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REVIEW ARTICLE

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Advances in managing COPD related to α_1-antitrypsin deficiency: An under-recognized genetic disorder

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Abstract

α_1-Antitrypsin deficiency (AATD) predisposes individuals to chronic obstructive pulmonary disease (COPD) and liver disease. Despite being commonly described as rare, AATD is under-recognized, with less than 10% of cases identified. The following is a comprehensive review of AATD, primarily for physicians who treat COPD or asthma, covering the genetics, epidemiology, clinical presentation, screening and diagnosis, and treatments of AATD. For patients presenting with liver and/or lung disease, screening and diagnostic tests are the only methods to determine whether the disease is related to AATD. Screening guidelines have been established by organizations such as the World Health Organization, European Respiratory Society, and American Thoracic Society. High-risk groups, including individuals with COPD, nonresponsive asthma, bronchiectasis of unknown etiology, or unexplained liver disease, should be tested for AATD. Current treatment options include augmentation therapy with purified AAT for patients with deficient AAT levels and significant lung disease. Recent trial data suggest that lung tissue is preserved by augmentation therapy, and different dosing schedules are currently being investigated. Effective management of AATD and related diseases also includes aggressive avoidance of smoking and biomass burning, vaccinations, antibiotics, exercise, good diet, COPD medications, and serial assessment.

KEYWORDS
α_1-antitrypsin, α_1-antitrypsin deficiency, asthma, augmentation therapy, COPD, emphysema

1 | INTRODUCTION

α_1-Antitrypsin (AAT) is a serine protease inhibitor (PI) that protects lung tissue from proteolytic damage by inhibiting neutrophil elastase, a powerful enzyme with broad substrate specificity.[1] Therefore, individuals with AAT deficiency (AATD), an autosomal codominant condition, are at increased risk of developing chronic obstructive pulmonary disease (COPD).[2,3] In addition, these individuals are often at risk of liver disease due to polymerization and retention of AAT in hepatocytes, where the majority of AAT is produced.[2]

Between 0.02% and 0.04% of individuals suffer from AATD.[3] However, despite being commonly described as a rare disease, AATD is highly under-recognized, with less than 10% of individuals with AATD identified [4-6] and with delays of more than 5 years between initial symptoms and diagnosis.[7] Although younger individuals who are often asymptomatic may understandably escape medical attention, data suggest that, despite a majority of adults with the deficiency allele PI*ZZ manifesting COPD-related symptoms in the fourth and fifth decades, few clinicians identify AATD as the cause.[5] The lack or delay of a diagnosis of AATD inevitably delays the initiation of augmentation therapy with AAT if indicated, transplantation,

TABLE 1 Genotypes, serum levels of AAT, and risk of lung and liver disease

Genotype	Serum levels of AAT[a]	Risk of lung disease	Risk of liver disease	Explanatory information
MM	Normal			The PI*M allele encodes normal AAT.[2]
Null/null	Absent	+++		Rare null alleles are characterized by absent circulating AAT due to transcriptional or translational errors.[2]
ZZ	Very low	+++	+++	The PI*Z allele leads to polymerization in hepatocytes and less frequent binding to neutrophil elastase in the lungs.[2]
MZ	Low to normal	+	+	A well-designed study recently observed an increased risk of developing COPD due to exposure to cigarette smoke in individuals with the PI*MZ allele,[52] although other studies have found both increased and no association.[119-122]
SS	Borderline normal to low	+/-		No conclusive evidence links homozygous PI*SS to increased risk for lung or liver disease. However, the PI*S allele is associated with increased degradation of AAT in hepatocytes.[2]
SZ	Low	+		The PI*SZ allele has been variably associated with increased risk of disease. A recent study, based on data from 6 previous studies, found an increased odds ratio (3.26, 95% CI: 1.24-8.57) for the development of COPD.[123]

[a]AAT levels can increase during inflammation. Cigarette smoke and infections lead to an increase in neutrophils and neutrophil elastase in the lungs, thus predisposing exposed individuals with AATD to develop COPD.[83,84]

+/−, indicates the risk of disease; −, indicates the absence of disease; AAT, α_1-antitrypsin; AATD, α_1-antitrypsin deficiency; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Reproduced with modifications from Henao and Craig.[124]

supportive therapies such as smoking cessation, and genetic and psychological counseling.

Since the discovery of AATD in the 1960s, knowledge and understanding of AAT and its deficiency have progressed significantly, although effective screening methods and non-intravenous therapy have remained elusive. The following is a comprehensive review of AATD primarily for physicians who treat COPD or asthma, highlighting advances into the epidemiology, screening, and treatment of AATD. These data are especially important for allergists because a third of AATD patients enter the healthcare system through allergists, and unfortunately, as noted in reference 9, this often delays the appropriate diagnosis and treatment.[8,9]

2 | GENETICS, SERUM AAT LEVELS, AND EPIDEMIOLOGY

Individuals with AATD have a homo- or heterozygous mutation of the Serpina1 gene,[2] of which more than 150 alleles are recognized.[8] The most common allele (M, for "medium mobility" through an isoelectric gel) encodes normal AAT, with PI*MM the most common homozygous allele. The most common deficiency alleles are Z (slowest) and S (slower), which, in both cases, result from single amino acid substitutions.[2] The PI*Z allele accounts for 96% of known clinical cases of AATD, although the two most frequent deficiency alleles are thought to be PI*S (50%-60% of carriers) and PI*Z (10%-20% of carriers).[2,10,11] Rare null and dysfunctional alleles also exist, the former characterized by absent circulating AAT due to transcriptional or translational errors.[2] Lastly, the epigenetic silencing of Serpina1 has been reported which may explain the AATD effects in genetically unaffected individuals.[12]

