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European Respiratory Society (ERS) Statement: Diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin deficiency

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is the most common hereditary disorder in adults. It is associated with an increased risk of developing pulmonary emphysema and liver disease. The pulmonary emphysema in AATD is strongly linked to smoking, but even a proportion of never smokers develop progressive lung disease. A large proportion of individuals affected remain undiagnosed and therefore without access to appropriate care and treatment.

The last international statement on AATD was published by the American Thoracic Society and the European Respiratory Society in 2003. Since then there has been a continuous development of novel, more accurate and less expensive genetic diagnostic methods. Furthermore, new outcome parameters have been developed and validated for use in clinical trials and a new series of observational and randomised clinical trials have provided more evidence concerning the efficacy and safety of augmentation therapy, the only specific treatment available for the pulmonary disease associated with AATD.

As AATD is a rare disease, it is crucial to organise national and international registries and collect information prospectively about the natural history of the disease. Management of AATD patients must be supervised by national or regional expert centres and inequalities in access to therapies across Europe should be addressed.

Keywords: Alpha-1 antitrypsin deficiency; COPD; emphysema; diagnosis; treatment; augmentation therapy.

Introduction

It has been over 50 years since the first cases of Alpha-1-antitrypsin deficiency (AATD) were described (1) and much has been learnt about the condition since then, especially in recent years. More than 100 genetic variants have been described and those associated with severe plasma deficiency (<11μM or 0.5g/L) are recognised as increasing the susceptibility to the development of emphysema even in never smokers. The PiZZ homozygous is by far the most prevalent severe deficiency state and its additional extra-pulmonary associations with liver cirrhosis, hepatocellular cancer, vasculitis and panniculitis are well recognised. Knowledge has progressed by the development of local, national and international registries and the mechanisms leading to emphysema and cirrhosis and the natural history of the disease are now documented in greater detail. The prevalence of AATD in Europe varies from 1/1368 in Denmark to 1/58319 in Poland following migration patterns (2).

The complexity of interpreting the genetic variants, their importance, the role of patient and family screening as well as disease management requires expertise only gained by seeing patients on a regular basis. The role and instigation of augmentation therapy and transplantation need careful and multidisciplinary approaches. The development of new therapies such as gene silencing strategies, small molecule drugs and other anti-inflammatory and anti-proteinase therapies requires the application of novel approaches to the design and implementation of clinical trials to overcome some of the inherent challenges of conducting clinical research in rare diseases. The establishment of patient advocacy organisations and close collaboration with clinicians and other health care workers have played and will continue to play, a key role in the acquisition of new knowledge and the design and delivery of new clinical trials. The views and concerns of patients were undertaken through the European

Lung Foundation with National AATD patient organisations. These have both added to the development of the current document and are include in the text and summarised verbatum in the supplementary material.

This European Respiratory Society (ERS) statement provides a broad update of the "state of the art" knowledge in the study and management of pulmonary disease associated with AATD.

METHOD

The task force co-chairs (RAS, MM) led all aspects of project management and selected the panellists, which included 13 specialists with experience in AATD and/or non deficient COPD management, basic and clinical research. The co-chairs and panellists discussed the evidence and formulated the statements. All panel members were required to disclose any potential conflict of interests. At least one third of the panel was free from any such conflicts.

Task force members compiled a list of issues that they considered important and relevant to the diagnosis and management of pulmonary disease in AATD. Our literature search used the previous American Thoracic Society/European Respiratory Society (ATS/ERS) statement published in 2003 as a starting point (3). The following databases were searched up to January 2016 with no language restrictions (Supplementary material): MEDLINE, MEDLINE In Process and EMBASE (via Ovid), Cochrane Library (Wiley) CENTRAL, CDSR, HTA, EED, and DARE. In addition, Conference Proceedings Citation Index via Web of Science and British Library's ZETOC were searched for conference proceedings and abstracts. References of included studies and reviews were checked. The search was confined to alpha-1-antitrypsin deficiency of homozygous Z genotype, Null genotype or Null/Z

genotype, all abbreviated for this document as AATD. The searches and the formulation of statements were supervised by one of the ERS methodologist (DR).

AATD and lung disease

The initial 5 cases of AATD reported by Laurell and Eriksson (1) included 3 patients with emphysematous lung disease and one young and one old person without obvious signs of COPD. Subsequently Eriksson collected a further 33 patients via hospital records and hence represented a partially biased cohort (4). Again variability in the presence and severity of lung disease was noted, although, in general, the patients had early onset of COPD and basal panlobular emphysema. This pattern of disease became recognised as the classical clinical phenotype leading to predominant testing of younger patients presenting with severe lung disease. However, existing guidelines recommend testing all COPD patients irrespective of age and severity (3,5-7). The pathophysiology has been thought to reflect the lack of AAT function (a primary serum and lung inhibitor of serine proteinases) protecting the lung tissues from proteolytic destruction, which is largely neutrophil-dependent. However, although smoking amplifies neutrophil recruitment to the lung and is recognised as an important risk factor, it fails to explain the diversity of clinical and structural impact in both smokers and never smokers with AATD.

More recently the establishment of AATD registries (8,9) and follow-up data from the 1972 Swedish birth cohort (10) have highlighted the diversity of impact and type of lung disease, including its effect on health status and lung physiology. One of the most comprehensive databases is the UK national registry, which now includes in-depth data and longitudinal follow-up data from over a thousand patients (11). The clinical features of these patients have highlighted many facets of the disease that are not entirely consistent with a simple AAT/Neutrophil proteinase balance concept.

Firstly, there is lack of concordance found between siblings raised with the same environmental background. There is no relationship between the FEV_1 of such siblings even though gas transfer is related (12). This raises two issues, namely, that FEV_1 is a poor surrogate measure for emphysema for these patients, and that other unknown environmental or genetic influences may play a role in determining the outcome.

Secondly, the FEV_1 decline reflects a late physiological change in the disease process only starting to deviate from normal in the 4^{th} decade, whereas gas transfer is reduced much earlier indicating that it may be a more sensitive and specific test of emphysema development (13,14). This is supported by the observational monitoring of the Swedish birth cohort, where abnormal gas transfer was present in some patients in their fourth decade whilst FEV_1 remained within normal ranges (15).

Thirdly, a proportion of never smokers develop emphysema with reduction in FEV_1 in middle age, whereas some retain normal spirometry into old age (16) and the life expectancy of never smokers is close to normal (17).

Fourthly, physiological assessment confirms a discordance of lung function with some patients retaining normal gas transfer even with reduced FEV_1 and vice versa (18) which reflects (at least in part) the distribution of emphysema (14,19). Indeed, the classical basal distribution of emphysema is not always present and a proportion of patients display a pattern of emphysema distribution more typical of non-AATD deficient COPD (19). These issues have a significant bearing on monitoring patients for stability/progression. As indicated above, the earliest change is a decline in gas transfer, which may be independent of and faster than FEV_1 decline (20). This is

particularly evident in very severe disease when gas transfer impairment and progression is greatest and average FEV_1 decline is least (21,22).

