drug.
Campos 2009[18] Uncontrolled Observational	AATD;-members of AlphaNet (a not-for-profit health management company responsible for co-ordinating services for subjects with AATD), AAT augmentation recipient; presence of obstructive lung disease	N= 1062 Participants were members of AlphaNet USA. Of the 922 eligible: Mean Age (yrs.) (SD): Int: 54·5(9·6) Sex (male) n (%): Int: 485(52·6) Mean FEV1% predicted (SD): Int: 37·5 (19)	AAT Augmentation (n=922) Augmentation type and duration not available· All had been established on treatment for 12 months prior to inclusion to study.		Health Status - No clinically significant changes in SGRQ Exacerbation Rates – oldest sub group had significantly lower exacerbations (p<0·05) Health Care Utilisation - No differences pre and post treatment
Campos 2009[19] Uncontrolled Observational	AATD;-members of AlphaNet, AAT augmentation recipient; presence of obstructive lung disease	N= 1062 Members of AlphaNet USA. Of the 922 eligible: Mean Age (yrs.) (SD): Int: 54·5(9·6) Sex (male) n (%): Int: 485(52·6) Mean FEV1% predicted (SD): Int: 37·5 (19)	AAT Augmentation (n=) Prolastin: intravenously infused data on dosing and frequency was unavailable.		Health Status - No clinically significant changes in SGRQ Exacerbation – No significant differences in frequency.

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Tonelli 2009[20] Observational Controlled study	AATD PIZZ genotype; ≥2 post bronchodilator FEV1, ≥6 months apart.	N=164 The Alpha-1 Foundation DNA and Tissue Bank. Multiple sites across the USA Mean Age (yrs.) (SE): Int: 61·3(0·7) Cont:65·1(1·9) Sex (male) n (%): Int: 59(47·6) Cont: 20(50) Mean FEV1% predicted (SE): Int: 43(2) Cont: 77(5)	AAT Augmentation (n=124) The augmentation therapy used was predominantly weekly intravenous Prolastin 60mg/kg/week (88% of patients) but also Aralast and Zemaira. Insufficient data on dosing and frequency. Patients were on their own Rx and study team had no input. Mean follow up of 41·7 months.	Control (n=40) Usual care no augmentation therapy	Lung Function - statistical difference (p=0·05) in FEV1 decline between 2 groups, augmented group FEV1=10·61± 21·4 mL/yr. non-augmented group FEV1 -36·96 ± 12·1 mL/yr. Survival - No differences were observed in the 5-year mortality rate.
Stocks 2010[21] RCT Double-blind crossover	≥ 18 years; AATD genotype PiZZ, PiZ Null, PiNullNull and serum levels of < 11 µM, or other predefined "at-risk" alleles; recipient of augmentation therapy with Prolastin for at least 1 month prior to study start; FEV1 20%-80% predicted value within the previous 6 months.	N= 24 Multi-centre 16-week crossover study USA. Mean Age (yrs.) (SD): Int: 57·0(9·33) Cont: 58·4(6·86) Sex (male) n (%): Int: 4(33·3) Cont: 6(50·0) Mean FEV1% predicted (SD): Int: 43·8(13·2) Cont: 41·8(13·8)	AAT Augmentation (n=12) Prolastin/Prolastin-C: Weekly intravenous infusions of 60 mg/kg body weight of Prolastin for 8 weeks followed by weekly intravenous infusions of 60 mg/kg body weight of Prolastin-C for 8 weeks followed by an 8 week open label study with 60 mg/kg Prolastin-C	Control (n=12) ProlastinC/Prolastin: Weekly intravenous infusions of 60 mg/kg body weight of Prolastin-C for 8 weeks followed by weekly intravenous infusions of 60 mg/kg body weight of Prolastin for 8 weeks followed by an 8 week open label study with 60 mg/kg Prolastin-C	Adverse Events - No difference. Safe and well tolerated. Biochemical – no inferiority in treatment was observed. Exacerbation Rate – No difference
Vidal 2010[22] Uncontrolled Observational	AATD with pulmonary emphysema; recipient or planned recipient of AAT augmentation	N= 23 9 Hospital sites across Spain. Median Age (yrs.) (IQR): Int: 49(43-61) Sex (male) n (%): Int: 11(47·8) Median FEV1% predicted (IQR): Int: 46·3(39·0-58·0)	AAT Augmentation (n=23) Trypsone: Infusions of 60mg/kg 5 Subjects – 60mg/Kg once a week 18 subjects – 180mg/kg every three weeks		Adverse events – Safe and well tolerated Vital Signs - No Clinically significant changes in vital signs.
Barros-Tizón 2012[23] Observational Controlled study	>18 years; diagnosis of severe AATD (i.e. PI*ZZ genotypes and combinations of Z, rare and null alleles expressing AAT serum concentrations <11 µmol or 50 mg/dl); recipient of continuous augmentation therapy with Trypsone or Prolastin ≥18 months prior to inclusion; available medical records of 18 months before starting augmentation therapy.	N=127 Multicentre study across Spain Mean Age (yrs.) (SD): Int: 51·7(9·1) Sex (male) n (%): Int: 81(63·8) Mean FEV1 L (SD): Int: 1·25(0·5)	AAT Augmentation (n=127) Differing treatments and dosing regimes Prolastin: 68 patients (53·5%) Trypsone: 59 patients (46·5%). Weekly Therapy: 8 patients (6·3%) Bi-Weekly Therapy: 22 patients (17·3%) Every 3 weeks: 97 patients (76·4%) The average AAT concentrate dose administered was 60·7 ± 3·8 mg/kg/week		Exacerbation rate - Reductions in administration of systemic antibiotics prior to and following commencement of augmentation therapy was observed, p<0·05. Reductions in exacerbations per patient (p<0·01). Lung Function - Statistically significant decline FEV1 (L) for the total patient population p < 0·05 were observed however this is within normal decline. Health care cost (Hospitalisation only) – Saving of €416·76 per patient Adverse Events – Safe and well tolerated.
Subramanian 2012[24]	≥18 years old; FEV1/VC < 0·7; AAT serum level < 11 µM or < 80 mg/dL and PiZ	N=29 Single centre open label UK study. 3 groups; healthy control, non AAT related COPD, and	AAT Augmentation (n=10) Prolastin: 12 Weekly intravenous infusions of 60		Change in Neutrophilic inflammation measured by PET scanning – No Changes pre and post treatment.