Different alleles are associated with different risks of developing lung and liver diseases (Table 1). Despite PI*ZZ is the allele most associated with increased likelihood of developing COPD, PI*SZ and PI*MZ also show an increased risk, and data imply that disease progression in PI*SZ patients might be similar to Pi*ZZ.[2,13] As shown in Table 1, AAT concentrations vary according to genotype, with normal levels in the range of 20-53 μmol/L.[2,4,14,15] Individuals with the PI*MM genotype have 105%-164% of normal levels, PI*MS 88%-137%, PI*SS 73%-106%, PI*MZ 66-100%, PI*SZ 49%-66%, while <15%-20% would suggest that an individual has the homozygous PI*ZZ, Z null, or null-null genotype.[4,15,16]

While PI*Z and PI*S alleles are particularly prevalent in the north and south of Europe, respectively, deficiency alleles have been detected across diverse populations worldwide.[10,17-26] By combining data from epidemiological studies, in 2012 de Serres and Blanco [10] estimated the prevalence of AAT alleles across 10 geographic regions worldwide, encompassing 97 countries and 5.26 billion people. The prevalence of PI*ZZ is 0.1% of deficiency genotypes worldwide (181 894 individuals), with 41% of cases in Northern and Central Europe and 24% in North America.[9] PI*SZ accounts for 0.7% (1 269 054 individuals), with 48% of these in Northern and Central Europe, 20% in North and Central America, and 16% in South America.[10] Approximately 75% of deficiency genotypes are PI*MS, and 24% are PI*MZ and PI*SS.[10] In the United States, more than 20 million people (6.6%) are estimated to have at least one deficiency allele; 2.3% and 1.1% of the general population have PI*S or PI*Z, respectively, and 0.01% have PI*ZZ.[10] PI*Z alleles appear to be as prevalent in the United States as the lower ranges in northern European countries, whereas PI*S alleles occur more frequently than in that region.[17]

3 | CLINICAL PRESENTATION

3.1 | Pulmonary characteristics

Differential diagnosis of AATD-related COPD versus COPD from other etiologies and even asthma with fixed obstruction is complicated by shared signs and symptoms; these similarities partly explain why AATD is highly under-diagnosed. Nevertheless, while not unique to AATD-related COPD, several characteristics indicate that AATD may be the cause of COPD. Individuals with AATD tend to experience earlier onset of symptoms, often in the third or fourth decade, particularly in smokers, whereas COPD of other etiologies often occurs in the fifth decade or later.[8] There may also be more extensive emphysematous damage to the lung bases, which can be detected by chest radiography or computed tomography (CT) (Figure 1).[2] In an analysis of 1129 patients enrolled in the National Heart, Lung and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT, common symptoms included dyspnea (84%), cough (42%), phlegm (46%), and wheezing and upper respiratory infections (76%).[27] Airflow obstruction is often reversible; about 61% of patients in the NHLBI Registry had a 12% and 200 mL increase in forced expiratory volume in one-second (FEV_1) or forced vital capacity postbronchodilator.[27] Asthma is also common in patients with severe AATD (affecting 35% of individuals in the NHLBI Registry) and may increase the risk of developing AATD-related COPD.[9,27]

Another reason why AATD is highly under-diagnosed is that about 40% of individuals with PI deficiency alleles are asymptomatic for COPD.[1,2,28,29] In CT lung scans, no clinically significant signs of emphysema were found in 14% of 119 patients with severe AATD.[30] Similarly, in the Swedish National Registry of AATD, no signs of COPD were evident in 30% of nonsmokers and 16% of smokers.[31] In a series of postmortems of individuals with AATD, no signs of COPD were found in 20% of cases.[31]

In several studies, the rate of decline of FEV_1 in PI*ZZ patients was anywhere between 23 mL/y and 316 mL/y.[32-44] Several factors increase this rate of change, including smoking, male sex, age 30-44 years, FEV_1 between 35 and 79% of predicted, serum AAT level, chronic bronchitis symptoms, and bronchodilator responsiveness.[36,40,43,44] Moreover, lung function declines more rapidly when individuals are exposed to air pollution, ozone, and particulate matter less than 10 μm in diameter,[45,46] while respiratory infections may also exacerbate lung disease.[47] Smoking is a notable risk factor, given the association with earlier onset of respiratory symptoms in patients with AATD.[47,48] In a recent Swedish study, reporting outcomes 35 years after screening for PI deficiency alleles at birth, PI*ZZ ever-smokers showed early signs of emphysema versus PI*MM ever-smoking controls, whereas PI*ZZ and PI*SZ never-smokers had normal lung function versus never-smoking controls.[48] Nevertheless, while the cause of death for nonsmoking PI*ZZ individuals is respiratory failure in an estimated 45%-60% of cases, PI*ZZ nonsmokers are more likely than PI*ZZ ever-smokers to die of liver disease, particularly when elderly, as they do not die earlier of lung disease.[49-51] With regard to patients with PI*MZ deficiency alleles, a statistically significantly increased risk of developing lung disease was only detected for smokers.[52] In addition to the emphysematous symptoms of COPD, patients with AATD may also develop bronchiectasis, although it is unclear whether AATD causes bronchiectasis. In a case-control study of patients with a diagnosis of bronchiectasis with and without AATD, no association was found between AAT genes and bronchiectasis.[53] In another study of CT scans, clinically significant bronchiectasis was present in 27% of individuals with the PI*Z allele.[54] In accordance with these studies, the recommendation is to test for AATD whether the etiology of bronchiectasis remains unknown.[1,2]