Fifthly, patients can demonstrate the same clinical features as non-deficient COPD, including increased evidence of bronchiectasis, chronic bronchitis, bacterial colonisation, frequent exacerbations (but with a greater degree of pulmonary inflammation and associated progression), impaired health status and a degree of reversibility of airflow obstruction (20,23,24). Therefore, the WHO guidance for testing every patient with a diagnosis of COPD or adult onset asthma for AATD should be standard (25).

Statement

The clinical impact of AATD is highly variable. Heterogeneity in lung disease is only partly explained by exposure to known risk factors, such as cigarette smoke.

Lung disease in AATD generally presents at a younger age than “usual” COPD and may be misdiagnosed as asthma.

Although the patients’ clinical phenotype may vary they are more likely to have basal emphysema than patients with usual COPD.

The WHO recommends all patients with a diagnosis of COPD or adult onset asthma should be tested for AATD

Laboratory diagnosis and hierarchy of testing

The laboratory diagnosis of AATD has evolved over the last 50 years since the first cases of the disorder were reported, based on a low or absent alpha-1 band seen on paper electrophoresis (1). We have reviewed the testing hierarchy for the diagnosis of AATD.

The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Original methods, such as radial immunodiffusion and rocket electrophoresis, are no longer used in laboratories. Nowadays, the measurement of AAT levels in blood is mostly performed by nephelometry or, less commonly, a comparable latex-enhanced immunoturbidimetric assay (26).

In the last decade, more reproducible and reliable quantitative techniques based on the use of dried blood samples (DBSs) have become more widely available and have facilitated centralisation of testing. (27-29).

AAT is a polymorphic protein with more than 100 genetic variants coded for by two alleles in a codominant manner. Many of these reflect point mutations in the gene sequence leading to amino acid substitutions, which may affect the electrophoretic mobility of the resulting AAT protein. Isoelectric focusing detects these variants, which are given letters A-Z depending on their mobility, i.e. faster or slower, compared to the most common (normal variant) labeled M labeled as earlier or later letters respectively. Other common variants are S and Z with MM, MS, MZ, SS, SZ and ZZ protein phenotypes accounting for over 99% of all variants in most of population surveys (30). Although phenotyping can only identify protein that is present in the blood, it remains a routine test for AATD. The rarer null variants that include a variety of gene insertions, deletions and point mutations can result in the absence of AAT production, and null heterozygotes can appear to be normal (Mnull)

or abnormal (Znull) based on the electrophoretic pattern of protein phenotyping, though not consistent with expected family inheritance. Other deficient mutations such as M_{Malton}, $M_{Wurzburg}$, $M_{Heerlen}$ also display an M protein electrophoretic phenotype. For these reasons, including the necessity for pre- and post- test genetic counselling, access to central laboratories and/or AATD expertise is essential (31). Standard manual methods have been improved by semi-automation (32) in the last decade and result in easier and faster testing, although significant expertise is still required for interpretation (33).

The ranges of serum AAT in the general population, determined according to the main genotypes, have been summarised recently (34).

The optimal threshold level for AAT to discriminate normal PI*MM from other genotypes carrying at least one deficient S or Z allele was 24.4μM (1.1g/L) with 73.4% sensitivity and 88.5% specificity (34). AAT is an acute phase protein and, despite average concentrations varying with protein phenotype, there is a high degree of overlap, such that plasma level alone is an insufficient parameter to diagnose intermediate deficiency due to M heterozygosity with certainty. The acute phase response known to influence AAT can be partly recognised by the simultaneous quantification of C reactive protein (CRP). However, these issues are overcome by protein phenotyping or specifically by genotyping, both of which are independent of AAT level.

Genotyping describes the detection of specific AAT gene mutations, mainly S and Z. This approach utilises the principles of polymerase chain reaction (PCR) and can also detect rare and null variants such as the M_{Malton} (35-37). However, it can only detect known sequence defects and requires specific primers for each of these, some of

which (e.g. F and I) are routinely used by some laboratories. The absence of specific primers can lead to false results.

Whole gene sequencing (which is becoming cheaper) will detect stop mutations and help elucidate the nature of rarer variants such as E, F, G, I and P without the need for specific primers, as well as identify currently unrecognised variants. The optimal results of genotyping are obtained when performed in expert laboratories and interpreted in conjunction with the protein level and familial relationships by experienced AATD clinicians/geneticists.

Each specialised laboratory has developed its own flow chart for local or national AATD detection programmes, starting from sample collection (blood, plasma, DBS) (31). The initial step is usually to measure the AAT plasma level, separating severely deficient subjects (ZZ, Znull, Nullnull and most SZ) from intermediate levels for M heterozygotes (MZ, MS and Mnull) and normal levels (MM). This step is usually followed by protein phenotyping, genotyping or whole gene sequencing depending on availability and/or the need for more detailed interpretation. With ever reducing costs for PCR and gene sequencing, it is likely that genotyping will become the second step in the testing algorithm in the future.

Figure 1 shows a testing algorithm with initial quantitation of the AAT level in blood together with a measure of CRP to determine whether the AAT level could be higher than usual due to a possible acute phase response. Thereafter protein phenotyping by isoelectric focussing or genotyping where specific primers for known mutations are available, will identify the most common variants. Whole exon sequencing can be undertaken especially if null variants are expected. The role of intron sequencing is currently uncertain.

Since AATD is hereditary, family testing should be conducted after identification of an index case. Parents of an index case are most commonly PiMZ heterozygotes but may be informative if available for testing when a null gene is suspected. In reference centers siblings are offered testing as well, because with MZ parents there is a 1 in 2 likelihood of being heterozygote and a 1 in 4 chance of being PiZZ. Identified PiZZ siblings are offered follow up as for the initial (index) case. PiMZ siblings should be advised against smoking and may be offered testing for their partner as the PiMZ protein phenotype is relatively common (1-3% prevalence) and hence the risk of subsequent PiZZ children who, by this strategy, will be identified and can be monitored during maturation and into adulthood. For the same reason, checking the index patient's partner may detect any deficiency allele and, where present, the children would also have a 1 in 2 likelihood of having severe deficiency. Early detection of the deficiency in these children is considered best practice, providing no legal barrier exists for testing (Figure 2). More widespread testing (beyond first degree relatives) may be conducted in some families depending on family history of lung disease or parental results (such as one parent being PiZZ).

It is imperative that appropriate genetic counselling is provided, both before and after genetic testing, and in accordance with national legislation (38). Patients need to be made aware of all potential implications of having a genetic test prior to testing in order to be able to give informed consent. Therefore, patients should be referred for expert genetic testing by their doctor.

Statement

The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD.

Protein phenotyping by isoelectric focusing identifies variants where AAT is present in the sample including the rarer variants F, I and P etc.

Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants where specific primers are available.

Gene sequencing remains necessary for those cases where a null variant or a rare pathological variant is suspected.

Testing of relatives of identified patients should be considered after appropriate counselling

Genetic testing should be carried out only after informed consent is given and in accordance with the relevant guidelines and legislation.

Lung disease progression in AATD

The proportion of individuals with AATD who develop lung disease is largely unknown although cross sectional studies indicate that perhaps 50% of never smokers retain spirometric lung function in the normal range in later life (16,17). Nevertheless, once established it is generally believed that progression is more rapid than in non-AATD patients with COPD, especially in smokers. However, smoking cessation can "normalise" this progression to that of AATD never smokers (20).