Uncontrolled Observational	phenotype.	AATD related COPD. Only data for AATD patients used. Of the 10 AATD patients: Mean Age (yrs.) (SE): Int: 57·2(2·9) Sex (male) n (%): Int: 9(90) Mean FEV1% predicted (SE): Int: 51·5(5·7)	mg/kg body weight		
Campos 2013[25] RCT Double bling Cross-over	Aged 18-70 years; severe AATD; serum AAT level<11 µM; diagnosis of COPD; FEV1 of ≥30% and ≤80% of predicted.	N=30 5 centre across the USA. Mean Age (yrs.) (SD): G1: 57·4(6·34) G2: 59·7(6·89) Sex (male) n (%): G1: 7(46·7) G2: 7(46·7) Mean FEV1% predicted (SD): G1: 49(12·4) G2:54(14·5)	AAT Augmentation (n=15) Group 1-Prolastin-C 120/60: Weekly intravenous infusions 120mg/kg for 8 weeks. After a 2 week washout period patients were crossed over to the alternate dose of 60mg/kg for a further 8 weeks.	Control (n=15) Group 2-Prolastin-C 60/ 120 :Weekly intravenous infusions 60mg/kg for 8 weeks. After a 2 week washout period patients were crossed over to the alternate dose of 120mg/kg for a further 8 weeks.	Biochemical - trough serum alpha PI concentration higher in 120mg/Kg than 60 mg/kg Adverse Events - No clinically significant defences between treatment groups. Drug well tolerated
Sandhaus 2014[26] RCT double blind, partial crossover	≥18 years; lung disease related to "at-risk" alleles i.e. null and deficient alleles associated with plasma levels <11 µM organ transplant	N=50 3 Sites across the USA Mean Age (yrs.) (SD): Int: 55·4(7·7) Cont: 55·7(9·2) Sex (male) n (%): Int: 17(51·5) Cont: 8(47·1) Mean FEV1% predicted (SD): Int: 46·05(17·17) Cont: 47·24(22·8)	AAT Augmentation (n=33) Glassia: 12 weekly intravenous infusions 60mg/kg per week. An optional 12 week open label trial was an option after this time.	Control (n=17) Prolastin: 12 weekly intravenous infusions 60mg/kg per week. An optional 12 week open label trial was an option after this time.	Adverse Events - No clinically significant defences between treatment groups. Biochemical – No inferiority observed Lung Function - Mean FEV1 and % predicted were similar at baseline, week 12 and 24 for both groups.