AATD-related COPD has traditionally been associated with more emphysematous damage to the lung bases.[2] However, emphysema is not always present. In a study of PI*ZZ patients, 20% had emphysema in radiographs [55] and, in another study using CT scans,

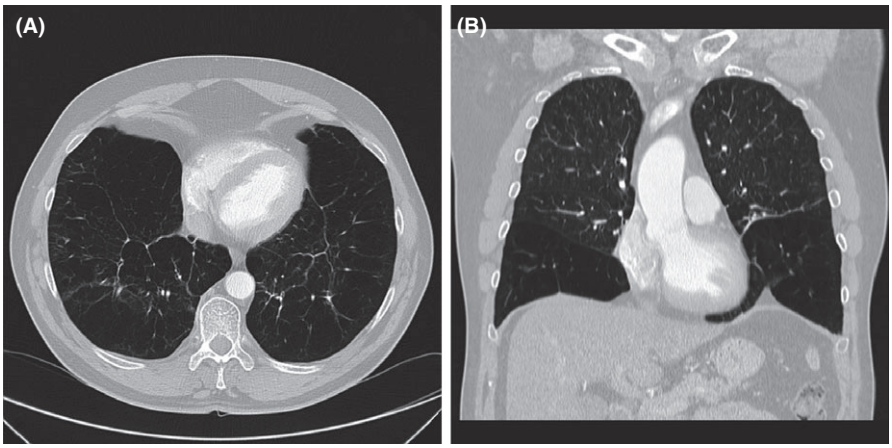

FIGURE 1 CT scans showing extensive emphysematous damage to the lungs. A, Axial plane of thorax; B, Coronal plane of thorax. CT, computed tomography. CT scans were kindly provided by Prof. Dr. Andreas Rembert Koczulla, Fachzentrum für Pneumologie Schön Klinik Berchtesgadener Land, Germany, and Klinik für Pneumologie, Marburg, Germany

emphysema was present in 86% of PI*Z patients.[30] The latter study also demonstrated that a single physiologic parameter should not be used as a surrogate measure of disease severity.[30] In particular, basal emphysema was associated with greater impairment of FEV_1, but less impairment of gas exchange and alveolar-arterial oxygen gradient versus apical distribution.[30] In the latter study, 36% of PI*Z patients with emphysema had apical damage. Notably, the traditional description of AATD-associated emphysema as predominantly basal and panacinar originates from limited autopsy studies and case series using chest radiographs, which has now been superseded by CT.[11,55]

3.2 | Extrapulmonary characteristics

Individuals with alleles associated with intrahepatocyte polymerization, such as Z, M_{malton}, and S_{iiyama}, are predisposed to liver disease, including hepatitis, cirrhosis, and hepatoma.[2,56] In individuals with AATD, liver disease presents in a bimodal distribution, that is, neonatal hepatitis and cholestasis in infants and chronic liver disease in adults most of who are ZZ and usually over 50 years of age.[57] It is estimated that 10% of adults may develop symptomatic cirrhosis. In the first 20 years of life, about one-third of PI*ZZ carriers may develop liver disease, although most recover.[58,59] In another study, based on 161 infants with liver dysfunction and use of isoelectric focusing, 15% had severe AATD and 12% moderate AATD.[60] Similarly, in a Swedish study, 18% of 120 newborns with PI*Z alleles during 6 months of follow-up often presented with jaundice, minor laboratory abnormalities, and liver dysfunction. Biopsies revealed typical Periodic acid Schiff diastase-positive intracellular inclusion bodies and AAT-positive staining (Figure 2).[61,62]

AATD is also associated with various other conditions, including panniculitis (a skin condition that affects an estimated 1 per 1000 individuals with AATD) and granulomatosis with polyangiitis.[2,27,63-65]

4 | SCREENING AND DIAGNOSIS

To address the issue of under-diagnosis, several guidelines for screening and targeted testing of AATD are available.[1,66-69] In 1997, the World Health Organization (WHO) recommended screening all patients with COPD and adults and adolescents with asthma by quantitative testing, followed by PI typing for individuals with abnormal results.[66] In 2015, the Global Initiative for Chronic Obstructive Lung Disease stated that the WHO suggests screening COPD patients from areas with a particularly high prevalence of AATD.[67] In 2017, the European Respiratory Society (ERS) proposed particularly inclusive guidelines that recommended testing in specific groups of individuals (Table 2).[69]