Conventionally, FEV_1 has been used as the major indicator for the presence, progression and severity of lung disease. However, FEV_1 is a poor surrogate of emphysema, whilst gas transfer is more specific. Although these two measures correlate in cohort studies, both have to be measured to a high degree of specification and do not provide the same information on the clinical phenotype or the rate of progression or stability. Similarly, the progression of emphysema measured by lung density in CT continues even when FEV_1 is stable (14,18,20,22).

Monitoring the progression of lung disease in alpha-1-antitrypsin deficiency

Physiology/lung function

The complexity of interpretation of results obtained by common lung function measures such as spirometry and CO gas transfer is illustrated by the discordance between these two measures as the disease progresses. Rapid FEV_1 decliners can be identified even when lung function is initially found to be in the normal range and rapid decline of gas transfer can occur even when there is severe airflow obstruction and little decline in FEV_1. This raises the issue of the need to monitor all patients (at

least for a time) to assess treatment options including augmentation therapy where available. This careful monitoring would include parameters such as FEV_1, DLco (or DLco/VA), 6-min walking distance and health-related quality of life parameters.

CT densitometry

CT densitometry has been established as the most specific and sensitive surrogate endpoint for the evaluation of therapeutic benefit of augmentation therapy and represents a paradigm imaging biomarker. Validation of the methodology as an objective and specific measure of emphysema has been extensive (39-44): cross-sectional studies have shown a close correlation with pathology, lung function indices including FEV_1 and gas transfer (45-47), health status (47) and exercise capacity (48). Longitudinal observational studies demonstrate that, although the progressive loss of lung density correlates with deteriorating lung function and health status as emphysema worsens (22,49), CT densitometry is a more sensitive means of detecting emphysema progression than these 'traditional' clinical measures (13,22,50).

This novel surrogate outcome measure has facilitated the successful completion of several randomised placebo-controlled studies over a compressed time frame and with smaller sample sizes (51-53) than were estimated to be required in studies that used FEV_1 as an endpoint (54). As a consequence of the published evidence, a meeting of the Blood Products Advisory Committee of the Food and Drug Administration (FDA) (55) concluded in 2009 that it accepted 'serial lung density measurements by HRCT as a clinically meaningful endpoint to assess efficacy of augmentation therapy with intravenous AAT on emphysema disease progression' and its use as a primary endpoint in Phase 4 studies.

Notwithstanding this progress, the validity of CT densitometry as evidence of treatment efficacy is still being questioned because of a lack of coexisting signals in conventional surrogate measures, such as lung function or health status. The power calculations that have been used historically to design the latest interventional study predicted that a study of 130 patients over 3 years would be sufficient to demonstrate treatment efficacy if CT densitometry was the outcome (51), whereas the use of FEV_1 as outcome would require at least 550 patients per arm over the same period (54). Power calculations based on health status as an outcome have not been performed.

Our systematic review of the literature (see supplement) assessed 200 manuscripts. Table 1 shows the results for annual decline in lung density measured as the 15^{th} percentile point (abbreviated as PERC15 or PD15) and expressed as g/L annual change of density together with FEV_1, DLco and Kco (the latter two corrected for haemoglobin concentration). The numbers in the Table are based on placebo-treated patients in randomised controlled clinical trials, except for the last two where the data were collected in follow-up studies. Clearly, there is high variability in the mean values in each of the progression parameters. In the AATD population, only repeatability of lung density is reported in the literature (56). In fact, variation for the 15th percentile point, corrected for differences of total lung volume between two scans is minimal, (intraclass correlation coefficient= 0.96; 95% CI: 0.86–0.99) (56).

A larger set of information on monitoring of emphysema progression comes from non-AATD individuals. In the 2005, ATS/ERS Task Force document relating to interpretation for lung function tests (57) indicated the optimal method for expressing the short-term variability (measurement noise) is to calculate the coefficient of repeatability (CR).

Statement

Annual measurement of lung function including post bronchodilator FEV_1 and gas transfer provides information about disease progression.

Lung densitometry, as performed in observational cohort studies and randomised clinical trials is the most sensitive measure of emphysema progression

The correlation between change in lung density and any short-term change in measures of pulmonary function is weak. However in the longer term, CT lung density decline correlates with reduction in FEV_1 and health status.

The role of CT in the follow up of patients in routine clinical practice requires further validation.

The risk of lung disease in heterozygotes

The risk in individuals with MZ genotype

The susceptibility of patients with the MZ genotype for developing COPD has been explored in a meta-analysis by Hersh et al in 2004 (58). Sixteen studies were case-control or cross sectional with the binary outcome of COPD or airflow limitation and 7 cross-sectional studies with FEV_1 (% of the predicted value) as a continuous outcome. One study included both outcome measures and was included in both

analyses (59). Pooled odds ratio (OR) for COPD in heterozygotes compared with normal genotype individuals was significantly increased at 2.31 (95% CI 1.60 to 3.35) although large heterogeneity was detected among the studies (58). Cross-sectional studies and those adjusting for smoking status showed lower and non-significant risk estimates compared with case-control studies and those not adjusting for smoking status. In the pooled analysis, there was no difference in mean FEV_1 (% predicted) between PiMM and PiMZ individuals. A subsequent case control study from Norway and a multicentre family-based study from Europe and North America (60) found that the PiMZ genotype was associated with lower FEV_1/(F)VC ratio and more severe emphysema on chest CT scan. However, the number of MZs in the two groups was small and the study samples were not population based.

A family-based genetic association study by Molloy et al. (61) tested for PiMZ COPD risk specifically within families that already had an identified PiMZ COPD subject. The study compared 99 PiMM and 89 PiMZ non-index subjects recruited from 51 index PiMZ probands with COPD Gold Stage II-IV. These results indicated conclusively that PiMZ individuals who smoke have more airflow obstruction and clinical COPD than carefully matched PiMM individuals.

The risk in individuals with SZ genotype

The number of PiSZ individuals worldwide is less than PiMZ, however the risk for COPD is still not fully elucidated. Dahl et al (62) performed a meta-analysis of the risk of COPD in individuals with the PIS allele. Twenty one studies were included and there were six case-control and cross-sectional studies. In the pooled analysis there were 42 PiSZ individuals of whom 27 had COPD. The summary OR for COPD in PiSZ individuals was significantly elevated at 3.26 (95% CI:1.24-8.57) compared

with PiMM, however, when a significant outlier was removed from the analysis (63) the OR was no longer significantly increased. Seersholm et al (64) in a study of 94 PiSZ individuals, of whom 66 were non-index cases observed that index PiSZ cases had a reduced survival. Data from the Italian and Spanish registries (24,65) found that PiSZ subjects were older at diagnosis and had more preserved lung function despite higher smoking exposure than PiZZ patients. Similarly, a more recent study (66) suggested that PiSZ subjects were less susceptible to cigarette smoke than PiZZ and that the pattern of emphysema on CT scan at diagnosis was similar to that seen in patients with usual COPD rather than the predominantly basal distribution of panlobular emphysema of PiZZ individuals.

Taken together, these data suggest increased susceptibility of the SZ phenotype for the development of COPD in smokers, but more research is needed, including the effect of environmental factors in a similar way to that undertaken for MZ subjects (61).

