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Review

Alpha 1 Antitrypsin Deficiency: a rare multisystem disease, predominantly affecting the lung

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Abstract

Introduction: α-1-antitrypsin deficiency (AATD) is a rare hereditary disorder associated with early onset emphysema, chronic obstructive pulmonary disease, liver cirrhosis and panniculitis. The pathophysiology contributing to lung disease in patients with AATD involves the inter-play of several complex molecular pathways. AAT is produced by hepatocytes and liver disease is most commonly associated with the Z allele which causes polymerization and accumulation of mis-folded AAT proteins leading to inflammation and cirrhosis.

Areas covered: A literature search was conducted through Ovid to search Medline, Embase and the Cochrane Library. This article aims to review the clinical features of AATD and the latest evidence available on treatment will be discussed, including AAT replacement therapy, gene therapy and stem cells. Furthermore, ways in which current research could impact global practice as well as current problems faced by researchers will be discussed. This review article also includes a section about the future of AATD management.

Expert opinion: Recent randomized clinical trials have concluded that intravenous augmentation therapy slows progression of lung disease. However, more research is needed to identify the optimum regimen of AAT administration to stop disease progression as well as other effective treatment modalities that can be used in conjunction with or instead of augmentation therapy.

Keywords

Alpha 1 antitrypsin deficiency, emphysema, chronic obstructive pulmonary disease, augmentation therapy, treatment, gene therapy

Article highlights box

- More research is needed to identify the optimum treatment regimen of AAT augmentation therapy to stop disease progression.
- The advent of liver directed therapy in the form of siRNA offers hope that combination treatment could address both lung and liver disease
- Less expensive treatment options such as oral Neutrophil-Elastase inhibitors and recombinant AAT are key topics in current research
- Personalized treatment regimens accounting for underlying pathogenic drivers are likely to be the future of management

1. Introduction

Alpha 1 antitrypsin deficiency (AATD) is an autosomal codominant inherited disorder and the gene that codes for Alpha 1 antitrypsin (AAT), known as *SERPINA1*, is found on chromosome 14(1). AAT is a protease inhibitor mainly secreted by hepatocytes and protects the lung tissue from unopposed proteolytic degradation mediated mainly by neutrophil elastase (NE). It also confers a smaller degree of protection against damage caused by other serine proteases, such as cathepsin G (2). Neutrophil elastase is involved in the migration of neutrophils to sites of inflammation, plays a key role in degrading invading pathogens as well as products of inflammation(3) and induces alveolar damage(4) leading to the hypothesis that a reduced serum level of AAT leads to an imbalance between proteases (mainly NE) and antiproteases(5) resulting in lung disease. Hence those affected by AATD are predisposed to the development of early onset emphysema and chronic obstructive pulmonary disease (COPD).

Although AATD significantly increases the likelihood of developing COPD, and its associated phenotypes, not all those with AATD will develop lung disease. This indicates that genetic, epigenetic and environmental factors may play an important part in variations in clinical phenotype (6). The single most important risk factor in the development of lung disease in subjects with AATD has been identified to be smoking (1, 7). Several studies have shown that cigarette smoking further worsen the imbalance between proteases and anti-proteases by inactivating AAT (8).

About 10-20% of AATD patients suffer from clinically significant liver disease (9), suggesting that this phenotype also has significant modifying factors. Some genetic polymorphisms which cause deficiency lead to the synthesis of abnormally folded AAT protein which polymerises in the endoplasmic reticulum

of hepatocytes(10). The accumulation of such abnormally folded protein in hepatocytes leads to endoplasmic reticulum stress, hepatocyte damage, fibrosis and ultimately cirrhosis. The presence of risk factors such as alcohol consumption plays a key role in liver disease progression in patients with AATD (11).

This review will cover aspects of epidemiology, diagnosis, clinical assessment and the licensed orphan drug(s) relevant to the condition, concluding with a short section on possible future directions for treatment.

1.1 Search strategy

Using Ovid, the following databases – Medline (1946 to April 14) and Embase (1974 to week 15) including the Cochrane Library were searched. The search was limited to papers written in English and that had been published in the last 20 years. The search terms used were “alpha-1 antitrypsin deficiency”, “alpha-one antitrypsin deficiency”, “clinical features”, “management” and “treatment”. Papers older than 20 years were used as reference when there were no other suitable latest alternative.

2. Prevalence of AATD

It has been estimated that AATD affects 3.4 million people worldwide(12) with the most common severely deficient polymorphism (Z allele) present in around 1/5000 European Caucasians, with this racial group being more likely to be affected than others. It is thought that the Z allele arose in Northern Europe, and travelled with the Vikings such that a North-South gradient can be seen in the distribution of the Z allele. Similarly the S allele is thought to have arisen in South-West Europe and is consequently more common in Spain and Portugal, exhibiting a lower prevalence with distance from these regions(13). Many maps of the geography of common allele distribution have been made, and recent data expanding the earlier epidemiological research worldwide shows that the disease is not as restricted to Europe as once thought(14) . In addition to the more common S and Z alleles many other rare variants exist, which historically were named after the place in which they were first discovered (15). Broadly speaking their risk of disease relates to the resultant level of AAT (for lung disease) and the degree of polymerization (for liver disease). Importantly, the prevalence of the genetic abnormality is not the same as prevalence of disease due to AATD, due to the multiple modifying factors present. In our own country the estimated