Screening asymptomatic individuals for AATD is particularly useful because positive correlations exist between smoking cessation and better physical and psychosocial outcomes, due to individuals' awareness of their predisposition to COPD.[7,70] Similar findings were recently published for adults admitted to a large newborn screening program in Sweden.[71-73] However, it is debatable whether this evidence will lead to widespread screening of newborns, as a diagnosis of AATD has been shown to increase stress in families.[71] Additional caveats include the lack of specific treatment for the AATD-associated liver disease, which is the primary cause of childhood morbidity, and the need for additional conclusive evidence that newborn screening ultimately results in better outcomes in longitudinal studies.[73] A pilot study of newborn screening for AATD recently commenced in New York State.[73]

Screening and diagnosis of AATD usually begin with a quantitative measurement of serum AAT concentrations, often using radial immunodiffusion, nephelometry, or latex-enhanced immunoturbidimetry.[2,14,73-79] Below a protective threshold of 11 μmol/L (normal range 20-53 μmol/L), the risk of accelerated airflow obstruction increases. However, a post hoc analysis in the recent RAPID study suggests that patients on augmentation therapy with AAT may experience greater benefit when serum levels increase to well above 11 μmol/L, relative to patients with lower levels that were also above the protective threshold (Figure 3).[74,80] Studies are presently being performed to reevaluate the protective threshold.

Either when serum AAT levels are found to be low or simultaneously when measuring AAT levels, additional diagnostic assessments can be used to identify AAT alleles and, therefore, strengthen the diagnosis of AATD. These assessments may include phenotyping by

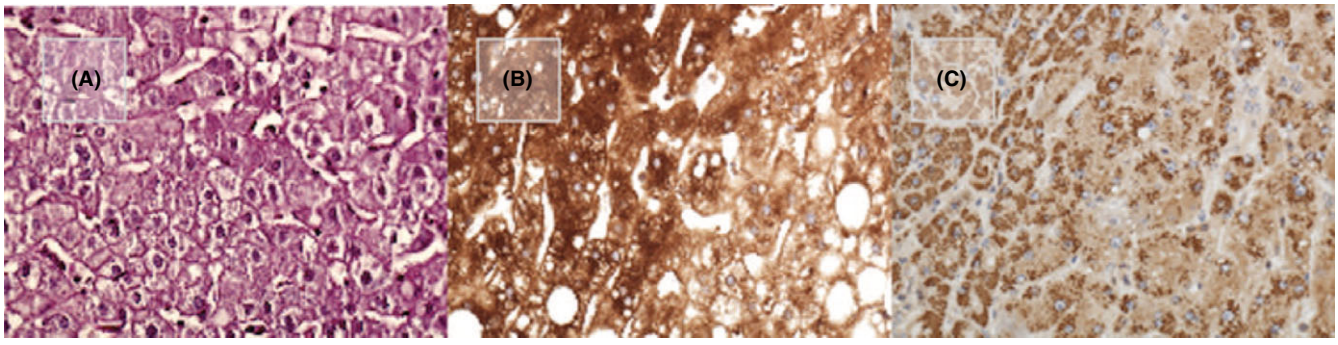

FIGURE 2 Liver damage in patients with α_1-antitrypsin deficiency. A, Periodic acid Schiff diastase (PAS-d) staining showing intracytoplasmic accumulation of PAS-d–resistant material; B, Immunohistochemical staining of the case patient's hepatocytes; and C, Control immunohistochemical staining of a known α_1-antitrypsin–deficient patient. From: Rider and Craig[61]

TABLE 2 Recommendations for quantitative testing of AAT

No.	Recommendation
1	Patients with a diagnosis of COPD
2	Patients with a diagnosis of adult-onset asthma
3	Individuals with cryptogenic cirrhosis or liver disease
4	Individuals with GPA
5	Adults with bronchiectasis of unknown etiology
6	Adults with necrotizing panniculitis
7	First-degree relatives of patients with AATD

AAT, α_1-antitrypsin; AATD, α_1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; GPA, granulomatosis with polyangiitis. Reproduced with modifications from Miravitlles et al[69]

isoelectric focusing or genotyping by amplification of PI*S or PI*Z alleles or by deoxyribonucleic acid extraction from circulating mononuclear cells or from mouth swabs for polymerase chain reaction analysis.[2] Dried blood samples are also widely used for genotyping, often along with testing for AAT levels. Moderate-to-good correlation with serum AAT concentrations can be achieved using dried blood samples.[81] Notably, after enrollment in the Alpha-1 Coded Testing Study, genotyping using dried blood spot kits is available for free (https://alphaoneregistry.org/research_registry). Discrepancies between AAT protein levels and genotype results from dried blood samples need to be investigated further, either by additional assessment of phenotype or using more expensive diagnostic techniques such as gene sequencing.[79,81,82] Moreover, a recently developed lateral flow assay, which can deliver results within 15 minutes, can detect the most clinically significant PI*Z alleles. However, the test is only designed to detect PI*Z alleles and additional testing is required to determine whether the patient is homo- or heterozygous.[74]

5 | CURRENT TREATMENTS

As shown in Table 3, a series of assessments, medications, and vaccinations should be considered for individuals with AATD, in addition to a healthy lifestyle that includes a good diet, exercise, and avoidance of stimuli of neutrophilic inflammation, including cigarette smoke, air pollution, and infections.[83,84] Asthma should be treated aggressively.[85] Similarly, respiratory infections should be treated promptly and, as indicated by a study of completed questionnaires from 267 individuals with AAT, vaccinations against pneumococci (both protein conjugated and polysaccharide pneumococcal vaccines) and influenza should result in fewer exacerbations of lung disease.[47,85] In addition, maintaining ideal body weight, limiting alcohol consumption and hepatitis A and B vaccine should be administered to prevent exacerbating already compromised liver disease from obesity-, toxicity-, and viral-induced hepatitis. Otherwise, inhaled therapy mimics the treatment of non-AATD COPD. As disease progresses, pulmonary rehabilitation and oxygen therapy may be essential.

