

majority of treatment for AATD is similar to non-AATD related COPD; intravenous augmentation of Alpha-1 Antitrypsin is a specific treatment but is inequitably used across Europe and not used in the UK. There is a pressing need to systematically investigate efficacy since the publication of a new placebo controlled RCT and to identify patient centred, clinically meaningful outcomes.¹

Methods A systematic review was conducted using standard review methodology with meta-analysis and narrative synthesis (registered with PROSPERO-CRD42015019354). Eligible studies were those of any treatment used in severe AATD. RCT's were the primary focus however case series and uncontrolled studies (n > 10 patients receiving treatment or usual care, with baseline and follow-up data >3 months), were eligible for inclusion to ensure natural history of disease outside RCT's could be determined.

Results 7296 unique records were reviewed with 51 trials analysed on 5632 participants: 26 AAT-augmentation (3 for meta-analysis); 17 surgical intervention (5 Lung volume reduction (LVR) surgery, 1 Bronchoscopic valve LVR and 11 Lung transplantation); 3 medical interventions and 3 trials completed but not published.

Meta-analysis of AAT-Augmentation demonstrated slower lung CT density decline, difference 0.79 g/l/year (95% CI: 0.29–1.29; p = 0.002), and a small increase in annual exacerbations 0.29/year (95% CI: 0.04–0.54; p = 0.02) compared to placebo (Figure 1).

Survival benefit of transplant was observed in one study (p = 0.006) but not in a second with more stringent matching for groups; however significant improvements in health status, total SGRQ and all domain scores, at one year (p < 0.01) were observed. Mortality post lung transplant was comparable between AATD and non-AATD related COPD cohorts. Surgical lung volume reduction demonstrated inferior outcomes when compared to non-AATD related emphysema.

Conclusion CT density, FEV1, DLCO, health status and exacerbation rates were frequently used as outcomes in AATD related treatment trials. AAT-Augmentation is able to slow the progression of severity of emphysema when measured by CT density change compared to placebo. This systematic review will help

assist in the improved monitoring and management of patients with AATD.

REFERENCE

1 Chapman KR, et al. Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *The Lancet* 2015;**386**(9991):360–368.

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RELATIONSHIP BETWEEN PROGRESSION OF LUNG DISEASE IN ALPHA-1 ANTITRYPSIN DEFICIENCY AND CARDIOVASCULAR RISK

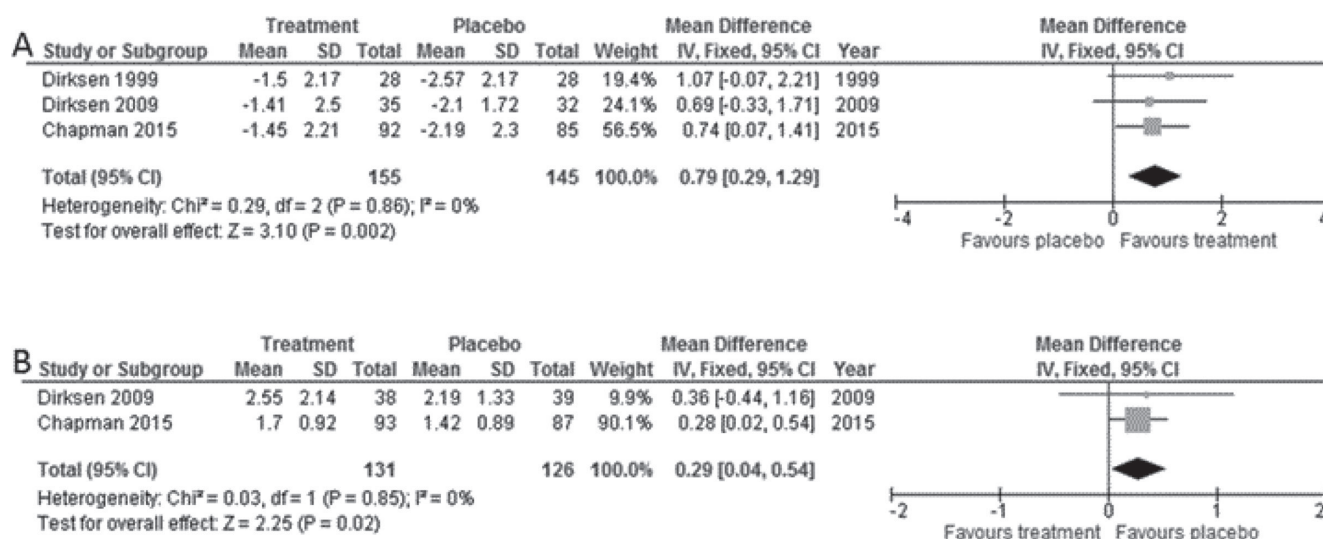
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10.1136/thoraxjnl-2016-209333.279