Rarer mutation heterozygotes (such as FZ, IZ, M Malton and M Null mutations)

There is a paucity of data for rarer AATD mutations but some studies are emerging indicating that the F, I and M_{Malton} mutations confer increased susceptibility to COPD when inherited with a Z allele. Although the Null mutations associated with AATD are rare, studies have shown that Null homozygotes have more severe lung disease than PiZZ or PiSZ individuals (67-70) and MNulls have increased lung symptomatology and obstructive lung disease (71).

Statement

Never-smoking PiMZ subjects do not have an increased risk for COPD.

Smoking PiMZ and PiSZ subjects have an increased risk of COPD compared to smoking PiMM subjects.

The role of other heterozygotes remains unknown due to their rarity and potential ascertainment bias from measuring AAT in unusual cases of lung or liver disease.

Role and benefits of screening

There are different approaches to identify individuals with AATD. The first is population-based, in which unselected groups have been tested (screening studies). The second is targeted-detection studies where patients with an enhanced suspicion of having AATD have been tested including those with early onset (<40 yrs age) COPD, basal panlobular emphysema, family history of COPD or AATD and those with perinatal jaundice, cirrhosis, vasculitis or panniculitis.

No randomised, control study determining the efficacy of screening programs for AATD has been performed. Most screening studies have been selective and did not involve random population samples, but include individuals healthier (blood donors) or sicker (hospital outpatients) than the general population. A few population-based studies that randomly screened the general population (72,73) or large numbers of

new-borns (10,74) provided a less biased and more accurate prevalence estimate of specific AATD phenotypes. The new-born studies have also provided valuable insight into the natural history of AATD, with unbiased assessments in the risks of liver and lung diseases. More specifically, these studies have found that individuals tested, often had lung function in the normal range at mean ages of 15 (75) and 30 years, respectively (76). Data collected at age 35 years suggest that at least some have developed a reduction in gas transfer and lung density (15). This is consistent with the retrograde analysis that highlighted the higher sensitivity of these measures to detect early changes compared to spirometry (14). The most recent birth cohort information at ages 37 to 40 years showed that 2 of the 4 current smokers already had COPD (77)

Potential benefits of systematic screening include genetic counselling, life-style recommendations (smoking prevention or cessation, avoidance of high-risk occupations, alcohol intake limitation), and consideration for earlier augmentation therapy. The potential harms include psychological effects, social discriminatory effects and costs. These effects can be addressed, at least partially, by reassurance as never smokers who are non-index cases with AATD have a normal life expectancy (17,78).

The largest population-based study published for AATD was carried out in 200,000 new-born children in Sweden between 1972 and 1974 leading to the identification of 127 PIZ individuals and 48 PISZ individuals (10). The major purpose was to reduce exposure of the child to parental smoking during childhood and adolescence and to prevent active smoking. Neonatal screening reduced the smoking rates for 18-20 years old compared to age-matched subjects (79) with 6% being current smokers *vs* 17% ($p<0.05$) and 88% being never smokers *vs* 65% ($p<0.05$), though this failed to affect smoking among the parents. Similar results were also found in another neonatal

screening study in Oregon, with significantly lower smoking initiation rates in subjects who had been diagnosed with AATD than in control subjects (27.3% vs 56.9%; p=0.02) (75).

Neonatal screening produced no adverse psychological effects in adolescents identified at birth with AATD, though parental distress and adverse effects were identified in the mother-child relationship (80) and 20 years later the mothers had significantly more anxiety than control mothers (81). These concerns have inhibited the re-introduction of neonatal screening in Sweden although a clearer understanding of the risks/benefits and natural history of the disease are both helpful and reassuring.

Statement

Most screening studies have been biased as they did not involve random population samples

Population-based screening studies provide less biased prevalence estimates of specific AATD protein and clinical phenotypes as well as valuable insight in the natural history of AATD

Neonatal screening has been shown to be effective in reducing the smoking rates for 18-20 years old compared to age-matched individuals.

Screening may have negative psychological effects on parents and on mother-child bonding. However, these negative effects can be addressed by comprehensive genetic counselling and care provision at centres of excellence for AATD

Augmentation therapy for AATD

Since augmentation is currently the only specific therapy for AATD, it has been a topic of intense debate in the literature and the subject of numerous review and opinion articles. In rare diseases such as AATD, the difficulty of recruitment to clinical trials, coupled with the lack of sensitivity to change of typical outcome measures has challenged the development and delivery of clinical trials. Furthermore, there is the unusual situation where augmentation has been advocated (and given) for some time on the basis of biochemical effect (namely raising AAT level) (82) and hence has become established as treatment in many areas of the world, without the level of evidence now expected for respiratory outcomes such as FEV_1, quality of life and mortality. There have been two previous systematic reviews, one focused on randomised controlled trials (RCT) of augmentation (83) and the other which considered all controlled study designs of augmentation (including non-randomised studies) and presented analyses of FEV_1 decline (84). In addition, an individual patient data analysis of the CT densitometry data from 2 of the randomised controlled trials has been reported (85). The latter two studies were supportive of augmentation as a treatment capable of reducing, albeit not eliminating, emphysema progression (84,85). The meta-analysis conducted by Gotzsche et al (83) also indicated that CT density decline was lower on augmentation therapy than placebo but concluded that this did not equate to efficacy. A similar view was also expressed in the more recent update by the same authors (86) following publication of the RAPID trial (53).

In order to obtain all evidence about augmentation and minimise bias we used standard systematic review methods as described in the online supplement. There have been 8 RCTs of intravenous augmentation, 3 against placebo (51-53,87) and 5 against another active comparator (88-92), generally a newer brand of augmentation

therapy. In addition there have been 6 observational studies reporting a control group (8,93-97), largely assessing data from registries, and 11 uncontrolled observational studies (82,98-108), focussed on pharmacokinetics, safety or novel outcomes. There are also 2 ongoing trials (NCT00242385 and NCT01213043). In the interests of brevity, the published placebo controlled RCTs are discussed here in detail, whereas other published studies are shown in table 3, which contains a brief summary of study characteristics and results.

The RCTs included a total of 315 patients. The earliest RCT included 58 ex-smoking PiZZ patients with mild to moderate emphysema, treated for a minimum of 3 years and randomised to an infusion of AAT at 250mg/kg or human albumin every 4 weeks (51). FEV_1 was the primary outcome; secondary outcomes included Kco, DLco and change in lung density measured by CT scan. There was no difference in physiological decline, but a strong trend towards reduced decline in CT-measured lung density.

The EXACTLE trial included 77 participants with severe alpha-1 antitrypsin deficiency treated using weekly infusions of AAT at 60mg/kg or placebo for 2 years, with an optional 6 month extension (52). Primary outcome was progression rate of emphysema determined by annual CT lung density at TLC, but this was in part an exploratory study, as the optimum method of image analysis was uncertain at the time. A strong trend toward reduced density deterioration was seen, consistently with the four different analytical methods used. In one of these, conventional statistical significance was reached ($p=0.049$). Secondary outcomes included patient reported exacerbation frequency, DLco and quality of life. No trends in these measures were seen between active treatment and placebo, although there was a reduction in hospital admissions for exacerbations in the active treatment arm.