5.1 | Transplantation and lung volume reduction surgery

Although the efficacy of lung transplantation for AATD-related COPD is not firmly established, the condition accounted for the fourth-highest percentage (5.8%) of lung transplants in adults between January 1995 and June 2012.[86] In a retrospective study of 83 lung transplant recipients with PI*ZZ alleles, median survival times were significantly longer (11 years, 95% confidence interval [CI]: 9-14) versus 70 nontransplanted controls (5 years, 95% CI: 4-6) patients.[87] A recent UK study demonstrated improved quality of life postsurgery, with no difference in mortality when compared with controls.[88] In most cases, referral for a lung transplant is deferred until FEV_1 decrease to 30% or below.

With regard to liver transplantation, there are few reports of outcomes in patients with AATD.[89] Reviews of patient databases and case series suggest that AAT levels may normalize following liver transplantation in adults and children, although it is unclear whether this procedure has an impact on pulmonary outcomes.[90] Further research is required to assess the benefit-risk profile of liver, single-lung, and double-lung transplantation in patients with AATD and the need to augment patients' status postlung transplant.[69] Evidence for the use of augmentation therapy after lung transplantation is

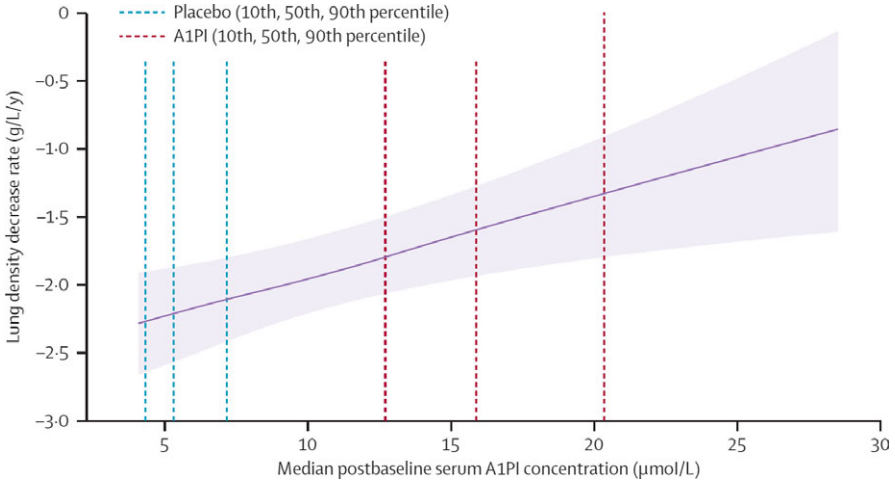

FIGURE 3 Rates of lung density decrease at total lung capacity versus trough A1PI serum concentrations achieved (RAPID trial). A1PI, α_1 proteinase inhibitor. From: Chapman et al[80]

TABLE 3 Care of the patient with AATD

Vaccination	Medications	Holistic health	Assessments
Polysaccharide pneumococcal vaccine	Short-acting beta-agonists as needed	Good diet to preserve weight. Limit alcohol consumption.	Follow spirometry regularly
Yearly influenza vaccine	Long-acting beta-agonists as per COPD guidelines	Exercise to maintain condition	Check liver function tests regularly
Protein conjugate pneumococcal vaccine	Anticholinergics as per COPD guidelines	Oxygen supplement, if needed	Ultrasound of liver for hepatoma yearly
Tetanus/diphtheria/pertussis vaccine	Inhaled corticosteroids	Respiratory therapy	When FEV_1 falls below 30% consider lung transplant assessment
	Augmentation with AAT	Lung healthy living	Assess for depression and anxiety at each appointment
		Liver healthy living	Lung cancer screening, if indicated

AAT, α_1-antitrypsin; AATD, α_1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s. Constructed using information from Henao and Craig,[124] Köhnlein et al,[47] O'Brien et al,[83] Alam et al,[84] and Sutherland and Cherniack.[85]

insufficient, and there is no consensus whether lung transplantation recipients with AATD should receive augmentation therapy. According to the data, only 13%-19% of AATD patients receive augmentation therapy after lung transplantation. Furthermore, the putative influence of previous augmentation therapy on lung recipients who discontinued this therapy following transplantation is entirely unknown.[91]

In general, lung volume reduction surgery (LVRS) is not recommended for patients with AATD. In a study of 10 patients with severe AATD, 2-year mortality was higher and exercise tolerance and FEV_1 were worse in patients randomized to LVRS versus medical treatment.[92] The recent ERS guidelines state that LVRS may be considered in selected patients with AATD, after careful appraisal of risks and benefits, but further studies are needed to confirm the role of such therapy.[69]