Surgical management

Lung Transplant

Author year Study design	**Population Inclusion Criteria**	**Participants**	**Intervention (N)**	**Comparator (N)**	**Outcomes**
Breen 1992[27] Retrospective registry review	Recipient of Lung transplant in the USA between October 1987 to December 1991	N=8959 thoracic organ transplants. Only Lung transplants were considered due to data reporting. Of all 699 lung transplants: Sex (male) n (%): 325(46·5%)	Lung Transplant (n=99) due to AATD related emphysema within the USA within study period	Control (n=600 of which 396 list primary indication for transplant) Lung Transplant: for other cause not due to AATD related disease within the USA within study period	Mortality - COPD/Emphysema group (75·4%±4·4SE) over the AATD group (64·4%±5·4SE). No statistical significance.
Cassivi 2002[28] Retrospective	Standard lung transplant recipient criteria was used. Disabling lung disease with a limited prognosis and no	N=306 Single centre retrospective registry review between 1988 and 2000 in USA. Mean Age (yrs.) (SD):	Lung Transplant (n=86) Lung transplantation due to AATD. Follow up to 5 years	Control (n=220) Lung transplantation not due to AATD related disease.	Morbidity and Mortality – No superior survival rates. Lung Function - FEV1, FVC, PaCO2 No significant differences

registry review	other systemic illness that would complicate or be complicated by lung transplantation and immunosuppression.	Int: 48·9(6·3) Cont: 55·2(6·4) Sex (male) n (%): Int: 57(66·3) Cont: 86(39·1) Mean FEV1% predicted (SD): Int: 54(17) Cont: 51(14)			6 Minute walk test - No significant differences.
de Perrot 2004[29] Retrospective registry review	All transplants at the site were considered for inclusion and recipients were selected according to the guidelines outlined by the International Society for Heart and Lung Transplantation and the American Thoracic Society.	N=501 Single Canadian site Lung Transplantations between 1983 and 2003. Total cohort of 501 only 151 have report of AATD and Non-AATD related emphysema. Only full cohort demographic available. Sex (male) n (%): Full cohort: 263(52·5)	Lung Transplant (n=63) Patients with a diagnosis of AATD undergoing lung transplant	Control Lung Transplant (n=88) Patients with normal AAT serum levels and non-AATD related emphysema undergoing lung transplant.	Mortality – Significantly better survival for control group, COPD, compared to AATD group=0·04.
Burton 2005[30] Retrospective registry review	Selection for transplantation was in accordance with the Institute for Heart and Lung Transplant and the European Respiratory Society.	N=362 Single Danish site report of Lung Transplantation 1992 - 2003. 349 had a reason for transplant recorded; analysis limited to these Of the 349 with diagnosis: Age, yrs. (range): Int median: 49(18-65) Cont mean: 39(11-71) Sex (male) n (%): Int: 16(53·5) Cont: 107(40·7)	Lung Transplant (n=86) Patients undergoing lung transplantation with a primary diagnosis of AATD. All transplant types were considered including Single, Double (sequential or bloc) and heart lung transplant.	Control Group (n=263) Patients undergoing lung transplantation with a primary diagnosis of COPD, Cystic Fibrosis, Pulmonary Fibrosis (PF), Eisenmengers or Primary Pulmonary Hypertension. All transplant types were considered as in AATD	Mortality: 90day survival better than PF, Eisenmengers or 1e Pulmonary Hypertension. Improved Survival at 1 and 3 years over PF. Comparable 5 and 10 year survival with other reasons for Tx
Gunes 2006[31] Retrospective registry review	Standard Lung transplant screening was carried.	N=173 Single centre registry 1989–2003 in Australia. Mean Age (yrs.) (SD): Int: 47·8(6·1) Cont: 51·7(4·7) Sex (male) n (%): Int: 18() Cont: 57() Mean FEV1% predicted (SD): Int: 17(8) Cont: 16(8)	Lung Transplant (n=61) Patients undergoing lung transplantation with a primary diagnosis of Emphysema related to AATD. All transplant types were considered including Single, Double and heart lung transplant.	Lung Transplant (n=112) Patients undergoing lung transplantation with a primary diagnosis of smoking-related emphysema. All transplant types were considered as for AATD	Mortality – no survival difference between the groups.
Christie 2008[32] Retrospective registry review	Eligible for Lung transplantation in accordance with the Institute for Heart and Lung Transplant guidelines.	N=19792 The Registry of the International Society for Heart and Lung Transplantation (ISHLT), USA, between 1984 and 30/06/2007. No subgroup demographic data available.	Lung Transplant (n=1509) Patients on the ISHLT registry with a primary diagnosis of AATD.	Lung Transplant (n=18283) Patients on the ISHLT registry with a primary diagnosis other than AATD	Mortality - superior 10 year survival in AATD over COPD and IPF
Tanash 2011[33]	Eligible for Lung transplantation in accordance	N=153 All patients in Swedish AATD Registry 1990 –	Lung Transplant (n=83) 83 PiZZ patients with severe	Control (n=70) After exclusions 70 matched	Mortality - 1, 3, 5 and 10 years. Survival benefit in lung transplant