numbers based on genetic factors alone is more than 4 times the number known to registries and databases(14, 16) which implies either widespread underdiagnosis or poor disease penetrance. Clearly, the number of AATD patients diagnosed is influenced by local and national guidelines relating to screening. It has been proposed that a case finding approach may be a better way to identify those in need of treatment rather than whole population screening for this reason(17), and although the World Health Organisation has recommended screening for AATD in patients with COPD or adult onset-asthma since 1996 (18), the use of the word screening in this context actually aligns to more of a case finding approach, whereby testing is only done in symptomatic people. This has been further emphasized in the recent European Respiratory Society statement on the diagnosis and treatment of lung disease in AATD patients (19).

3. Diagnosis of AATD

In general the diagnosis is made after testing in a symptomatic individual, first by assessment of AAT level, and then ascertainment of genotype. An algorithm for testing has been proposed by the European Respiratory Society working group for AATD (19) with testing being possible using whole blood or dried blood spots. Accreditation of laboratories is available in some countries. Normal serum concentrations of AAT are observed in individuals with the genotype protease inhibitor (Pi) MM (or homozygous M), with the most common deficient alleles being PiZ and PiS. Homozygous Z genotype is responsible for the most severe AAT deficiency and is characterized by AAT serum concentrations 10% of the normal MM genotype(5). The serum concentration in healthy adults lies between 20-53μM but a serum concentration of 11μM has been hypothesised to represents a protective threshold below which the risk of developing emphysema increases. However this level is far from clear, in that it was suggested based on the observation that PiSZ patients, whose levels lie at around this, appeared initially not to be at risk of accelerated lung disease. Later studies have shown that these patients have a similar rate of decline to PiZZ patients once confounders are accounted for, after disease has developed (16). This implies that by the time disease develops the level may of lesser importance than once thought.

4. Clinical features of AATD

AATD deficiency has been associated with COPD, bronchiectasis(20), neonatal jaundice(21), liver fibrosis and cirrhosis, vasculitis(22) and panniculitis(23).

4.1 AATD and the lungs

Patients with AATD often present with non-specific symptoms and this leads to a delay in diagnosis. An observational study (24), using pooled data from Germany and Italy found that the delay between presentation of symptoms and diagnosis was 6 years. Patients typically present in their 3rd or 4th decade of life (25) with breathlessness with or without cough, wheeze and phlegm (26). They typically present at a much younger age and having had less cigarette smoke exposure than people with non-AATD COPD.

Classically, AATD patients develop panacinar emphysema (27) that predominantly affects the lower lobe although all lobes can be affected (Figure 1). This is in contrast to non-AATD COPD patients who most commonly develop centrilobular emphysema which predominantly affects the upper lobes (28). Plain chest x-rays commonly show hyperinflation of the lungs and bullae may also be present in the patient with emphysema. Reduced forced expiratory volume in 1 second (FEV1) and reduced FEV1 to forced vital capacity (FVC) ratio are diagnostic characteristics of airflow obstruction. A study conducted from the Irish National AATD Registry concluded that cigarette smoking was the greatest predictor of FEV1 impairment in PiZZ patients(29). Furthermore, FEV1 decline in PiZZ and PiSZ patients severely affected by AATD may be steeper during the first 20 pack years of cigarette smoking(30). An interesting finding in an Irish study was that rate of FEV1 decline in ex-smokers was the same as non-smokers(29); this has not been borne out in other registries, but it remains possible that ascertainment biases are affecting results, since non-smokers with no decline above that of normal aging are not likely to be symptomatic, and are therefore less likely to be tested. Other studies have demonstrated variable rates of FEV1 decline in never-smokers, ex-smokers and current smokers with severe AATD(31). Hence, further studies focusing on environmental factors and other measures of lung function might be able to provide experts with more reliable data.

As mentioned earlier, the extent of airway obstruction in the AATD patient is commonly out of proportion with the smoking history. Often AATD patients present with symptoms that are very similar to asthma such as dyspnea, wheezing, mucous production. Moreover, bronchodilator response in patients with AATD is highly variable. A study conducted by the National Heart Lung and Blood Institute (NHLBI) registry found that 49% of patients with AATD met the diagnostic criteria for asthma when taking into account all their visits (26). Hence, it is very common for patients to be misdiagnosed with asthma, and equally it is possible for an AATD patient to have concomitant asthma. Delineating the predominant pathology in such cases, as in usual COPD-asthma overlap, is key to optimizing management, such as inhalers, long term.

The measure chosen to assess lung disease is also of paramount importance. Gas transfer is a measure classically thought to reflect parenchymal lung disease, and may therefore be a more specific marker of emphysema than FEV1. This is supported by the fact that change in lung density on CT scan (the most sensitive measure of emphysema progression) aligns better to change in gas transfer than to change in FEV1(32). Furthermore, patients may also have discordance between gas transfer and spirometry, such that some patients have abnormality in one but not the other; those that have abnormalities of both are more likely to be smokers(33). Measuring both FEV1 and gas transfer is therefore the ideal way to monitor patients for disease progression.

