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Guidelines for the Diagnosis and Management of α_1-Antitrypsin Deficiency

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Introduction

α_1-antitrypsin (AAT) deficiency is the most common potentially fatal hereditary disease in the adult population. Despite this, the condition continues to be underdiagnosed, and diagnosis is often only made when the patient is already in the advanced stages of lung disease. It is therefore important to draw the attention of the physicians who treat patients with chronic obstructive pulmonary disease (COPD) to both the World Health Organization (WHO) recommendations and the standards published jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) on this topic. Both sets of guidelines state categorically that serum AAT concentrations should be measured in all patients with COPD as part of the routine diagnostic protocol for this disease. Another important question is when and how additional laboratory tests and diagnostic techniques, such as phenotyping and genotyping, should be performed. Finally, the data currently available on the intravenous administration of augmentation therapy need to be updated and made available to the physicians who treat these patients. With these objectives in view, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) set up a working group to compile the present recommendations for the diagnosis and management of AAT deficiency. This statement deals with the epidemiological importance of this disease (with particular reference to the results of studies carried out in Spain), the clinical characteristics of patients with the deficiency, the current protocols for clinical and laboratory diagnosis, and indications for augmentation therapy. We hope that these recommendations will be of use to clinicians attending patients with COPD, and will resolve the most common doubts that arise concerning the care of individuals with suspected or confirmed AAT deficiency.

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The Characteristics and Consequences of AAT Deficiency

Molecular Characteristics

AAT is a 52-kD glycoprotein composed of a single chain of 394 amino acids and 3 carbohydrate side chains. The gene that codes for AAT is expressed primarily in hepatocytes.[1] AAT is the protease inhibitor found in greatest abundance in human serum, where it normally circulates in concentrations between 120 and 220 mg/dL as determined by nephelometry. Under normal conditions, the liver secretes 34 mg/kg of AAT every 24 hours, but production can increase 2- to 5-fold in the presence of inflammatory processes, tumors, and infections. The AAT found in serum represents only 40% of the total in the body; the remaining 60% is located in the extracellular space, where it impregnates tissues.

In addition to its ability to inhibit trypsin,[2] AAT can also inhibit most neutrophilic serine proteases. Its specific target, however, is neutrophil elastase, an enzyme that digests elastin, basement membrane, and other extracellular matrix components. Apart from this antiprotease activity, AAT also neutralizes neutrophil alpha-defensins as well as both leukotriene B-4 and interleukin-8, which are potent chemoattractants of neutrophils to the focus of inflammation.[3] Furthermore, it regulates the adhesion of neutrophil elastase to the phosphatidylserine neutrophil membrane receptor, an initial prerequisite for apoptosis, and in this way it may play an important role in the resolution of inflammation. In addition to the properties described above, AAT also has 9 methionine radicals, making it a potent antioxidant. AAT is also capable of inhibiting or slowing down the replication and infectivity of viruses and bacteria, including human immunodeficiency viruses. All of these facts, considered as a whole, indicate that the probable function of AAT—a natural broad-spectrum anti-inflammatory molecule—is to regulate the inflammatory reactions that occur continuously in the human body.[3,4]

The AAT gene is transmitted by simple autosomal codominant Mendelian inheritance by means of 2 alleles, 1 from each parent, which are expressed independently in 50% of the offspring.[1] The AAT gene is highly polymorphic. Using isoelectric focusing methods, over 70 variants of AAT have been identified to date, and this number has been growing with advances in identification techniques. The group of alleles involved is known as the protease inhibitor (Pi) system. Most of the variants have no clinical significance, but around 30 that may have pathologic consequences have been identified.[1] The variants are classified according to their rate of electrophoretic migration in a magnetic field at different pH gradients. The first researchers used the letter M to denote variants of medium mobility, F to denote fast mobility, and S to denote slow migration. As new variants were discovered, those that migrated towards the anode were designated with the initial letters of the alphabet and those that migrated towards the cathode the last letters of the alphabet. The normal allele, present in 90% of normal individuals, is called PiM. The most common deficient alleles are PiS (which expresses approximately 50% to 60% of AAT) and PiZ (which expresses approximately 10% to 20% of AAT).[1] The S and Z alleles express abnormal proteins that polymerize in the liver. In individuals with these phenotypes, 80% to 90% of the AAT-Z molecules and 40% to 50% of the AAT-S molecules are retained inside the hepatocyte grouped in polymers and normally degraded by the proteasome proteins.