Retrospective case control Study	with international criteria; PiZZ; aged >18.	June 2010. Mean Age (yrs.) (Range): Int: 52(32-66) Cont: 54(35-70) Sex (male) n (%): Int: 48(58) Cont: 42(60) Mean FEV1% predicted (SD): Int: 22(9) Cont: 23(6)	emphysema underwent Lung Transplant in Sweden. Mean follow up 7±5 years	AATD controls who fulfilled the international criteria for Lung Transplant were included who were not transplanted during the same period.	(p=0·006); improved estimated median survival in transplant of 11 years (95% [CI] 9 to 14 years) compared to no transplant median survival 5 years (4 to 6).
Banga 2014[34] Retrospective Cohort	Lung transplant recipients with an indication of COPD (AATD or AAT-replete) within study investigation period.	N=276 Patient undergoing LT at a single centre from June 1991 – Jan 2008 USA. Registry data Cleveland Clinic LT patients Mean Age (yrs.) (SD): Int: 49(7·5) Cont: 57(6·1) Sex (male) n (%): Int: 27(60) Cont: 114(49) Mean FEV1% predicted (SD): Int: 20(5·4) Cont: 20(7·1)	Lung Transplant (n=45) Patients undergoing Lung Transplant with an indication of COPD related to AATD	Controls (n=231) Patients undergoing Lung Transplant with an indication AAT-replete COPD	Lung Function - No significant differences Mortality - No significant differences Post-transplant cellular rejection - No significant differences.
Bredahl 2014[35] Retrospective observational cohort study.	Lung Transplant recipient at the single site study; AAT levels <11 µM or 0·5g/L, Genotype PiZZ or PiSZ.	N=258 Single Danish centre recruited between Jan 2004 and Dec 2012. Comparisons between COPD/Emphysema group and AATD. Of the 126 COPD/Emphysema and AATD groups: Mean Age (yrs.) (SD): Int: 53·0(7·2) Cont: 54·6(6·9) Sex (male) n (%): Int: 31(61) Cont: 27(36)	Lung Transplant AATD (n=51) Patients undergoing Lung transplant who have confirmed AATD	Lung Transplant (n=75) Patients undergoing Lung transplant who have non-AATD related COPD/Emphysema.	Post transplant Laparotomy - AATD group has significantly increased risk of early post-operative laparotomy (estimated odds ratio 5·74, 95%CI 2·15 to 15·35) Mortality – No differences between groups
Inci 2014[36] Retrospective registry review.	Lung transplant recipient within study investigation period.	N= 108 Single centre review between November 1992 and August 2013 in Switzerland. Only group demographics supplied as conference abstract. Of the completers: Mean Age (yrs.) (range): 56·6 (31-68)	Lung Transplant (n=31) AATD patients receiving lung transplantation.	Lung Transplant (n=77) Non-AATD related COPD patients receiving lung transplantation.	Mortality – 30-day, 1 and 5 year. No survival benefits.
Stone 2016[37] Retrospective Registry Cohort Study	Patients attending the ADAPT Programme (Antitrypsin Deficiency Assessment and Programme for Treatment), between May 1996 and 12th December	N= 170 AATD patients from the UK national registry. Transplant performed at multiple centres across the UK. 3 separate matching groups. Mean Age (yrs.) (SE): Int: 53·6(1·18)	Lung Transplant (n=32) AATD patients receiving lung transplantation at a UK centre.	Control (Group1 n=48 & Group 2 n=60, Group1 n=30) Matched AATD not receiving lung transplant. Group 1 – Matched at baseline for age, smoking, BMI, FEV1,	Mortality – No statistically significant survival benefit transplant 10·1years to non-transplant 8·4 years p=0·95 . Quality of Life – Improvements post transplant in SGRQ, p<0·01.