Several studies have demonstrated an association between AATD and bronchiectasis. Parr et al. found that the prevalence of bronchiectasis, diagnosed by high-resolution CT, in 74 patients with severe AATD was very high (94.6%)(20). Another set of data which supports the association between AATD and bronchiectasis is the targeted screening program in Germany. After analysis of 18,638 testing kits, 1835 patients with severe AATD were identified and bronchiectasis was identified as a strong predictor for the ZZ genotype (34). This study has been of interest to experts since earlier studies had given conflicting results on the link between bronchiectasis and AATD(35). Parr et al.'s study used regular sputum production' to differentiate between clinically significant bronchiectasis and clinically insignificant bronchiectasis; studies in usual COPD have sometimes shown discrepancy between radiological finding and symptoms that are indicative of classical bronchiectasis, so care must be taken not to overdiagnose on radiology alone. As the 74 subjects included in this study carried the ZZ genotype and were likely to also suffer from COPD, even regular sputum production might be an unreliable distinguishing factor(36) since chronic bronchitis is common in COPD, even in the absence of bronchiectasis. Moreover, it can be argued that the study sample is not representative of the actual prevalence of bronchiectasis in AATD patients in the general population as those with less severe lung disease were not included in this study. Hence by selecting a sicker population that is more likely to produce regular sputum, selection bias could have been introduced.

Estimates of the overall prevalence of different pulmonary phenotypes in AATD are illustrated in fig.2.

4.2 AATD and the liver

AATD is the most common genetic cause of liver disease in neonates and the second most common clinical condition necessitating a liver transplant in children after biliary atresia(37). Liver disease is caused primarily by the ZZ genotype; a single Pi Z allele increases the risk of cirrhosis and liver failure even in the

absence of other identifiable co-existing liver disease(38). The SZ genotype also seems to be a risk factor for liver disease although this risk seems to be marginal compared to the risk associated with the ZZ genotype(39). As the misfolded Z proteins accumulate within hepatocytes, they polymerise and trigger a response cascade leading to chronic hepatitis and cirrhosis(40). The usual presentation in neonates includes cholestatic jaundice and hepatomegaly. Conjugated bilirubin is raised and liver enzymes are disturbed(21). Gamma GT has been showed to be significantly raised in Pi ZZ individuals when compared to a control group(41). However, its use as a marker is confounded by the fact it is also linked to oxidative lung injury and airway obstruction(42). Nevertheless, the presence of high gamma GT levels along with deranged liver enzymes and respiratory symptoms in patients should lead the clinician to suspect AATD. Adult patients most commonly present with established signs of liver cirrhosis(40), although a greater awareness of the need to actively seek liver disease with (for example) elastography may change this pattern in years to come, with more patients being picked up in earlier fibrotic stages prior to development of decompensated cirrhosis. Factors such as male sex, age over 50 years, hepatitis, and the presence of repeated elevated liver function tests are associated with increased risk of liver disease in patients with the ZZ genotype(43). As mentioned earlier, alcohol consumption plays a key role in liver disease progression in patients with AATD. Studies have also suggested that patients with AATD are at higher risk of developing hepatocellular carcinoma(44) and cholangiocarcinoma(45), however there is considerable uncertainty in this area given that cirrhosis itself is a risk factor as well. Widespread heterogeneity of presentation implies genetic modifiers as well, but little is known in this area as yet.

4.3 AATD and the skin

Panniculitis associated with AATD deficiency is very rare. The estimated prevalence of panniculitis in patients with the ZZ genotype is 9 in 1000 in the UK registry (46) and 1 in 1000 in the U.S registry(47) . Its typical presentation is ulcerating subcutaneous nodules that may give off an oily discharge(48). Histologically, neutrophilic infiltrates are observed in the subcutis(23). Panniculitis may present independent of hepatic and pulmonary manifestations, hence accurate diagnosis of panniculitis plays an important role in the timely management of these patients(48).

4.4 Other clinical features of AATD

Patients with AATD have also been shown to be at increased risk of developing granulomatosis with polyangiitis previously known as Wegener's granulomatosis(22). Granulomatosis with polyangiitis is a vasculitis characterised by necrosis and granulomatous inflammation of small to medium blood vessels. It is associated with the presence antineutrophil cytoplasmic antibodies (ANCAs) in blood(49) and classically involves the ELK triad – ear, nose and throat (E), lungs (L) and kidneys (K). Its clinical manifestations are very broad but the most common ones include otorhinolaryngologic symptoms such as nasal bridge collapse, mucosal ulceration, sinus inflammation, sensorineural hearing loss and conductive hearing loss amongst several others. The respiratory tract is affected in 70-100% of cases(50). Other forms of ANCA positive vasculitis have also been reported to occur in AATD, notably eosinophilic vasculitis(51). ANCA positive vasculitides are rare disorder but can be rapidly progressive; if left untreated, mortality within 1 year of diagnosis is 90%. Treatment usually involves steroids and immunosuppressive agents(52). Other associations reported epidemiologically include inflammatory bowel disease(46), thyroid disease(46) and fibromyalgia(53). One hypothesis behind the multiple associations is that all inflammatory disorders are more common (or more severe when present) in AATD, presumably because of the relative lack of anti-inflammatory and anti-neutrophil elastase activity in such patients.