Diseases Associated With AAT Deficiency

Since patients with AAT deficiency are susceptible to developing diseases throughout their lives, primarily pulmonary emphysema and several types of liver disease (including neonatal cholestasis, juvenile hepatitis, cirrhosis in children and adults, and carcinoma of the liver), the disorder is considered to be a systemic disease.[5,6] The liver diseases are caused by intrahepatic polymer accumulation and the emphysema develops as a result of insufficient AAT concentrations in plasma and body tissues at levels too low to protect the connective tissue of the lungs from the destructive effects of proteases (Table 1). The evidence currently available is insufficient to prove that the presence of defective AAT alleles influences the frequency or severity of bronchial asthma.[7] It has also been suggested that AAT deficiency may confer an increased risk of developing neoplastic diseases (such as lymphomas, and cancers of the bladder, gall bladder, and lungs) and promote faster disease progression in such cases. The carcinogenic mechanism would be an excess of protease not neutralized by AAT. This excess would cause tissue damage and degrade the intracellular barrier, thereby facilitating the development and dissemination of cancer by means of tumor necrosis factor.

There is evidence of an association between AAT deficiency, systemic vasculitis, and necrotizing panniculitis.[1] At present there is only scant evidence available concerning the relationship between AAT deficiency and other diseases, such as rheumatoid arthritis, fibromyalgia, aneurysms, arterial dissections, psoriasis, chronic urticaria, pancreatitis, cancer, multiple sclerosis, etc,[1,4] and further research is necessary before any conclusions can be reached.

In clinical practice, risk of disease is mainly restricted to ZZ phenotypes (96%). The remaining 4% of individuals at risk have rare deficient variants—referred to generically as M-like and S-like variants—or very rare null phenotypes.[1] The data currently available on penetration (the percentage of AAT-deficient individuals with clinical disease) is currently scant, although it has been established that almost all individuals with null phenotypes develop pulmonary emphysema. These variants are not, however, associated with liver disease since no AAT is produced and consequently no inclusions are formed in the liver.[8] Up to 60% of individuals with a ZZ phenotype develop chronic airway obstruction,[1] and the most important risk factor is the patient's level of exposure to tobacco smoke, an indication that AAT deficiency alone is not usually enough to cause respiratory disease in the absence of other genetic and environmental risk factors.[9]

Epidemiology

According to the results of a recent meta-analysis,[10] the estimated frequency of S and Z alleles in Spain is 104 per 1000 population for PiS and 17 per 1000 for PiZ. Extrapolating these figures to the Spanish population as a whole, the total number of individuals with heterozygous AAT phenotypes in Spain would be 9 173 181 (95% confidence interval, 9 167 966-

TABLE 1
AAT Phenotypes and Concentrations and the Associated Risk of Pulmonary and Liver Disease*

Phenotype	AAT Plasma Concentration		Risk of Emphysema	Risk of Liver Disease
	µM†	mg/dl†		
MM	20-39	103-200	No increase	No increase
MS	19-35	100-180	No increase	No increase
SS	14-20	70-105	No increase	No increase
MZ	13-23	66-120	Possible slight increase	Slight increase
SZ	9-15	45-80	Slight increase (20%-50%)	Slight increase
ZZ	2-8	10-40	High risk (80%-100%)	High risk
Null	0	0	High risk	No increase

*AAT indicates α_1-antitrypsin. An AAT level below 15 µM (80 mg/dL) is associated with an increased risk of developing pulmonary emphysema.
†Values obtained by nephelometry.

TABLE 2
Estimated Number of Persons With Deficient Pi Phenotypes in Spain*

	MS	MZ	SS	SZ	ZZ
Total population of Spain: 40 217 413	7 358 263	1 222 041	436 023	144 827	12 026
Estimated number of persons with deficient phenotypes	(6 696 222-8 072 328)	(972 767-1 539 805)	(369 057-514 244)	(107 227-195 038)	(7788-18 493)

*Spain, with a population of 40 217 413 inhabitants, would have more than 9 million individuals with AAT deficiency. Most of these would be MS and SS phenotypes, neither of which are associated with any known risk of developing diseases. The estimated number of subjects with a PiZZ phenotype would be 12 000. These individuals have an increased risk of developing disease throughout their lives. The remaining 14.6% would be individuals with MZ and SZ phenotypes, both associated with a much lower risk of disease than the PiZZ phenotype. Adapted from Blanco et al.[10]

9 178 398), with the following distribution: MS, 7 358 263; MZ, 1 222 041; SS, 436 023; SZ, 144 827; and ZZ, 12 026. In accordance with these estimates, the overall prevalence in Spain of heterozygous phenotypes would be 1 in every 4.4 individuals, distributed as follows: MS, 1/5; MZ, 1/33; SS, 1/92; SZ, 1/278; and ZZ, 1/3.344 (95% confidence interval, 2175-5164) (Table 2). Figure 1 shows the estimated number of individuals with a ZZ phenotype in a number of European countries for the purposes of comparison. The estimated number of people in Spain with a deficient ZZ phenotype would be approximately 12 000—situating this country in second place after Italy—the country with the largest population of individuals with serious AAT deficiency in Europe.[11,12]