The most recently performed study (RAPID) included 180 patients with emphysema secondary to AATD and FEV_1 of 35-70% predicted (53). Patients received either weekly infusions of AAT at 60mg/kg or placebo for 2 years, with a 2- year open label extension for some participants (87). This study was the first to be powered to detect a treatment effect on the annual rate of decrease in lung density measured by CT scan; secondary outcomes included exacerbation rate, change in FEV_1 % of predicted, quality of life (QOL) using the St Georges Respiratory Questionnaire (SGRQ) and change in DLco. The CT imaging protocol obtained scans at full inspiration (total lung capacity, TLC) and at relaxed expiration (functional residual capacity, FRC). Whilst the chosen primary endpoint was a combination of CT lung density (PD15) measured at TLC and FRC (which failed to achieve statistical significance), the separate imaging series at TLC and FRC were included as secondary outcomes. The main finding was a reduced rate of lung density decline, as measured by CT scanning, in the treated patients. This treatment effect was statistically significant when quantified using CT imaging obtained at full inspiration (TLC), as in previous studies (see above). During the open label extension, the patients previously on placebo exhibited a change in CT density decline becoming similar to that seen in patients treated in the randomised phase. However, as in previous RCTs in this area, no significant effect was seen on other outcome measures, such as lung function and QOL (87). A supplementary report to the trial has also detailed reduced circulating desmosine, indicating an effect of augmentation on body elastin breakdown (109).

Augmentation is considered safe across the larger number of studies where this is reported. Adverse event rates were similar between treated and placebo groups in both EXACTLE (52) and RAPID (53) , but were not reported in the earlier RCT (51).

The consistency of the trial data with respect to CT density decline, and the fact that CT density has been shown in cross-sectional and longitudinal studies to relate well to other clinical outcomes, such as mortality and QOL (47,110) indicates that it is a clinically relevant measure. Moreover decline in CT density has also been shown to relate to mortality (111), indicating that the RCT results with respect to CT density decline are consistent with the longer observational work suggesting a mortality benefit (8). Survival was also reported in the most recent RCT, (1 death on augmentation, 3 on placebo) but the low mortality rate prevented any conclusion.

Whilst many of the observational studies imply a benefit of treatment on the rate of FEV_1 decline, the potential for bias is greater than in a RCT, and the data should be interpreted with caution. The effect of augmentation on exacerbations of AATD lung disease remains uncertain, with inconsistent effects in those RCTs, which reported them (52,53), and reduced rates in one retrospective observational study (97). Longer duration trials, with use of symptom diaries, and/or selection for frequent exacerbations might help to confirm any treatment effect on clinical symptoms, but again such studies would require large sample sizes and the inclusion of a placebo control group would likely be considered unethical given the evident benefit on CT density decline.

Statement

Several randomised clinical trials in severe AATD have shown intravenous augmentation therapy to reduce the progression of emphysema as assessed by CT densitometry.

There is no evidence to support efficacy of AAT augmentation therapy in PiSZ, PiMZ or current smokers of any protein phenotype.

Clinical trials have used fixed doses of AAT determined by body weight. Whether individualising dosage based on trough levels for each patient has any benefit requires confirmation.

Suggested patient assessment and management steps

This stepwise approach describes the current practice of how members of the task force assess and treat patients with AATD and is intended as a guidance not as a general recommendation.

1. Identify patient with severe AAT deficiency.

2. Ensure smoking is stopped if the patient was a smoker.

3. Identify and modify any other potential risk factor/s.

4. Optimise current COPD therapy.

5. Assess patient in an expert reference centre.

6. Instigate augmentation therapy if indicated.

7. Continue monitoring.

Lung volume reduction surgery in AATD

Patients with severe emphysema suffer breathlessness in part due to emphysematous hyperinflation. It is well established that targeted resection of these areas, in selected patients with COPD, can result in significant improvements in quality of life and mortality. The last ATS/ERS statement concluded that bilateral lung volume reduction surgery (LVRS) offered short term benefit only and was not recommended for AATD related emphysema until more data was available (3). Stoller et al (112) reported outcomes from NETT study in 10 AATD patients having bilateral LVRS (5 with upper lobe predominant emphysema). The authors identified a higher mortality than medical treatment and a trend towards reduced magnitude and duration of beneficial effect compared to usual COPD. Specifically with respect to unilateral LVRS in AATD, Dauriat et al (113) compared outcomes in 17 patients with AATD versus 35 individuals with non AATD related COPD, finding improvements in both groups in FEV_1, dyspnoea score and PaO2 at 3-6 months. There was a loss of effect on walking distance, but preserved FEV_1 and dyspnoea score at 12 months in the AATD group.

These studies were performed a decade or more ago, since when there have been significant advances in patient selection, surgery, and the advent of randomised controlled clinical trials utilising devices to achieve medical lung volume reduction without the need for surgery; i.e. endobronchial valves (EBV), endobronchial coils,

lung sealant, thermal vapour. Patient selection is currently advocated through a multi-disciplinary team approach comprising physician, surgeon, radiologist and interventional bronchoscopist with special interest in LVR. It is recognised that patients being considered are, by definition, those with advanced disease and thus at higher risk, hence risk/benefit analysis is central to the multidisciplinary team assessment. Early outcomes from surgical LVR are now improved likely to reflect improved patient selection, MDT approach and the fact that most cases involve minimally invasive video assisted thoracoscopic surgery (VATS) and a unilateral rather than a bilateral procedure. Whether this has an influence on long term outcomes is unknown. However, mortality rate is 3% over 20 years post LVRS (114), with benefit in both lower and upper lobe disease and very low mortality from unilateral VATS (115).

The range of treatments in development may allow specific patterns of emphysema to be treated. The two best evaluated devices are endobronchial coils and EBV. Coils have been evaluated in patients with emphysema and significant improvements have been shown in 6 minute walking distance, FEV_1 and quality of life. Some patients with emphysema associated with AATD have been treated with coils, but no results have been provided for this specific subgroup of patients. Studies have shown that morbidity is increased and therefore personalised risk/benefit analysis is critical (116,117). Endobronchial valves are unidirectional valves placed bronchoscopically in the airways supplying the target lobe. In common with LVRS, the success of this approach remains optimal patient selection – in the case of EBV the absence of collateral ventilation between target and non-target lobe is vital to a successful outcome. The most recent RCT demonstrated significant improvements in 6 minute walking distance, FEV_1 and quality of life at 6 months, and also demonstrated that

centres need to be aware of potential morbidity of pneumothorax related to non-target lobe expansion and be proactive in performing valve maintenance to a high standard (118). The study also included some AATD individuals treated with EBV. However, owing the rarity of AATD large studies are not currently available to provide detailed assessment of coils, EBV or LVRS in AATD alone. Unlike EBV, coils can be used in patients with homogeneous emphysema, irrespective of collateral ventilation, but there is no specific data on in AATD. The promising results from EBV therapy have meant that specialist LVR units no longer exclude appropriate AATD individuals from these therapies, though more research is required..