5. Management of AATD

5.1 Lung disease

All patients who have AATD related lung disease should be managed according to guidance for optimal COPD management, including smoking cessation, bronchodilation and (in selected cases) inhaled steroids(19). Pulmonary rehabilitation, influenza vaccination and oxygen should be used similar to usual COPD; whilst little evidence exists specific to AATD of efficacy of many of these general treatments there is no reason to suspect that they would be harmful, or that they would work less well. Indeed there is growing evidence that phenotype-treatment relationships apply in the same way as usual COPD; for example AATD patients who have relative high blood eosinophils exhibit a greater treatment effect from inhaled steroids than those without (54), similar to usual COPD(55).

As lung disease in AATD is driven by the imbalance in proteases and antiproteases, a logical treatment would be to correct the AAT deficiency and achieve physiological serum concentrations. Studies have concluded that patients with the Pi SZ genotype have a significantly lower risk of developing emphysema

compared to patients with the Pi ZZ genotype(56, 57). Consequently, a 'protective serum threshold' of 11µm was established and this is considered the cut-off value below which patients with AATD would be eligible for augmentation therapy(16). This cut off value represents the 10th percentile of the AAT serum concentration range in individuals with the Pi SZ genotype(58). Augmentation therapy was first tested and subsequently licensed by the United States Food and Drug Administration (FDA) for emphysema secondary to AATD in 1987. It is now licensed across Europe although it has not been funded for this purpose in all countries yet. The products used are all derived from plasma and the most common ones that have been adopted in clinical practice worldwide are Prolastin®, Zemaira®, Aralast®, Trypsone®, Glassia® and Kamada API®. The strongest clinical evidence to date has been provided by Prolastin®. However, the dosing regime of these products is not uniform globally.

5.1.1 Intravenous augmentation therapy

The first study that used AAT derived from human plasma to restore serum concentration levels to the protective threshold was conducted by Wewers et al. and adopted a treatment dose of 60mg/kg weekly(59). Although there have been several studies exploring different treatment doses at different frequencies of administration(60-62), the treatment regimen in clinical practice has remained 60mg/kg/week. When augmentation therapy was first introduced as a treatment, the measurement standards available to evaluate decline in lung function associated with AATD were based on little empirical data. Randomised Clinical Trials (RCTs) provide the gold standard in proving clinical efficacy of a treatment regime. However, when augmentation therapy was first introduced, the number of patients with AATD identified was too small to carry out an RCT. In addition, for RCTs to deliver valid results, well-defined clinical end-points need to be established and 30 years ago, those which were available (such as FEV1) had low sensitivity. Even quality of life scores were only validated specific to respiratory disease(63) after augmentation was first tested. It required development of more sensitive tests, such as CT densitometry of the lung, to power RCTs appropriately, although the outcomes accepted by drug regulators vary(64).

Several observational studies have demonstrated the clinical efficacy of augmentation therapy. Seersholm et al. found that in AATD patients with FEV1 31–65%, augmentation slowed the decline of FEV1 by 21 ml/year compared to the control group when data analysis was conducted by FEV1 strata(65). One of the largest observational studies, carried out from the NHLBI Registry for Severe Deficiency in AAT Registry,

also supported Seersholm et al.'s findings that augmentation therapy reduced FEV1 decline. However, their findings differed per FEV1 strata (66). Augmentation therapy was also shown to be associated with decreased frequency of lung infections(67) and reduced the levels of leukotriene B4 hence supporting the anti-inflammatory effects of augmentation therapy and therefore its efficacy(68). Until then, FEV1 decline had commonly been used to assess the effect of augmentation therapy on progression of emphysema.

Dirksen et al. were the first to use CT densitometry to assess disease progression in AATD and two small RCTs were published in 1999 and 2009(69, 70). The 1999 RCT showed a trend towards augmentation having benefit and data from this trial was used to calculate how large the sample size would need to be in order to obtain statistically significant results to prove the clinical benefit of augmentation therapy in lung disease in AATD patients. The 2009 RCT (EXACTLE Trial) concluded that there was treatment benefit to be gained from augmentation not only in the form of reduced lung density decline but also in the form of less severe exacerbations. It also demonstrated that CT densitometry was a more reliable assessment tool for monitoring emphysema progression in patients receiving augmentation therapy compared to FEV1(70). These 2 RCTs were underpowered not only to detect clinically significant changes using CT but also the other outcomes that were being assessed such as exacerbation frequency and severity. While these two RCTs alone, did not yield statistically significant results, Stockley et al. combined the data from both RCTs and concluded that IV augmentation therapy significantly reduces the decline in lung density (71). In 2010, the Cochrane Collaboration published a systematic review that analysed the same data and concluded that there was not enough evidence to recommend its use. The Cochrane Review authors showed skepticism towards the validity of CT densitometry for this purpose. This systematic review was later updated with results of the RAPID-RCT in 2015 but its conclusions remained unchanged(72), however the skepticism toward densitometry is not a view held by clinicians working in the field. Inter- and intra-patient variability of FEV1 along with the fact FEV1 changes over time in patients with AAT, may make FEV1 not specific enough to be used for monitoring patients or conducting trials (73).