	2011; PiZZ genotype, AAT augmentation therapy naïve.	Cont1: 53·0(0·98) Cont2: 54·8(0·9) Cont3: 53·8(47·8-57·6) [Median (IQR)] Sex (male) n (%): Int: 23 (72) Cont1: 34(71) Cont2: 42(70) Cont3: 21(70) Mean FEV1% predicted (SE): Int: 32·1(1·47) Cont1: 26·3(1·08) Cont2: 25·1(1) Cont3: 25·3(21·3-31·4) [Median (IQR)]		Co-morbidity. Group 2 – As Group 1 but matched at point of transplant with the addition of measures of gas transfer. Group 3 - As Group 2 with the addition of measures of SGRQ.	

Lung Volume Reduction

Author year Study design	Population Inclusion Criteria	Participants	Intervention (N)	Comparator (N)	Outcomes
Cassina 1998[38] Prospective cohort observational	FEV1<1·1 L and TLC >120% of the predicted value; MRC dyspnoea score >2 Poor QoL (SF 36) Radiographic evidence of heterogeneous emphysema with target zones for LVRS; absence of bullae >5cm; matched ventilation–perfusion scan.	N=30 Consecutive patients attending single centre for LVRS in Switzerland. Mean Age (yrs.) (SD): Int: 49(10) Cont: 58(11) Sex (male) n (%): Int: 7(58·3) Cont: 15(83·3) Mean FEV1% predicted (SD): Int: 24(7) Cont: 31(6)	LVRS (n=12) Bilateral LVRS for AATD related disease: patients with a diagnosis of AATD undergoing bilateral LVRS	Control LVRS (n=18) Bilateral LVRS for Non-AATD related disease: patients undergoing bilateral LVRS who do not have AATD.	Lung Function - FEV1 superior benefits at 6, 12 and 24 months in non-AATD related COPD p<0·05. 6MWT significant benefits control v AATD at 12 and 24 months, p<0·05 MRC dyspnoea score – Non AATD COPD patients less breathless than AATD at 24months
Fujimoto 2002[39] Prospective observational.	Marked hyperinflation; radiographic evidence of heterogeneous emphysema; FEV1<1·2 L or FEV120–35%; TLC >120%; RV >250%; MRC dyspnea score ≥2; poor QoL (SF-36); Abstinence from smoking; Acceptable nutritional status; and rehabilitation potential	N=88 Prospective enrolment from single site in Essen Germany of patients undergoing LVRS for severe Emphysema. Only whole group data available: Mean Age (yrs.) (SD): Int:56·1(9·1) Sex (male) n (%): Int: 62(70·5) Mean FEV1% predicted (SEM): Int: 27·5(0·8)	LVRS (n=11) Bilateral LVRS for AATD related disease: Patients with a diagnosis of AATD undergoing bilateral LVRS Mean Follow up was 54·2 ±2·2 months	LVRS (n=77) Bilateral LVRS for Non-AATD related disease: Patients undergoing bilateral LVRS who do not have AATD.	Lung Function – AATD only observes FEV1 benefit for 6 months whilst control group maintain benefit up to 2years. Mortality – No survival benefit between the two groups.
Tutic 2004[40] Prospective cohort observational	Severe A1-ATD; selected for LVRS according to previously published Criteria.	N= 42 patients recruited prospectively from a single centre in Switzerland. Of the completers: Mean Age (yrs.) (SE): Int: 56(2) Cont: 57(1·8) Sex (male) n (%):	LVRS (n=21) LVRS for AATD related disease meeting the published criteria for LVRS at the single site	LVRS (n=21) LVRS for Non-AATD related COPD meeting the published criteria for LVRS at the single site that have emphysema but a clinically normal level of circulating AAT.	No significant differences between AATD and non AATD related lung disease. Lung Function – Significant improvements in FEV1, IVC, RV/TLC p<0·05 at 6 months. Physiologic measures - Significant improvements in 6minute walk test distance and MRC Dyspnoe score p<0·05 at 6 months.