Statement

Data is emerging for a successful outcome in selected patients with AATD from EBV placement or surgical volume reduction

The optimal results of these techniques are obtained when a careful appraisal of risks and benefits are performed by a multi-disciplinary team experienced in LVR and AATD

Lung Transplantation for emphysema associated to AATD

Severe AATD related emphysema has accounted for 5.4% of all lung transplants performed between 1995-2014 (119). Since the last ATS/ERS statement (3), there have been several publications reporting outcomes in many established transplant

centres in different countries, but all studies have been retrospective. De Perrot et al (120) reported a higher early mortality from sepsis in AATD and lower 10-year survival in AATD post transplantation compared to usual non deficient COPD, and, similarly, Thabut et al (121) have shown that patients with AATD had less survival benefit than patients with non deficient COPD. This may relate to associated excess inflammation at times of infection in post-transplant AATD individuals (122,123), due to the lack of the normal anti-inflammatory role of AAT (124). However, this higher, early mortality in AATD post-transplant has not been comfirmed e.g. Burton et al (125) reported no differences in early or late mortality for AATD compared to non deficient COPD.

In terms of survival compared with non transplanted AATD patients, Tanash et al (126) observed that transplantation increased survival considerably from 5 to 11 years compared to non transplanted AATD patients matched for FEV_1, age, sex and smoking history. The most common cause of death was pulmonary infection among the transplant patients and respiratory failure among the controls. In contrast, a UK study (127) also matched transplanted and non-transplanted AATD individuals for FEV_1, age and sex, but found that AATD patients who underwent lung transplant had lower gas transfer and quality of life pre-transplant compared to non-transplant patients. Further matching adjusted for quality of life (SGRQ), gas transfer factor and pre-transplant rate of lung function decline showed that transplantation did not increase post-surgical survival although quality of life was much improved. These controversial results underscore that the survival benefit of lung transplant is complex to assess and studies that compare matched patients with and without transplant are (by nature) biased (128). Consequently, survival benefit remains unclear and thus the main indication for transplantation relates to improvement in quality of life.

The evaluation of comorbidities is crucial in the assessment of candidates for lung transplantation and, hepatic evaluation is particularly critical in AATD, (129). Some centers perform systematic liver biopsy in candidates, although the detection of liver disease per se does not preclude lung transplant in these patients. There are experiences of combined liver and lung transplantation with satisfactory results.

Statement

The survival benefit of lung transplant in AATD patients is not clear.

In general, patients with AATD have improved quality of life following lung transplantation.

Referral timing, rate of decline in lung function, health status and social support differ from patient to patient and have an influence on the evaluation for transplant.

The role of post-transplant augmentation therapy in particular needs to be explored

New lines of research in AATD

There are several aspects of lung disease in AATD that require further research; the main topics identified by the group are:

Biomarkers of emphysema progression in AATD

Biomarkers of response to augmentation therapy

Research on the minimum clinically important difference (MCID) in rate of decline in lung density

Personalised augmentation therapy, with individualised selection of therapeutic regimen according to the patient needs

Development of genetic and regenerative therapies

Other types of treatment, such as biochemical inhibitors of neutrophil proteinases.

Development of specific patient-reported outcomes (PROs) for patients with emphysema associated with AATD.

Efficacy of augmentation therapy after lung transplant in AATD patients

Organisation of care: reference centres and registries

Due to the low prevalence and underdiagnosis, AATD is considered a rare disease. It is almost impossible for an individual clinician or a single centre to accumulate enough expertise in diagnosis and management of the disease; therefore, the care for patients with AATD is best organised in reference centres that can provide the highest standard of care and advice to the individuals affected and their families whilst also contributing to knowledge accumulation. An optimised format of service provision by a reference center in AATD is outlined in Figure 3 although other models may be applicable.

The European Commission also recommends the development of reference centres for rare diseases. The establishment of European reference networks (ERNs) for rare diseases should therefore serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERNs should also reflect the need for services and expertise to be distributed across the EU. In a document released by the European Commission in 2006, the criteria for reference centres of rare diseases are clearly specified (130) (Table 4)

Reference centers must establish a registry of their activity and collect information prospectively about the natural history of the patients being monitored. These data can be shared at national and international levels and be the foundation of the registries of AATD. The development of registries is crucial as the only way for the successful accumulation of knowledge about the clinical characteristics, evolution, natural history and response to treatment of patients with rare diseases, such as AATD.

Europe was pioneer in the development of national registries for AATD. As early as the 70s Sweden (15) and Denmark (78) initiated their registries, followed by other countries such as the Netherlands, Spain, Italy, Germany, Ireland, the UK and more recently Switzerland, Latvia, Estonia, Czech Republic, Poland, Austria, Belgium and France, among others. However, the low prevalence of the disease stimulated the organisation of an international registry, not restricted to Europe, but with predominance of European countries, the Alpha One International Registry (A.I.R.) that was founded in 1997 (9) following the recommendation from the World Health Organisation (WHO) to establish such a registry of AATD (25). AIR has been a successful platform for the development of clinical trials with new and existing therapies for the disease and has contributed to increase the awareness of the disease among healthcare professionals across Europe (131).

Statement

According to the European Council, management of patients with AATD should be supervised by reference centres of excellence at national or regional level.

The systematic collection of data concerning clinical characteristics and natural history of patients with AATD in national and international registries will enhance knowledge about the evolution of this disease and its optimal management.

For many AATD individuals, a respiratory service is the first point of diagnosis. The operational pathway includes varying assessments and follow up depending on personalising the patients' risk and defining the respiratory phenotype. Links to multi-disciplinary teams will ensure the best quality of care.

Access to optimal care and augmentation therapy for AATD in Europe

In Europe, health care policy is largely a devolved matter and decisions related to provision of healthcare services, disease management and prescription medicines rest with national, regional or local policy makers, health technology assessment (HTA) agencies and payers. This results in different standards of care for AATD and contributes to geographic inequalities in access to optimal healthcare services, clinical expertise and effective therapies. Notably, access to high-cost, rare disease therapies, such as augmentation therapy for AATD, can vary significantly across jurisdictions (132). Augmentation therapy is fully reimbursed in some countries such as Germany, Italy, Spain, Portugal, France and others, but not reimbursed in the majority of

Eastern European countries and in some Western European countries such as the UK, Ireland, Denmark or Sweden (table 5).

Increasing efforts are being made by policy makers to ensure that patients with rare diseases such as AATD have timely, better and more equitable access to high quality care. Examples of these initiatives include the European Council Recommendation on an action in the field of rare diseases, that required all EU member states to adopt national plans and policies for rare diseases by the end of 2013 (133), the European Network of HTA agencies (EUnetHTA) that aims to assist in the development of reliable, timely, transparent and transferable information to contribute to HTAs in European countries (134), and the European Medicine Agency's (EMA) adaptive pathways pilot for medicine development and data generation which allows for early and progressive patient access to a medicine (135).

In the absence of harmonised legislation that regulates AATD healthcare provision and access to augmentation therapy and other specific treatments across Europe, only multi-stakeholder collaboration and continuous improvement of the available evidence-base for efficacy and cost-effectiveness of AATD therapies is likely to achieve greater equity in implementation of best practice.