Clinical and Functional Evolution

The age of onset of respiratory symptoms is highly variable, although they rarely appear in individuals under 25 years of age. This variability depends on tobacco consumption, the presence of bronchial hyperreactivity, and repetitive respiratory infections. In smokers with severe AAT deficiency, symptoms appear between 35 and 40 years of age, while in nonsmokers onset tends to occur around 10 years later.[13] The most common symptom is dyspnea, which is found in 80% to 90% of patients; 65% to 75% report wheezing, in some cases chronic and in others related to respiratory infections, and up to 40% present with a productive or nonproductive cough associated with bronchiectasis. In a study of the National Heart, Lung, and Blood Institute (NHLBI) Registry, 35% of participants reported a history of asthma and over 50% had a positive bronchodilator response.[14] A study evaluating the presence of wheezing, atopy, increased serum immunoglobulin (Ig) E, and positive bronchodilator response as markers of asthma found 3 or more of these markers in 22% of AAT-deficient patients and only 5% of AAT-replete patients with chronic obstructive pulmonary disease (COPD).[15]

While our understanding of the natural history of this disease has improved thanks to the study and follow-up of homozygous PiZZ individuals, many aspects still require further clarification. During infancy and childhood, the only important threat to the health of these individuals is the possibility that they may develop liver disease. In one study, no differences in lung function were found between 103 adolescent PiZZ subjects who had been diagnosed by neonatal screening

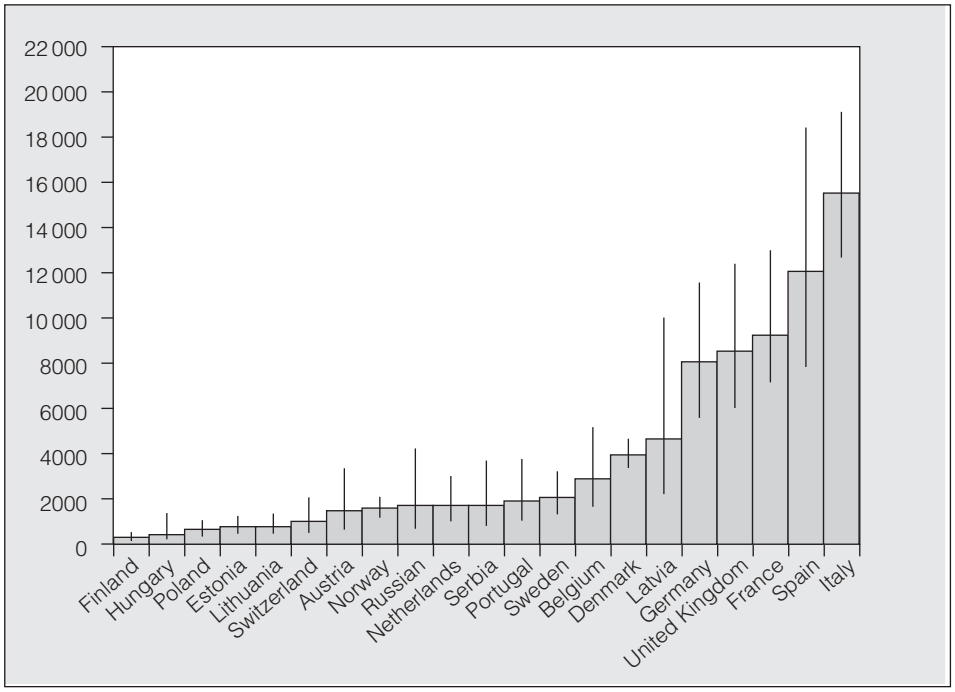

Figure 1. Estimated number of individuals with the ZZ phenotype in 21 European countries based on reliable available data. Adapted from Blanco et al.[11]

and a control group of the same age.[17] However, less is known about the natural history of AAT deficiency in adults over 20 years old. One of the reasons for this is the difficulty of drawing conclusions from studies with differing designs and/or study populations. For example, most of the studies include a mix of smokers, ex-smokers, and nonsmokers, and smoking may obscure the effects on lung function of other risk factors. More recent studies of PiZZ nonsmokers indicate that exposure to domestic kerosene heaters, agricultural occupations, a history of occupational exposure to respiratory irritants, the presence of wheezing, repetitive respiratory infections, and pneumonias are all associated with significantly greater lung function impairment.[18,19]

Table 3 shows the decreases in forced expiratory volume in 1 second (FEV_1) in case series of PiZZ patients not receiving augmentation therapy (both index and nonindex cases). In all of these studies, the annual decline in FEV_1 is greater among smokers and significantly less among ex-smokers.[16,20-22] The findings are not, however, equivalent to those found in AAT-replete ex-smokers with COPD in whom the decrease in FEV_1 may be as small as that found in nonsmokers (30 mL/y). The data are less consistent when the results are analyzed according to initial FEV_1 values.[23-26]