		Int: 11(52·4) Cont: 12(57·1) Mean FEV1% predicted (SE): Int: 27(1·9) Cont: 28(1·9)			
Dauriat 2006[41] Observational cohort	Severe airflow obstruction (FEV1<40% predicted); hyperinflation; Fletcher dyspnea score > 2; CT scan evidence of heterogeneous emphysema.	N=52 All procedures performed at a single French centre by the same surgeon. Of the completers: Mean Age (yrs.) (SD): Int: 56(9) Cont: 54(11) Mean FEV1% predicted (SD): Int: 22·2(5·7) Cont: 28(11·9)	LVRS (n=17) Patients with AATD underwent unilateral LVRS performed in all cases via unilateral thoracotomy. The worst areas of emphysematous lung were resected by stapling guided by the results of CT and lung perfusion scan.	LVRS (n=35) Patients with Non-AATD related emphysema treated as per AATD patients	Lung Function – At 1 year FEV1 is statistically more improved in the non AATD deficient, p<0·005
Stoller 2007[42] Retrospective secondary analysis of larger RCT.	AAT serum <80 mg/Dl; PiZZ, PiNull or PiZNull phenotypes or others recognised as severe deficient; or PiSZ and AAT<80mg/Dl	N=16 Sub-group of the National Emphysema Treatment Trial (n=1218) RCT in LVRS in the USA. Median Age (yrs.) (Range): Int: 65·8(55·4-77·0) Cont: 67·5(50·1-70·8) Sex (male) n (%): Int: 8(80) Cont: 6(100) Median FEV1% predicted (IQR): Int: 27·0(26·0-32·0) Cont: 25·0(21·0-33·0)	LVRS (n=10) Patients data randomised to a larger trial was extracted and those receiving either unilateral or bilateral LVRS with a target goal of 20% to 30% resection of the most disease area. Follow up was a maximum of 60 months	Control (n=6) Medical treatment/usual care: Patients data randomised to a larger trial was extracted and those receiving usual care with no surgical intervention were grouped.	Mortality - higher 2 year mortality (20% compared to 0%) in the surgical group. Quality of Life – Surgical group demonstrated improvements in SGRQ.
Hillerdal 2014[43] Retrospective uncontrolled observational case series.	Homozygotic AATD;<80years of age; RV ≥140%; FEV1 15-45% predicted; CT confirmed severe heterogeneous emphysema; symptoms severely restricting QOL; Lack of other serious disease; Optimal medical management including Smoke Cessation; vaccination; LTOT and PR.	N=15 Single Swedish centre; all patients August 2008 –January 2012. Of the completers: Mean Age (yrs.) (range): Int: 64(48-79) Sex (male) n (%): Int: 7(46·7) Mean FEV1% predicted: Int: 25	Endobronchial Lung Volume Reduction (n=15) Consecutive AATD patients referred for and receiving Endobronchial Lung Volume Reduction (ELVR-Zephyr Valves-Pulmonx Inc.).		Lung Function change- significant benefits in mean FEV1 at 6 months, 1 year and 2 years (p=0.0022, p=0.0067 and p=0.033 respectively). Safety – valves can be safely deployed in carefully selected patients.