The Randomized, placebo-controlled trial of Augmentation therapy in Alpha-1 Proteinase Inhibitor Deficiency (RAPID-RCT) and RAPID-OLE (open-label extension of RAPID-RCT) study was the first large trial that showed statistically significant evidence for the clinical efficacy of augmentation therapy by demonstrating a significant reduction in the rate of decline of lung density as measured by CT. CT densitometry has been proven to correlate closely with more commonly used outcome measures such as FEV1 decline and mortality(74). The RAPID RCT included 180 subjects from 13 countries and was published in 2015. It concluded that subjects receiving 60mg/kg of AAT weekly had a

statistically significant reduced rate of lung density decline (measured with CT) compared to placebo : –1.45 g l^{-1} year $^{-1}$ *vs.* –2.19 g l^{-1} $year^{-1}$; difference 0.74 g l^{-1} $year^{-1}$ [95% CI 0.06–1.42], $P = 0.03$ (75). No differences in lung function, quality of life or mortality were seen, but the study was not powered to look at these outcomes. Notably decline was still present in the treated patients, which has raised questions about whether the current standard dose is sufficient, or whether treatment targeting other pathways may be required alongside augmentation to completely abrogate disease progression.

Subjects who were recruited for the RAPID-RCT trial could receive augmentation therapy for 2 more years to investigate the long-term effects of AAT augmentation on the progression of emphysema via the RAPID OLE trial. Data from both RAPID-RCT and RAPID-OLE was pooled together and the results concluded that the rate of lung density loss in patients receiving AAT augmentation therapy was lower than in the placebo group. Another finding from the pooled data was the importance of early treatment with augmentation therapy as lost lung density was never recovered(76). Therefore, RAPID-RCT and RAPID-OLE not only provided evidence of augmentation therapy slowing disease progression but of the disease-modifying properties of augmentation therapy; data analysis has suggested that early treatment in patients with severe emphysema could result in delayed time to death and lung transplant(77). Furthermore, a systematic review conducted published in 2017 confirmed that augmentation therapy remains the only disease-specific therapy in AATD patients with lung disease and concluded that there is strong evidence that augmentation therapy slows decline in emphysema as assessed by CT densitometry (78).

RAPID-RCT and RAPID-OLE were of key importance in assessing the clinical efficacy of augmentation therapy. However, as mentioned earlier, they assessed lung tissue loss using CT densitometry which is not commonly available. Studies have shown that CT densitometry is more sensitive in detecting lung tissue damage compared to other tests such as spirometry or scoring tools(70). However, spirometry and more complex lung function tests remain the most common means of assessing individuals with lung disease caused by AATD. Designing an RCT with these more commonly used clinical end point would require a larger number of subjects followed over a long period of time in order to detect clinically significant results. However, for clinical research to be carried out ethically it requires clinical equipoise – i.e that there is no current evidence that the treatment being tested is better than placebo. RAPID- RCT and RAPID-OLE have both shown that augmentation therapy leads to a reduced rate of lung function decline in patients with AATD. Hence, it would be challenging to enroll patients in a placebo-arm of such a RCT trial. An ongoing placebo controlled trial (SPARTA; NCT01983241) of several dosing regimes which is still using CT scanning as an outcome has had a long recruitment period to date, suggesting that this is a factor,

even in smaller studies. Future work in augmentation therapy may include studies of higher doses, studies examining the effect of augmentation on exacerbation severity and frequency, and use of augmentation post lung transplant.

5.1.2 Inhaled augmentation therapy

The time-consuming nature of regular intravenous infusions of plasma-derived AAT, the risk of infection associated with IV administration, its high cost and the fact that only 2-3% of AAT given intravenously reaches the lungs(79) has brought forward the need for a more efficient method of delivery to the lungs. It has been demonstrated that AATD patients with COPD have increased neutrophilic chemotactic activity caused by increased levels of LTB4. Uninhibited neutrophil elastase binds to alveolar macrophages resulting in increased levels of LTB4(80). Consequently, the combined effect of increased neutrophilic chemotactic activity and an inhibitor deficiency plays a key role in the process of inflammation contributing to lung parenchyma damage in patients with AATD(81). Intravenous augmentation therapy has been proven to decrease elastase activity and decrease LTB4 levels(68). Therefore, it has been hypothesised that inhaled AAT might be more effective at inhibiting elastase locally. Trials are currently underway to test this hypothesis and one study (NCT01217671) has been completed but its results remains unpublished(82). There are limitations to this approach, particularly for a large protein like AAT, in that it may be difficult to inhale beyond the large airways, in part due to the efficacy of inhalation devices and in part due to the particle size. Furthermore it may be that that the most relevant area of action is beyond the airway, in which case AAT would need to reach the interstitium, and this may be difficult when considering diffusion of such a large molecule. Further work in this area is therefore required.