Introduction Patients with alpha-1 antitrypsin deficiency (AATD) who are homozygous for the mutated Z allele (PiZZ) typically present with emphysema and liver cirrhosis, caused by the uncontrolled action of neutrophil elastase in the lungs and toxic gain-of-function AAT polymer aggregates in the ER of hepatocytes. The link between cardiovascular disease and COPD is widely accepted, but is less well understood in AATD. This study aimed to investigate how markers of lung function severity and the rate of disease progression are associated with cardiovascular risk in a cohort of PiZ patients.

Methods Cardiovascular (CV) risk was determined by the degree of arterial stiffness, measured using aortic pulse wave velocity (aPWV). This was recorded with the Vicorder device which uses the transcutaneous distance between the common carotid and femoral arteries, and the time delay between the feet of the 2 diastolic pulse waveforms to calculate the pulse velocity. Cardiovascular risk was additionally assessed using the QRISK2 algorithm. Pulmonary function was evaluated using FEV1, KCO and RV% TLC, and the degree of AATD disease progression used previous pulmonary function test (PFT) data to determine the rate of lung function decline.

Results We enrolled 48 PiZZ AATD patients (mean (SD) age 52.9 (15.9) years, 19 male) and found significant relationships (denoted by: **p < 0.01 and *p < 0.05) between both aPWV



Abstract P135 Figure 1 Forest Plots : A) Annual CT Lung Density Change (g/L per year) in 300 patients across three placebo controlled RCT's. B) Annual patient reported exacerbation episode in 257 patients across two placebo controlled RCT's.

and QRISK2 and the degree of airflow obstruction (FEV1: $r = -0.470^{**}$, $\rho = -0.325^{*}$), emphysema (KCO: $r = -0.493^{**}$, $r = -0.411^{**}$) and hyperinflation (RV%TLC: $r = 0.550^{**}$, $r = 0.433^{**}$). Including only patients with ≥ 3 PFT results, we found a significant relationship between emphysema progression and calculated but not measured cardiovascular risk: KCO change vs. QRISK2 ($r = -0.549$, $p = 0.015$, $n = 19$).

Conclusions Reduced lung function was associated with a greater magnitude of measured and calculated cardiac risk in the AATD cohort. However AATD-mediated lung disease progression was not significantly related to measured CV risk – an exception being a significant relationship between the rate of decline of KCO and QRISK2.

P137 WHY IS ERDOSTEINE RECOMMENDED AS A TREATMENT FOR ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS? A SYSTEMATIC REVIEW OF CLINICAL TRIALS

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10.1136/thoraxjnl-2016-209333.280

Background Exacerbations of chronic bronchitis or chronic obstructive pulmonary disease (COPD) are a significant health burden. A substantial component of these exacerbations in many patients is mucus-hypersecretion. Mucolytics, drugs that ‘thin’ mucus, have potential efficacy in these patients.

Currently, erdosteine is the only mucolytic in the British National Formulary (BNF) indicated for “symptomatic treatment of acute exacerbations of chronic bronchitis”, while other BNF mucolytics (carbocysteine, mecysteine and N-acetylcysteine) have had more general or non-respiratory indications, e.g. “reduction in sputum viscosity”. It is theorised that there is clinical evidence that erdosteine is useful in treatment of acute exacerbations of chronic bronchitis, unlike any of the other aforementioned mucolytics.