Medical managements used in usual COPD

Author year Study design	**Population Inclusion Criteria**	**Participants**	**Intervention (N)**	**Comparator (N)**	**Outcomes**
Campos 2008[44]	Verbal confirmation of diagnosis of AATD; members of AlphaNet;	N= 939 Participants were members of AlphaNet USA.	Influenza Vaccinated (n=766) Participants performed monthly telephone interviews for data	Not Vaccinated (n=173) Participants performed monthly telephone interviews for data	Lung Function – No effect Exacerbations – no differences between exacerbations between years.

Observational study	receiving AAT augmentation therapy; Confirmed obstructive lung disease.	Sex (male) n (%): Int: 86 (49·7) Cont: 87 (50·3)	collection including data on vaccination. They were requested to submit recent available lung function data. Between Week 40 2003 to week 20 2004.	collection including data on vaccination. They were requested to submit recent available lung function data. Between Week 40 2003 to week 20 2004.	Health Care Utilisation – Vaccinated participants had fewer unscheduled OPD Dr. visits (p=0·04 and ICU hospitalisation, emergency department visits, scheduled and unscheduled outpatient visits p=0·04, and fewer ICU admissions, 0·01
Campos 2009[45] Observational study	Verbal confirmation of diagnosis of AATD; members of AlphaNet; receiving AAT augmentation therapy; Confirmed obstructive lung disease.	N= 878 Participants were members of AlphaNet and self controlled with data from previous 12 months USA. Mean Age (yrs.) (SD): Int: 54·4 (9·6) Sex (male) n (%): Int: 465 (52·9) Mean FEV1% predicted (SD) n=627: Int: 36·8 (16·9)	Multi-modal self management programme (ADMAPP) (n=878) Combination of directed patient self-education, organised supervision, health care provider education and outcome measurements.	Self controlled (n=878) Use of year 1 data prior to implementation of ADMAPP. 878 patients completed 22 of 24 monthly surveys so data is restricted.	Exacerbations – Frequency, severity, duration, medication usage Health Care Utilisation – Statistically significant improvements in some medications (LABA p<0·001, Theophylline p=0·01, systemic steroids p=0·02) and supplementary oxygen p<0·01 compliance were observed and small reductions in annual exacerbations (p<0·001) and their duration (p=0·04) were observed. There were no significant changes to health status scores QoL - No significant changes.

Other

Author year Study design	**Population Inclusion Criteria**	**Participants**	**Intervention (N)**	**Comparator (N)**	**Outcomes**
Stolk 2012[46] RCT	>30 years of age; females non-childbearing potential; PiZZ, PiZNull or PiNull genotype; Never/ex-smokers ≥6 months; clinical/radiographic emphysema; TLCO or KCO <70% ; post-bronchodilator FEV1≤80% ; AAT augmentation therapy naïve; no oral steroids >28 days prior to enrolment.	N=262 Subjects from 10 worldwide AAT registries. Mean Age (yrs.) (SD): Int: 54·7 (8·6) Cont: 53·9 (8·6) Sex (male) n (%): Int: 71 (55·0) Cont: 73 (54·9) Mean FEV1% predicted (SD): Int: 46·4 (16·8) Cont: 46·8 (16·7)	Palovarotene (n=110) Two capsules per day of Palovarotene (RO3300074) 2·5 mg per capsule, following the first meal of the day taken for 12 months.	Placebo (n=110) Two capsules per day of Placebo following the first meal of the day taken for 12 months.	Lung Function - FEV1, SVC, TLC, FRC, RV, KCO, DLCO (12, 24, 36 and 52 weeks) Lung density - measured by CT scan (Baseline, 6 and 12 months). Exacerbations - Frequency Adverse Events –Safe Tolerated well