5.2 | Augmentation therapy

Intravenous augmentation therapy with infusions of purified AAT from pooled human plasma aims to raise and maintain serum AAT levels above the 11 μmol/L estimated protective threshold value.[2] Augmentation therapy is recommended only for patients who are below this protective threshold, that is, mainly those with the PI*ZZ genotype.[2] At present, augmentation therapy is the only approved medication that raises AAT levels both in the plasma and in the epithelial lining fluid (ELF), leading to a reduction in neutrophil elastase activity in the lungs.[93-95] Intravenous augmentation remains the only disease-specific therapy in AATD, and there is evidence that this slows decline in emphysema determined by CT density.[96] While the commercially available augmentation products (Prolastin, Zemaira/Respreeza, Glassia, and Aralast) have different purification processes and concentrations of AAT, there are only minor differences in storage, need for mixing, infusion rate, and cost, although there is a lack of comparative studies of the effectiveness of these products on lung parameters.[97,98]

Several recently completed or ongoing randomized clinical trials (including RAPID, EXACTLE, SPARK, and SPARTA) have increased our understanding of augmentation therapy with purified AAT preparations (Table 4). These new studies benefited from the increased accuracy of CT to detect changes in lung density, relative to the previous gold standard of FEV_1, which was used in studies in the 1990s.[82] Thus, the use of CT has overcome the impracticality of performing an adequately powered randomized placebo-controlled trial to assess the development of emphysema using FEV_1, which changes slowly over time.

The RAPID trials are the largest clinical trials of augmentation therapy completed to date, with a treatment period of 4 years, and are the only studies designed to investigate the disease-modifying effects of treatment. RAPID was a 2-year, multicenter, randomized placebo-controlled trial of 60 mg/kg weekly AAT (Zemaira, CSL Behring, KOP, PA, USA) in 180 patients with AATD. Most patients continued into the 2-year RAPID open-label extension trial, in which all patients were treated with active therapy; thus, the patients formed two groups: early-start (4 years of active treatment) and delayed-start (2 years of placebo followed by 2 years of active treatment). In both RAPID trials, the loss of lung parenchyma was statistically significantly slowed by approximately 34% in individuals treated with AAT, as ascertained by CT-measured lung density at total lung capacity.[80,99,100] The RAPID trials support the efficacy of augmentation therapy in slowing disease progression during 4 years of treatment and, as lost lung density during placebo treatment never recovered following augmentation therapy in the delayed-start group, the trials highlight the importance of early initiation of augmentation therapy (Figure 4). In a post hoc analysis of the RAPID trials, treatment with AAT was also associated with reduced elastin degradation as evident by biomarkers isodesmosine and desmosine (Figure 5).[101]

In the EXACTLE randomized placebo-controlled trial in 77 patients with AATD, CT scans suggested that patients could benefit from treatment with AAT (Prolastin C; Grifols, Barcelona, Spain) 60 mg/kg weekly.[41] In the SPARK randomized crossover trial in 30 patients with AATD, more physiologic levels of serum AAT were gained following treatment with AAT (Prolastin C; Grifols) at a dose of 120 mg/kg weekly vs. 60 mg/kg.[102] Importantly, while

TABLE 4 Randomized clinical trials in AAT deficiency

Study; reference	Year	Study design	Duration	Experimental drug; dosage and regimen	Comparator	No. of patients	Primary efficacy parameter
EXACTLE [41]	2009	Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	2-2.5 y	Prolastin C 60 mg/kg weekly	Placebo	77	Change in the 15th percentile lung density by CT
SPARK [102]	2013	Prospective, multicenter, randomized, double-blind crossover trial	16 wk	Prolastin C 120 mg/kg weekly	Prolastin C 60 mg/kg weekly	30	$AUC_{0\text{-}7\ days}$, C_{max}, elimination rate, $t_{1/2}$, t_{max}, C_{trough}
SPARTA [103]	2013	Prospective, multicenter, randomized, double-blind, placebo-controlled trial	156 wk	Prolastin C 120 mg/kg weekly	Prolastin C 60 mg/kg weekly or placebo	339	Change in the 15th percentile lung density by CT
RAPID [80,100]	2014	Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial followed by an open-label extension trial	4 y early-start (4 y of active treatment); delayed-start (2 y of placebo followed by 2 y of active treatment)	Zemaira 60 mg/kg weekly	Placebo	180	Change in the 15th percentile lung density by CT

AAT, α_1-antitrypsin; AUC, area under the curve; C_{max}, maximum plasma concentration; C_{trough}, lowest concentration prior to administration of next dose; CT, computed tomography; $t_{1/2}$, half-life; t_{max}, time to maximum plasma concentration.