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Table 1. Laboratory methodologies used in different central national laboratories across Europe for diagnosis of AATD

Country	Biological sample	First-line method(s)	Second-line method(s)	Further method(s)	Author, year (Ref.)
Ireland	Serum/plasma	AAT level	Phenotyping	Genotyping; sequencing	McElvaney, 2015 (136)
Poland	Serum/DBS	serum AAT level	determination of AAT levels on dry blood spot samples, phenotyping, genotyping	sequencing	Chorostowska-Wynimko, 2015 (137)
Serbia	Blood	Immunonephelometric assay for AAT; genotyping		IEF; DNA sequencing	Beletic, 2014 (138)
France	Serum	quantification of serum α1-AT concentration with possible complementary measurement of the elastase inhibitory capacity of serum	Phenotyping: genotyping	Direct sequencing	Balduyck, 2014 (139)
Germany	DBS	AAT level	AAT level by nephelometry; genotyping	Phenotyping; sequencing	Miravitlles, 2010 (31)
Italy	DBS	AAT level; genotyping	Phenotyping	Sequencing	
Spain	DBS	AAT level	Genotyping	Phenotyping; sequencing	
U.S.	Blood/serum	AAT level; genotyping	Phenotyping	-	Bornhorst, 2007

					(140)
Italy	DBS	AAT level; genotyping phenotyping	Sequencing		Ferrarotti, 2007 (141)
Poland		Serum level	Phenotyping	Gene screening	Kaczor, 2007 (142)
Italy	Blood/DBS	Serum Level	Phenotyping	Genotyping; sequencing	Corda, 2006 (143)
U.S.	Blood	AAT level; genotyping	Phenotyping		Snyder, 2006 (144)
U.S	Plasma-serum/DBS	Concentration of AAT protein in plasma or serum (immunoassay)	Phenotype (IEF)	Genotype (PCR); Function test (Inhibition of leukocyte Elastase)	Campbell, 2000 (145)

Footnote: AAT: alpha-1 antitrypsin; IEF: isoelectrofocusing; PCR: Polymerase chain reaction; DBS: Dried blood spot

Table 2. Annual change in lung density (Perc15 or PD15), FEV1 and gas transfer in placebo-treated patients in RCT's or studies on the natural course of AATD-associated emphysema.

Author, year (Ref.)	Patients (n=)	Follow up in months	Perc15 (PD15) value (gr/L)	FEV1 (ml/yr)	DLCO*	DLCO/Va** (Kco)
Dirksen 1999 (51)	28	36	−2.57 ± 0.41[a]	−59.1 ± 11.9[a]	−0.16 ± .04 [a]	−0.0162± 0.004[a]
Dirksen 2009 (52)	35	25	-2.241[b] (-2.90– -1.577)	-23 ml[b] (-0.043– -0.004)	-0.343[b] (-0.489– -0.196)	-0.035[b] (-0.051– -0.020)
Stolk 2012 (146)	110	14	-1.81 ± 0.5[a]	-50±13[a]	-0.23 ± 0.05[a]	NA
Stolk 2015 (147)	51	96	NA	-66 ± 60.9[c]	NA	-0.0275 ±0.00259[c]
Chapman 2016 (53)	87	24	-2.19±0.23[a]	-2.3±13.1%[d]	-1.5±19.5%[d]	NA
Green 2016 (111)	76	24	-3.2 ± 0.5	-44.67 ± 8.71	-0.37± 0.04	-0.01± 0.01

NA = not available in the manuscript; * unit is mmol/min/kPa; ** mmol/min/kPa/L;

[a](mean ± SE); [b](95% CI); [c](mean ± SD); [d](annual decline in percent predicted)

.

Table 3. Studies on augmentation therapy for AATD

Study design	**Author, year**	**Intervention**	**Comparator**	**Primary outcome**	**N**	**Duration of Rx**	**Effect of treatment**	**Ref.**
RCT v placebo	Dirksen et al, 1999	250mg/kg augmentation 4 weekly	625mg/kg albumin solution	FEV_1 decline	58	≥3 years	FEV1 decline ns diff 59 v 79ml/yr (p=0.25); Reduced CT decline 2.6 v 1.5g/l/yr (p=0.07)	(51)
	Dirksen et al, 2009	60mg/kg Prolastin weekly	2% albumin solution	CT densitometry	77	≥2 years	Reduced CT decline 1.4 v 2.2g/l/yr (p=0.06)	(52)
	Chapman et al, 2015	60mg/kg Zemaira weekly	Lyophilised preparation	CT densitometry	180	≥2 years	Reduced CT decline 1.5 v 2.2g/l/yr (p=0.03)	(53)
RCT v active comparator	Stoller et al, 2002*	60mg/kg Prolastin weekly	60mg/kg Respitin weekly	Serum AAT level	28	≥12 weeks	Equivalence for 1e outcome, ns diff FEV1, DL_{CO}, urinary desmosine	(88)

RCT v active comparator	Stocks et al, 2006*	60mg/kg Prolastin weekly	60mg/kg Zemaira weekly	Serum AAT level	44	≥10 weeks	Equivalence for 1e outcome	(89)
	Stocks et al, 2010*	60mg/kg Prolastin-C weekly	60mg/kg Prolastin weekly	Plasma AAT level	24	10 weeks	Equivalence for 1e outcome	(90)
	Campos et al, 2013*	120mg/kg Prolastin-C weekly	60mg/kg Prolastin weekly	Plasma AAT level, safety	30	8 weeks	Equivalence for 1e outcome, ns diff in adverse events	(91)
	Sandhaus et al, 2014*	60mg/kg Glassia weekly	60mg/kg Prolastin weekly	Plasma AAT level	50	≥12 weeks	Equivalence for 1e outcome, ns diff FEV1 or FVC	(92)
Observational with control	Seersholm et al, 1997	60mg/kg Prolastin or Trypsone weekly	No augmentation	FEV_1 decline	295	1 year	Reduced FEV1 decline 53 v 75ml/year (p=0.02)	(93)
	AAT registry group, 1998	60mg/kg Prolastin	↓frequency or no	FEV_1 decline, survival	1129	12-86 months	Better survival (p=0.001), ns diff FEV1 decline	(8)

		weekly	augmentation				overall (p=0.40), if FEV1 35-49%, decline lower on Rx (73 v 93 ml/yr, p=0.01)	
	Wencker et al, 2001	60mg/kg augmentation weekly	Data prior to augmentation	FEV_1 decline	96	≥12 months	Reduced FEV1 decline 34 v 49 ml/yr (p=0.02)	(95)
	Stoller et al, 2003	Any dosing regimen augmentation	Usual care	Adverse events	1129	12-86 months	83% augmented patients had no adverse events; rate 0.02 events/patient/month	(94)
	Tonelli et al, 2009	Any dosing regimen augmentation	No augmentation	FEV_1 decline	164	Mean 42 months	Reduced FEV1 decline 37 v 46ml/yr (p=0.05)	(96)
Observational with control	Barros-Tizon et al, 2012	60mg/kg Prolastin or Trypsone at any interval	Data prior to augmentation	Exacerbation rate	127	18 months	Reduced exac rate 1.2 v 1/pa (p<0.01), reduced hospitalisation costs	(97)
Observational,	Wewers et al,	60mg/kg	N/A	Serum AAT	21	6 months	AAT level improved v	(82)