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Supplementary table 2: Risk of bias in included studies

RCT

Study	Random sequence generation	Allocation concealment	Blinding of patients	Blinding of outcome assessments	Incomplete outcome data		Selective Outcome Reporting	Overall Bias
					Treatment group	Control Group		
Dirksen 1999[1]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
Stoller 2002[15]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Stocks 2006[17]	Low	Low	Low	Low	Low	Low	Low	Low
Dirksen 2009[2]	Low	Unclear	Low	Low	Unclear	Unclear	High	Unclear
Stocks 2010[21]	Low	Low	Low	Unclear	Low	Low	Low	Low
Stolk 2012[46]	Unclear	Low	Unclear	Unclear	Low	Low	Low	Low
Campos 2013[25]	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Sandhaus 2014[26]	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Chapman 2015[3]	Low	Low	Low	Low	Low	Low	Unclear	Low

Prospective Controlled Observational

Non Randomised Studies	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Bias
Campos 2008[44]	High	Unclear	Low	Low	Low	Low
Campos 2009[45]	High	Unclear	Unclear	Low	Low	Low

Prospective Uncontrolled Observational and Cohort

Non Randomised Studies	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Bias
Weber 1987[4]	Low	High	Unclear	Low	High	Low
Cassina 1998[38]	Low	Low	Low	Low	Low	Low
Fujimoto 2002[39]	Low	Low	Unclear	Low	Low	Low
Tutic 2004[40]	Low	High	High	Low	High	High
Dauriat 2006[41]	High	Low	Low	Low	Low	Low
Campos 2009[18]	Low	Low	Unclear	Unclear	Low	Low
Campos 2009[19]	High	Unclear	Unclear	Low	Low	Unclear

Retrospective Controlled Observational

Non Randomised Studies	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Bias
Wewers 1987[5]	High	Unclear	High	High	Low	High
Seersholm 1997[11]	High	High	High	Low	Low	High
Wencker 2001[14]	High	Low	Unclear	Low	Unclear	Unclear
Stoller 2003[16]	High	Low	Low	Low	Low	Low
Tonelli 2009[20]	Low	Low	High	Low	Low	Low
Tanash 2011[33]	Unclear	Unclear	Low	Low	Low	Low

RetroSpective Uncontrolled Observational

Non Randomised Studies	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Bias
Schmidt 1988[6]	High	High	High	High	High	High
Breen 1992[27]	Unclear	N/A	Low	Low	Unclear	Unclear
Barker 1994[7]	High	High	High	Unclear	Low	High

Miravitlles 1994[8]	Unclear	Low	Low	Unclear	Low	Low
Barker 1997[9]	Unclear	High	Unclear	Low	Low	Unclear
Schwaiblmair 1997[10]	Unclear	High	Unclear	High	Unclear	High
The Alpha-1-Antitrypsin Deficiency Registry Study Group 1998[12]	High	High	Unclear	Low	High	High
Wencker 1998[13]	Low	Unclear	Low	Low	High	Low
Cassivi 2002[28]	Low	Low	Low	Unclear	Low	Low
de Perrot 2004[29]	Unclear	N/A	Low	Unclear	Low	Unclear
Burton 2005[30]	Low	N/A	Unclear	Low	Low	Low
Gunes 2006[31]	Unclear	N/A	Low	Low	Low	Low
Stoller 2007[42]	Low	Low	Low	Low	Low	Low
Christie 2008[32]	Low	Unclear	Unclear	Low	Unclear	Unclear
Vidal 2010[22]	High	High	High	Low	High	High
Barros-Tizón 2012[23]	High	High	Unclear	Low	High	High
Subramanian 2012[24]	Low	Low	Low	Low	Unclear	Low
Banga 2014[34]	Low	Unclear	Low	Low	Low	Low
Bredahl 2014[35]	High	Unclear	Low	Unclear	Low	Unclear
Hillerdal 2014[43]	Low	Unclear	Low	Low	Low	Low
Inci 2014[36]	Low	Low	Low	Unclear	Low	Low
Stone 2016[37]	Low	Low	Low	Low	Low	Low

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