5.1.3 Drugs in clinical development for lung disease

There are two important upcoming trials which address important concepts in this area, namely development of recombinant AAT, and alternative routes of NE inhibition. These are a Phase 1 study to look at the safety profile, pharmacodynamics and pharmacokinetics of a recombinant form of AAT -INBRX-101 (NCT03815396) and a phase II trial of Alvelestat, a potent oral inhibitor of NE (NCT03679598). Recombinant AAT is an attractive proposition because it may reduce costs relative to plasma derived therapy. New formulations like this might even be able to reduce infusion time or frequency. However previous forms of recombinant AAT induced immune reactions which made them unusable beyond phase I. NE inhibition clearly links to the pathogenesis of AATD lung disease, hence has obvious potential,

although endpoint selection and power will be important factors, as in the augmentation studies, if it reaches phase III work.

5.2 Liver disease

Due to the pathophysiology of liver disease in subjects with AATD deficiency, augmentation therapy neither worsens nor improves liver disease. A recent systematic review concluded that the only effective treatment available for AATD patients with liver disease remains liver transplantation. The 5- year survival rate after liver transplantation was estimated to be over 90% in children and over 80% in adults(11).

5.2.1 Drugs in clinical development for liver disease

Drugs are now reaching later stages of clinical development for AATD, and a phase II/III study has recently been registered that takes short interfering RNA (siRNA) into this field. Reduction of AAT production is attractive for liver disease because by reducing polymer burden it may reduce the cellular stresses that ultimately lead to fibrosis and cirrhosis. A phase I clinical trial investigated hepatic targeted siRNA with the aim to silence defective AAT production in the liver of Pi ZZ patients, and showed promising results in the sense that AAT was knocked down sufficiently (83). This formulation used an excipient which was not ideal either for safety or for repeated administration, since it required intravenous use. Subsequent development, and the later phase trials, will therefore use a subcutaneous form, without the problematic excipient.

5.3 Skin disease

The first line treatment recommended for panniculitis, based on response to treatment in published cases, is dapsone followed by augmentation therapy (84). Augmentation therapy is used to treat panniculitis in some countries, but approval status varies. In the UK, access to centralised funds for therapy is only available on a case by case basis. The rarity of skin problems in AATD, coupled with the rarity of AATD make it unlikely that RCTs will be performed comparing management options.

5.4 Genetic and molecular therapies in development

5.4.1 Gene therapy

Treating AATD with gene therapy theoretically confers several advantages when compared to IV augmentation therapy, primarily it is attractive because it could treat all disease manifestations at source. Therefore, since IV augmentation therapy does not improve liver disease and there is no current specific treatment directed at treating liver disease in AATD subjects except from liver transplantation, gene therapy is an encouraging alternative(85). The basic principle for gene therapy in AATD is as follows: AAT is normally produced by hepatocytes but incorporating the normal M type AAT DNA into different cells using a gene transfer vector can allow transduced cells to secrete normal AAT. Two crucial factors that need to be considered when designing gene therapy are firstly, the vector chosen to deliver the gene and secondly the site target for the gene delivery(86). To this date, several viral vectors have been used in trials including adenoviruses(87) and adeno-associated viruses(88); non-viral vectors include naked plasmids(89) and plasmids in combination with liposomes(90). The route of administration of these vectors in studies conducted included, intravenous, intraportal, skeletal muscle, respiratory epithelium and intrapleurally(86). Of these approaches adeno-associated vectors (AAV) with an intramuscular route has been the most successful; this achieved higher levels of therapeutic AAT and was associated with less toxicity , eventually reaching a phase 2 clinical trial conducted by Flotte et al. which supported the feasibility and safety of using AAV mediated gene therapy in the treatment of AAT(88). However there remained issues with the dose that could be achieved by this route, and further development in human studies will require a different approach.

5.4.2 Stem cell-based treatment

Stem cell therapy offers the possibility of producing cells which not only secrete the normal AAT protein but also have self-renewing capacity. This implies that unlike augmentation therapy, regular infusions/injections of stem cells are not required. A study conducted by Wilson et al. showed sustained levels of human AAT expression in mice that had received a transplantation of lentivirally transduced hemapoietic stem cells. However, the level of AAT in serum was below the protective threshold. Moreover, this treatment option carries certain risks; complications of bone marrow transplant include risk of infection along with other complications from chemo or radio therapy. Also, integration of vectors with the aim to transduce stem cells carries the risk of oncogenesis(91). More recently, Baligar et al. found that bone marrow progenitor cells and human mesenchymal cells partially improve pathological consequences in livers of mice with AATD. Results have demonstrated suppressed inflammation, regression of fibrosis and apparent reduction of apoptosis. However, further studies are required to establish their safe use in clinical practice (92).

Induced pluripotent stem cells (iPSCs) are mature cells taken from patients with genetic diseases that have been reprogrammed to correct the genetic defect and to produce isogenic cells for autologous transplantation. Yusa et al. provided the initial evidence that genetically-corrected iPSCs could be used for the treatment of AATD, albeit only in animal models at this stage (93). Tafaleng et al. provided evidence that iPSC could also play an important role in determining liver disease susceptibility so that therapeutic strategies could be adopted in a timely manner(94). These findings were supported by another study conducted by Wilson et al. who, in addition, concluded that iPSCs could be used in predicting drug toxicity in individuals with the Pi ZZ genotype(95). The publication of the first report of 2 fatal cases of liver injury secondary to anti-tuberculosis drugs in patients with AATD in 2017 highlights the importance of drug toxicity prediction in this group of patients(96).Due to the risk of unplanned mutations arising from prolonged iPSCs cultures, more in vivo studies and careful screening is required to ensure that iPSC therapy is safe to use in clinical practice(6).