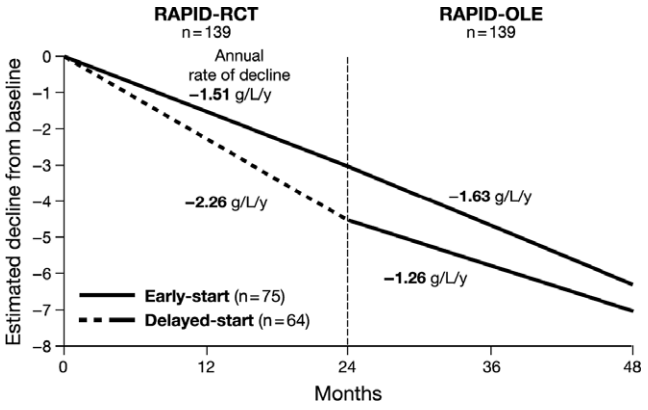

FIGURE 4 Estimated lung density decline over 48 mo (RAPID trial). n, number of patients. From: McElvaney et al[100]

improvements in lung function were not detected in the RAPID, EXACTLE, or SPARK trials (as the trials were not sufficiently powered to show this effect), augmentation therapy appears to be an effective treatment, which slows lung deterioration in patients with severe AATD and COPD, as noted by lung density measured by CT. As a follow-up to SPARK, the ongoing SPARTA randomized placebo-controlled trial in 339 patients with AATD is comparing AAT (Prolastin C; Grifols) 120 mg/kg weekly and 60 mg/kg weekly, to assess both the change in 15th percentile lung density and the number of severe COPD exacerbations.[103]

These recent randomized trials have added to less conclusive research from the 1990s and 1980s. In 1997, in a nonrandomized study of AAT 60 mg/kg weekly involving 295 patients, decline in FEV_1 was slower in treated versus untreated patients.[35] In 1999, the first randomized controlled trial of augmentation therapy performed with 56 patients; while no difference in FEV_1 was detected between the 250 mg/kg at 4-week intervals versus albumin, the decline in lung tissue was reduced in CT scans.[38] Since the late 1980s, several studies have demonstrated that 60 mg/kg AAT infused at weekly intervals maintained AAT levels above the protective threshold throughout the week in both plasma and ELF and, in the SPARK trial, 120 mg/kg weekly AAT was associated with increased serum AAT levels and was well tolerated.[102,104-106] However, when administered at bi-weekly intervals in another study, the 120 mg/kg dose did not maintain AAT levels above the protective threshold.[107] At present, while augmentation therapy is only approved at doses of 60 mg/kg weekly in the United States, some clinicians prescribe higher doses when patients are not gaining adequate benefit (Figure 3).[82]

Currently, the commercially available augmentation products have comparable safety profiles. No deaths or viral transmissions have been reported.[2] Adverse events, which are usually rare and transient, include headache, nausea, and dizziness (<0.03 events per patient month).[36] Anaphylactic reactions have been reported for four patients, all of whom recovered.[1,106,108] As pooled human plasma can contain small amounts of immunoglobulin A (IgA), anaphylaxis may be triggered in IgA-deficient individuals with anti-IgA antibodies.

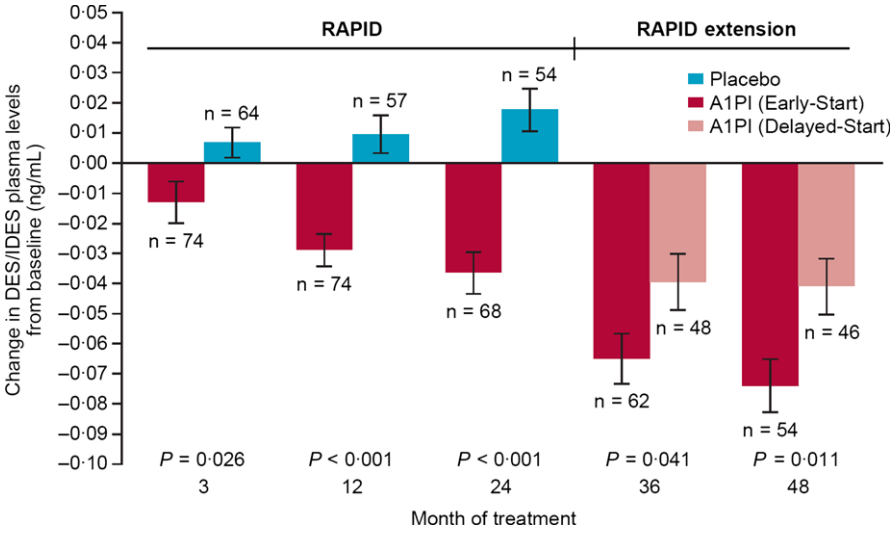

FIGURE 5 Changes in DES/IDES plasma levels from baseline in the RAPID trials. A1PI, α_1 proteinase inhibitor; DES/IDES, desmosine/isodesmosine; n, number of patients. Figure used with permission from Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation[101]

Therefore, it is suggested that patients should be checked for IgA deficiency before initiating augmentation therapy.[1]

At present, augmentation therapy is recommended only for adult patients with high-risk deficiency alleles, serum AAT levels below normal, nonreversible airflow obstruction by spirometry, and who avoid respiratory irritants, such as cigarette smoke.[103] Augmentation therapy is not recommended for individuals with heterozygous PI alleles when serum AAT levels are above the protective threshold.[109] For patients with severe COPD related to AATD, the efficacy of augmentation therapy is lower when FEV_1 is <30% predicted, although some clinicians argue that these patients may benefit even when changes in airflow obstruction and FEV_1 decline are small.[36,110,111]