Methods In this narrative systematic review, databases utilised included: Medline, Embase and PubMed. Studies for inclusion had to be Randomised Controlled Trials (RCTs) primarily investigating the effect of erdosteine in exacerbations of chronic bronchitis or COPD. For comparison, RCTs were also included if they investigated carbocysteine, mecysteine and N-acetylcysteine’s effects in exacerbations. A secondary outcome was to investigate the use of these mucolytics in improving COPD signs and symptoms.

Once selected, a two-stage publication elimination process was devised by the author to assess the quality of the trials.

Results Very few trials of adequate quality assessed the efficacy of mucolytics in chronic bronchitis or COPD. Of the 5,560 search results, only 62 trials investigated the aforementioned mucolytics use in chronic bronchitis or COPD, 41 were RCTs. Of the 41 RCTs only 13 were found to be of adequate quality; erdosteine (1 RCT), carbocysteine (3 RCTs), mecysteine (0 RCTs) and N-acetylcysteine (9 RCTs).

There was no evidence that erdosteine is useful in treating exacerbations, and very limited, weak evidence for some efficacy in exacerbation prevention. In contrast, carbocysteine showed some strong evidence of efficacy in preventing exacerbations, especially in Asian populations. N-acetylcysteine trial results were variable, and evenly distributed between positive and no effects,

with one study showing adverse effects. There were no trials of adequate quality investigating mecysteine.

Conclusion There is little evidence that erdosteine is useful in treating chronic bronchitis exacerbations, whereas, overall carbocysteine seems to be more efficacious in exacerbation prevention.

P138 AN INNOVATIVE APPROACH TO STUDY DESIGN: USING ELECTRONIC MEDICAL RECORDS TO INFORM THE FEASIBILITY AND DESIGN OF THE NOVELTY STUDY (A NOVEL OBSERVATIONAL LONGITUDINAL STUDY ON PATIENTS WITH ASTHMA AND/OR COPD)

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10.1136/thoraxjnl-2016-209333.281

Introduction Asthma and COPD have traditionally been viewed as distinct diseases. While they have overlapping biological mechanisms, past studies often focused on specific aspects of each disease based on a single diagnostic label, and many clinical trial populations were defined by strict enrolment criteria with limited generalisability. NOVELTY is a prospective, multinational, observational, longitudinal cohort study aiming to enrol 14,800 patients aged ≥ 12 years with a diagnosis or suspected diagnosis of asthma and/or COPD. In this population, the objectives of NOVELTY are to: (i) describe patient characteristics, treatment patterns and burden of illness over time in clinical practice; and (ii) use biomarkers and clinical parameters to identify phenotypes and endotypes associated with differential outcomes for symptom burden, clinical evolution and healthcare utilisation.

Aim This feasibility analysis of electronic medical records (EMRs) aimed to understand the potential study population, assess patient numbers across disease severities and evaluate EMRs as a data source for NOVELTY.

Methods EMRs from patients with asthma and/or COPD were identified from national databases covering primary and specialist care in 11 countries (Table). Disease severity was classified using treatment- and/or lung function-based algorithms for asthma and COPD. EMR variable coverage and completeness were assessed for standardised clinical, laboratory and physiological data and patient-reported outcomes (PROs).

Results EMRs for 921,888 patients with asthma, 958,945 with COPD and 117,893 with both diagnoses were identified. EMRs routinely documented patient demographics and characteristics, but many disease- and treatment-related data, and PROs/symptoms required for evaluation of disease severity and clinical outcomes were frequently missing (not collected or not documented; Table). Disease severity could not be classified in 561,837 patients (asthma) and 355,743 patients (COPD), representing 22–100% and 7–85% of patients across countries.

Conclusions EMR analysis revealed numbers of patients per country potentially eligible for NOVELTY. Many variables required to meet NOVELTY objectives were missing in EMRs (e.g. lung function and PRO/symptoms); therefore, variables in