5.4.3 Small molecules

Drugs which target the molecular defect in the Z protein, that is the propensity to polymerise, are also an attractive option capable of addressing the entirety of disease manifestations. However such therapies have mainly been studied in the in vitro setting(97), at least as far as published work is concerned. Nevertheless programmes of work targeting this concept continue, spurred on by successes in other

diseases such as cystic fibrosis which have seen therapies designed in this way reach regular clinical use(98).

6. Conclusion

AATD is a disease predominantly recognized in Caucasian individuals which is associated with lung disease (mainly emphysema) in approximately 75% of cases(99), and cirrhosis of the liver in a much smaller proportion (up to 20%)(11). Progression of AATD lung disease may be slowed down by use of AAT augmentation, but this does not stop progression in all patients and further research to optimize augmentation or adopt other treatment approaches in combination with, or instead of, this continues.

7. Expert opinion

7.1 How could current research impact real world practice?

Augmentation therapy appears to be a suitable treatment to reduce emphysema progression, and as such should be used in patients with progressive lung disease where possible. However, differences in treatment response may occur, and optimal patient selection requires further research. Current phase IV and II/III trials may bring changes to treatment guidelines worldwide as we understand the clinical effectiveness of treatment better. Very recently, the results from a pilot study conducted by Campos et al (NCT01669421) showed that patients who received double dose therapy (120mg/kg/ week) had reduced inflammatory mediators, protease activity and elastin degradation isolated in bronchoalveolar lavage fluid and plasma samples when compared to those on standard therapy (100). The Study of ProlAstin-c Randomized Therapy with Alpha-1 augmentation (SPARTA) phase 3 trial aimed at assessing the safety profile and efficacy of 2 separate dose of Prolastin-C in AATD patients with emphysema over 3 years(101) may shed more light on whether dose escalation is the answer to ceasing emphysema progression with augmentation therapy. If NE inhibitors other than augmentation prove successful in phase II, the lessons learnt from outcome selection in the earlier augmentation studies may allow phase III trials to be set up and run more efficiently. In addition ongoing efforts by the COPD research community to get biomarkers more sensitive than FEV1 (such as CT densitometry) to be recognized as appropriate primary outcomes for registration level trials could yield benefits in AATD. Major agencies that assess cost-effectiveness of treatment (eg NICE in the UK) are also appraising the economics of augmentation use, and their views

may have impact at a country specific level. In liver disease it is more difficult to infer how the current approach of siRNA would be adopted into practice, since it is currently at a relatively early phase of development, but the issues about how the surrogate outcomes chosen in trials and for economics of therapy in rare disease will no doubt be important for manufacturers to address as these have been the key elements in augmentation therapy that prevented, and in some places continue to prevent, adoption in clinical practice.

7.2 How can current problems and limitations be solved?

In the area of diagnosis of AATD, it is vital that clinicians are aware of how and when to test for the disease. If specific, economically viable therapies are widely available then early identification of cases will be important to prevent morbidity and mortality from lung and liver disease. At present AATD is not screened at birth in most countries, largely because in the absence of therapy it arguably does not meet screening criteria, though opinion on this does vary even in expert community. In order to make specific treatment more widely available it needs to be proven that our current surrogate outcomes used in major trials (mainly CT densitometry for the lung) relate to those which are accepted by payers and which typically drive traditional cost-effectiveness analyses, such as mortality and quality of life. Research is ongoing in this area. Studies of less costly forms of treatment, such as oral NE inhibitors and recombinant AAT, may also benefit from this work, as it might facilitate their use of surrogates in registration level trials. Finally it is crucial for negative results to be made available so that experts know where to focus on when designing future clinical trials; for example use of inhaled in patients with AATD have been completed but remained unpublished (82) so it is unclear whether this route still holds promise or not.

7.3 What potential does further research hold?

The advent of liver directed therapy in the form of siRNA offers hope that combination treatment could address both lung and liver disease in the foreseeable future. Approaches targeting molecular structure of AAT, and perhaps gene therapy, also offer this hope, which now seems more tangible as at least one molecular programme of research has been ongoing and partnered with the commercial sector for many years(102). Gene therapy seems less promising, given the issues encountered in other diseases, but it is important to note that research is now at the non-human primate level for new routes which allow higher doses to be used(103).

Another area to follow- up closely is the use of biomarkers in AATD COPD patients. Isodesmosine is an amino acid present in elastin and can be used as a marker of elastin degradation in AATD patients. The

RAPID-RCT trial also showed that patients receiving augmentation therapy had statistically significant reductions in isodesmosine when compared to the placebo arm (75, 104, 105). This correlation between a lung matrix injury biomarker and augmentation therapy suggests a therapeutic role for agents that can help preserve lung elastin structure and function. Hence the therapeutic potential of aerosol hyaluronic acid, a glycosaminoglycan which possibly prevents elastin degradation by elastase, is currently being investigated as part of a clinical trial in AATD patients with emphysema (NCT03114020)(106).