6 | EXPERT ANALYSIS AND FUTURE RESEARCH

Since the discovery of AATD in the 1960s, knowledge and understanding of AAT and its deficiency have progressed significantly, although effective screening methods and optimal therapy have remained elusive. Further advances are required to improve the detection of AATD and to improve treatment outcomes. It appears likely that the greatest barrier to diagnosis is lack of awareness of the condition and of screening guidelines among clinicians,[1,66-68,74] while other diagnostic hurdles include similarities between COPD related to AATD and other etiologies and the asymptomatic nature of AATD in many individuals. Some physicians may also avoid testing because they are unaware of effective treatments for AATD-related COPD although, in one survey, only 8% of physicians believed no therapy existed.[74,112]

To increase awareness, one investigated intervention was to issue an alert in electronic health records to test for AATD. The alert consisted of a pop-up reminder on the computer of all main-campus Cleveland Clinic physicians using the hospital's electronic health record system, suggesting to order an AAT serum level or phenotype test when the results of the patient's pulmonary function test show airflow obstruction consistent with ≥ Global Initiative for Chronic Obstructive Lung Disease stage 1 (ie, FEV_1/forced vital capacity <0.70, with FEV_1<80% predicted). However, this alert did not result in a higher diagnostic rate for severe AATD, possibly due to a high baseline detection rate before the electronic alert or due to the small percentage of physicians (19%) who requested testing after the alert.[113] It remains to be determined whether the use of electronic medical records, combined with increased awareness of AATD and testing guidelines, will increase the detection rate for AATD. With regard to diagnostic techniques, advances in "next-generation sequencing" may provide a highly sensitive, fast, and economical screening test for AATD.[74]

Several support groups for patients with AATD have now been set up around the world and have been praised as a paradigm for confronting rare diseases.[114] In addition to providing psychological support and helping to increase awareness of AATD, these groups have been integral to the development and maintenance of extensive registries for use in retrospective and prospective trials, and have raised large sums of money for research.[7,115] As of April 2017, AlphaNet has contributed over $50 million to research funding via the Alpha-1 Foundation. AlphaNet operates as a self-sustaining model where fees for services provided at no cost to individuals with AATD are covered by biologic and the pharmaceutical companies developing or manufacturing therapies for AATD.[114]

Ongoing and recent research has explored novel therapies for the treatment of AATD. Gene therapy is presently being studied, but the limitation is inflammation of the liver, which can possibly be overcome by immunosuppressive therapy. In the mouse model, there is selective advantage of the hepatocyte with wild-type AAT over the hepatocyte with the Z mutant, which may allow the repopulation of the liver with the edited hepatocytes and increase production of normal AAT.[116]

When developing potential treatments for AATD, in addition to assessing their effectiveness on AATD-associated pulmonary and liver parameters, product availability and financial viability also need

to be considered. At present, augmentation therapy is the only approved medication that effectively raises AAT levels both in serum and ELF. However, the costs of acquiring human plasma-derived AAT are high, and treatment costs of $60 000 to $150 000 per year (depending on body weight, pricing, and the costs of nursing care) exceed the standard criterion for cost-effectiveness of $50 000 per quality-adjusted life-year.[2,117] Thus, more cost-effective treatment would be welcomed. With regard to efficacy, some studies indicate that the protective threshold of serum AAT (11 μmol/L, relative to 20-53 μmol/L in healthy individuals) may need to be revised.[27,74,80] The results of dose-ranging studies of augmentation therapy are eagerly awaited.[102] Similarly, while previous trials were not successful, further research into increasing the interval between infusions may result in appropriate efficacy, potentially with lower treatment costs.

A recent attempt to develop a guideline on management and treatment of AATD was published in 2016.[118] This publication was more of a consensus than a guideline, but is important reading for those that are managing patients with AATD, and agrees with previous recommendations with only a few outstanding exceptions. One exception is that while augmentation should be given to those AATD patients with FEV_1 ≤65%, treating at FEV_1 >65% should be decided upon on a case-by-case basis. In addition, augmentation therapy is recommended for individuals with necrotizing panniculitis. Importantly, the guideline also clarifies augmentation should not be offered to patients with the PI*MZ genotype.

In summary, several key issues should be borne in mind. AATD is highly under-recognized; less than 10% of cases are diagnosed. For patients presenting with liver and/or lung disease, screening and diagnostic tests are the only methods to determine whether they are related to AATD. In accordance with guidelines issued by bodies such as the WHO, ERS, and American Thoracic Society, individuals at high risk of having AATD should be tested, including individuals with COPD, nonresponsive asthma, bronchiectasis of unknown etiology, or unexplained liver disease.[1,66] PI*ZZ is the allele most associated with increased likelihood of developing COPD, although individuals with PI*SZ may be at risk, and PI*MZ alleles show increased risk, but less than ZZ, null Z, or null-null. Current therapy is comprised of aggressive treatment of asthma, vaccinations, and antibiotics against respiratory infections, maintaining ideal body weight, exercise, good diet, limiting alcohol, COPD medications and, if necessary, augmentation with AAT.

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CONFLICT OF INTERESTS

Timothy J. Craig does research for Biocryst, CSL Behring, Grifols, and Shire. He speaks for CSL Behring, Pharming and Grifols. He consults with Biocryst and CSL Behring. He is also on the Advisory Board of the HAE-A. Maria Paula Henao has no conflict of interests or financial disclosures.

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