no control	1987	augmentation weekly		level, safety			baseline, low adverse event rate i.e. safe	
	Schmidt et al, 1988	60mg/kg augmentation weekly		Serum AAT level	20	6 months	AAT level maintained at 35% of normal (equivalent to PiMZ)	(98)
	Barker et al, 1994	60mg/kg Prolastin weekly#		Functional status	14	12-48 months	12/14 patients stabilised self-reported functional status	(99)
	Miravitlles et al, 1994	60mg/kg Prolastin weekly$		Safety, AAT level	13	Up to 6 years	No significant adverse events; 10/13 trough AAT >50mg/dl	(101)
Observational, no control	Barker et al, 1997	120mg/kg Prolastin fortnightly		AAT level, safety	23	20 weeks	Trough levels inadequate with fortnightly dosing, Rx safe	(100)
	Schwaiblmair et al, 1997	60mg/kg Prolastin weekly		FEV_1	20	3 years	FEV1 decline 36ml/yr	(102)
	Wencker et al, 1998	60mg/kg Prolastin		FEV_1 decline, safety	443	3.1-82.8 months	FEV1 decline 57ml/yr on Rx, which was deemed	(103)

		weekly					safe	
	Campos et al, 2009	Any form of augmentation		Compared age >60 to <60	1062	1 year	Older subjects exhibited more indolent disease with fewer exacerbations	(106)
	Campos et al, 2009	Any form of augmentation		Exacerbations	922	1 year	Mean exacerbations 2.4/year, 17 days/episode	(105)
Observational, no control	Vidal et al, 2010	60mg/kg Trypsone weekly		Safety	23	24 weeks	1/555 infusions had a treatment related adverse event	(108)
	Subramanian et al, 2012	60mg/kg Prolastin weekly		PET CT	10	12 weeks	Ns difference in PET signal on Rx	(107)

*=Crossover study (either wholly, or as follow on for placebo group) #some patients changed to 120-180mg/kg 2-3 weekly $changed to 240mg/kg 4 weekly

Rx= treatment; RCT=randomised controlled trial; FEV_1=forced epiratory volume in 1 second; CT=computed tomography; AAT=alpha 1 antitrypsin; 1e=primary; DLco=gas transfer;

Table 4. Criteria required for reference centres for rare diseases (From ref. 130)

- Appropriate capacity to diagnose, monitor and manage patients with evidence of good outcomes when applicable
- Sufficient capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- Demonstration of a multi-disciplinary approach
- High level of expertise and experience documented through publications, grants or honorary positions, teaching and training activities
- Strong contribution to research
- Involvement in epidemiological surveillance, such as registries
- Close links and collaboration with other expert centres at the national and international levels and a capacity to network
- Close links and collaboration with patient associations where they exist
- Perform education, information, communication activities to empower patients
- Although an ENCR should fulfil most of the above criteria, the comparative relevance of these various criteria will be influenced (in part) by the particular disease or group of diseases covered

Footnote: ENCR: European National Centre of Excellence

Table 5. Description of access to care for AATD patients in some Eastern and Western European countries.

East European Centers of A1AT				A1AT deficient subjects			
Country	Population (million) *	National Centers (number)	National Centers (location)	Patients Monitored	Access to Augmentation	Augmentation Treatment	Reimbursement (status in January 2017)
Bulgaria	7.09	0	0	by university clinics on individual basis	no access	0	not covered by public health insurance
Croatia	4.22	0	0	by university clinics on individual basis	no access	0	not covered by public health insurance
Czech R.	10.55	1	Thomayer Hospital Prague	by National Center (63 PiZZ pts)	unrestricted	26/18 (in sum, now)	100% covered by public health insurance
Hungary	9.81	4	plan to set up 4	by National Centers	no access	0	not covered by public health

			National Centers at universities (2016)				insurance
Latvia	1.95	1	Centre of TB and Lung Disease, Riga East University Hospital	by National Center (approximately 20 PiZZ pts)	limited access	1	not covered by public health insurance
Poland	38.59	1	National Institute of Tuberculosis and Lung Diseases in Warsaw, The Children´s Memorial Health Institute in Warsaw	by National Center (70 pts)	no access	0	not covered by public health insurance
Romania	19.34	1	Marius Nasta Institute of Pneumology, Bucharest	by National Center (7 pts)	no access	0	not covered by public health insurance
Russia	143.44	0	0	by university clinics on individual basis	no access	7	not covered by public health insurance

Serbia	8.80	0	0	by university clinics on individual basis (approximately 20 pts)	no access	0	not covered by public health insurance
Slovakia	5.43	3	plan to set up of centers (Kosice, Bratislava, Vysne Hagy)	by National Centers	limited access	1	every single patient has to be individually agreed with health insurance
Slovenia	2.09	0	0	NA	no access	0	not covered by public health insurance
West European Centers of A1AT				A1AT deficient subjects			
Country	Population (million) *	National Centers (number)	National Centers (location)	Patients Monitored	Access to Augmentation	Augmentation Treatment	Reimbursement (status in January 2017)
Austria	8.49	8	Wien, Salzburg, Graz, Hörgas-Enzenbach, Wels-Grieskirchen,	by general practitioners	unrestricted	130	100% covered by public health insurance

			Natters, Klagenfurt, Hohenems				
Belgium	11.48	NA	All over the country	university hospitals and local hospitals by pneumologists	unrestricted	56	100% covered by public health insurance, but only for patients who started therapy before 2010. No reimbursement for new patients after 2010
Denmark	5.70	1	Copenhagen	by university clinic follows up patients on individual basis	no access	0	not covered by public health insurance
France	64.73	NA	All over the country	by university hospitals, local hospitals, private practices	unrestricted (to PI SZ and PiZZ)	> 300	100% covered by public insurance
Germany	80.68	60	All over the country	by university hospitals, local hospitals, private practices	unrestricted	>1000	100% covered by health insurance
Italy	59.80	>20	All over the country	university hospitals and local hospitals by pneumologists	unrestricted	115	100% covered by public health insurance

Ireland	4.72	1	Dublin	by National Center	limited access	23	not covered by public health insurance
Netherlands	15.1	1	Leiden Univ Med Center	by National Center	no access	0	not covered by public health insurence
Portugal	10.29	27	All over the country	by university hospitals and local hospitals by pneumologists	unrestricted	118	100% covered by public health insurance
Spain	46.05	>40	All over the country	by university hospitals and local hospitals by pneumologists	unrestricted	170	100% covered by public health insurance
UK	65.20	5	Birmingham, Edinburgh, Cambridge, Coventry, London	major centres by experts and local hospitals by pneumologists	no access but some named patients with panniculitis (off label indication)	0	full if approved for Individual Funding Request (IFR) by local commissioners (in NHS England)

*SOURCE: http://www.worldometers.info/

NA non-available data, PTS - patients

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FIGURES

Figure 1. Algorithm for laboratory testing of AATD.

Footnote: This algorithm describes the current practice of how members of the task force treat patients with AATD and is not provided as a general recommendation. AAT: alpha-1 antitrypsin; CRP: C reactive protein

Figure 2. Algorithm for familial testing for AATD

Footnote: This algorithm describes the current practice of how members of the task force treat patients with AATD and their first degree relatives and is not provided as a general recommendation. Wider family testing may be indicated in some instances (see text)

Figure 3. Proposal of a services provision by a reference center in AATD

Footnote: This algorithm describes the current practice of how members of the task force treat patients with AATD and is not provided as a general recommendation CXR: Chest X-ray; CT: Computed tomography; MDT: multidisciplinary team