7.4 What does the future hold for AATD?

As in many areas of chronic disease the field of assessment and management of AATD is likely to evolve toward a more personalized approach in the future, either through use of detailed phenotyping or risk based approaches to select individuals for each of the specific treatment options that become available. For example molecular or gene based therapies would be chosen based on the patient's genotype, as is now occurring in cystic fibrosis. In order to move in this direction we need a detailed understanding of disease progression in all areas, and in particular a definition of what represents normal or accelerated deterioration in both lung and liver disease. This may enable us to better counsel patients and their families about what their future holds, and also to select burdensome treatments (such as augmentation) only for those patients in whom risk is highest, and treatment most likely to work well. Standard procedure may evolve to include routine use of CT densitometry for assessment and monitoring within the next 5 years, and it remains possible that a suite of therapies targeting single organs will be available in this time frame. Management of the underlying molecular defect is probably a little further away, but encouraging results in diverse programmes of work suggest that hope for 'a cure' remains.

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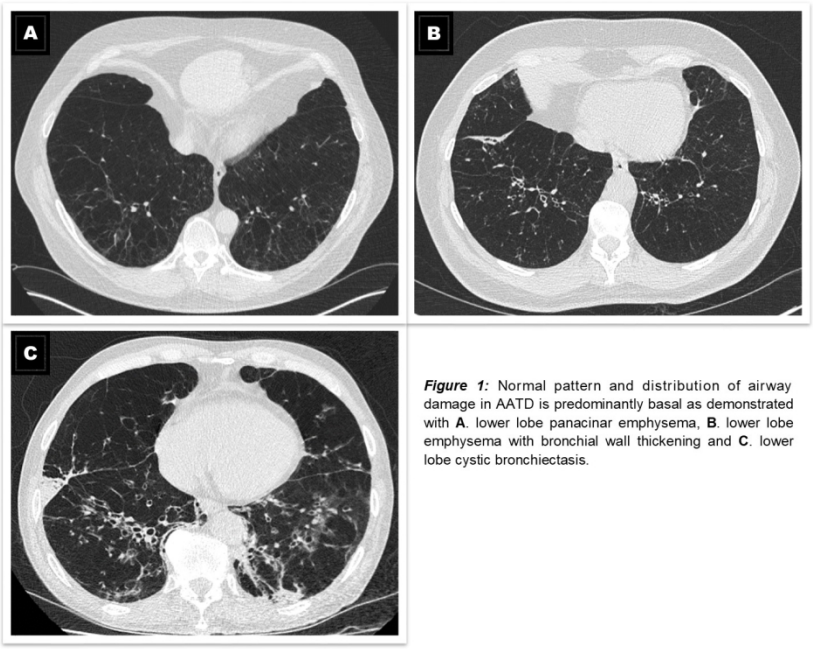

Figure 1: Normal pattern and distribution of airway damage in AATD is predominantly basal as demonstrated with **A**. lower lobe panacinar emphysema, **B**. lower lobe emphysema with bronchial wall thickening and **C**. lower lobe cystic bronchiectasis.

297x209mm (150 x 150 DPI)

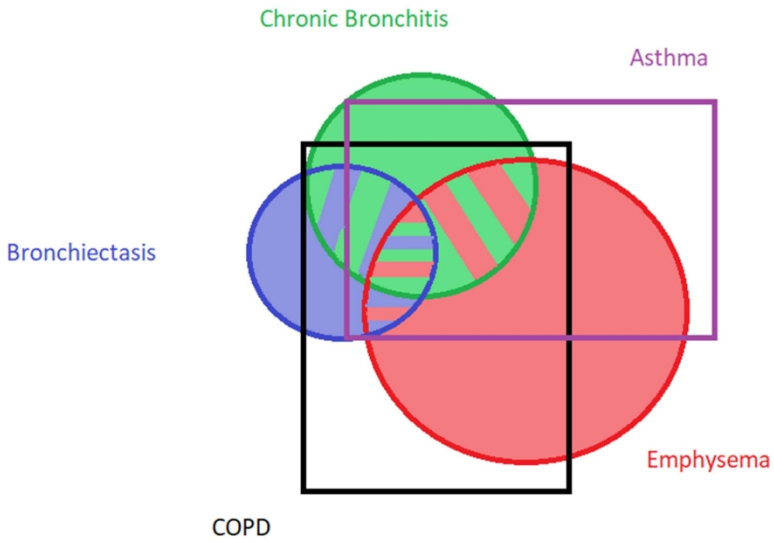

Figure 2: Pulmonary phenotypes observed in AATD
The diagram shows by the size of the circles the relative prevalence of each phenotype, and the degree to which they are observed in the same patient is shown by the overlap of the circles. The square boxes show the same principle for asthma and COPD. Thus the largest circle is for emphysema, since this is the most common lung phenotype seen, with a smaller number having chronic bronchitis or bronchiectasis, with some patients having all 3 phenotypes. Most patients with emphysema also have COPD, but not all.

254x190mm (300 x 300 DPI)