Several studies have shown FEV_1 values to be the main predictor of survival in patients with severe AAT deficiency.[16,20,27] Survival at 2 years is practically 100% until FEV_1 falls to 33% of predicted and, from this point on, it decreases exponentially, falling to 50% when FEV_1 is 15% of predicted.[27] One confounding factor that gives rise to discrepancies between studies is the inclusion of both symptomatic patients (index cases) and asymptomatic subjects who have been identified in the course of family studies or screening programs (nonindex cases). In a study of 52 individuals with a PiZZ phenotype (20 of whom were asymptomatic), a high level of variability was found in lung function test results and 3 risk factors for progression to emphysema were identified—bronchial hyperreactivity, repetitive respiratory infections, and family factor. The prevalence of parental emphysema was higher among type PiZZ persons with a low FEV_1 value than among the type PiZZ individuals with normal FEV_1 values.[13] Recent studies suggest the existence of genetic mutations that

TABLE 3
Decline in FEV_1 in Series of PiZZ Subjects Not Receiving Augmentation Therapy (Index and Nonindex Cases)*

Population	Reference	Year	Groups	N	Follow-Up, months	Decline in FEV_1, mL/year†
PiZZ index and nonindex	Buist et al[26]	1983	FEV_1 <30%	52	NR	45 (8)
			30%-65%	30	NR	111 (102)
			>65%	22	NR	42 (52)
PiZZ index and nonindex	Janus et al[20]	1985	Smokers	7	12-144	317 (80)
			Ex-smokers	6	12-144	61 (43)
			Nonsmokers	7	12-144	80 (38)
PiZZ index	Brantly et al[23]	1988	Overall	24	32	51 (82)
			FEV_1 <30%	17	35	51 (81)
			30%-65%	5	25	40 (109)
			>65%	2	23	71 (5)
PiZZ index and nonindex	Wu and Eriksson[16]	1988	Smokers	40	36	61 (170)
			Ex-smokers	22	36	81 (70)
			Nonsmokers	18	36	61 (100)
PiZZ index and nonindex	Seersholm et al[21]	1995	Overall	161	NR	81 (94)
			Index	113	NR	88 (99)
			Nonindex	48	NR	63 (87)
			Smokers	43	NR	132 (105)
			Ex-smokers	100	NR	58 (80)
			Nonsmokers	18	NR	86 (107)
			Nonsmokers and nonindex	11	NR	36 (50)
PiZZ index	Seersholm et al[24]	1998	Overall	97	70	74 (59)
			FEV_1 <30%	27	70	31 (36)
			30%-65%	58	70	83 (49)
			>65%	12	70	140 (83)
PiZZ index and nonindex	NHLBI (AAT Deficiency Registry Study Group)[25]	1998	Overall	277	12-82	56 (86)
			FEV_1 <35%	99	12-82	44 (99)
			35%-49%	26	12-82	94 (79)
			50%-79%	40	12-82	84 (93)
			>80%	152	12-82	39 (75)
PiZZ index And nonindex	Piitulainen et al[22]	1999	Smokers	46	66	70 (58-82)†
			Ex-smokers	351	66	41 (36-48)†
			Nonsmokers	211	66	47 (41-53)†

*FEV_1 indicates forced expiratory volume in 1 second; NR, not registered; NHLBI, National Heart, Lung, and Blood Institute; AAT, α_1-antitrypsin.
†Data in the seventh column are given as means (SD) except for the data from Piitulainen et al. ‡95% confidence interval

could modify the natural history of individuals with a PiZZ phenotype. One study found a significantly higher frequency of a polymorphism in the endothelial nitric oxide synthetase gene (C774T) in type PiZZ individuals with an FEV_1 less than 35% of predicted.[28] Rodríguez and colleagues[29] found a higher frequency of polymorphisms in glutathione S-transferase P1 (GST P1-105Val) in AAT-deficient patients. This finding, together with age and smoking history, explained 41% of the variability in FEV_1 values observed in these patients. Lung density as measured by computed tomography has also been used as a prognostic marker in AAT-deficient patients; a decline in this variable correlates significantly with an increase in mortality at 5 years.[30] Body mass index is another factor that has been independently associated with survival in AAT-deficient patients; a higher mortality rate has been found among individuals with a body mass index under 20.[31]

In summary, smoking is a key element in the natural history of patients with AAT deficiency. Both mortality and decreases in FEV_1 are influenced directly by the quantity of tobacco consumed. While patients who stop smoking can slow down the decline in FEV_1, their values remain lower than the normal range found in AAT-replete individuals. Other factors that condition the evolution of pulmonary diseases include occupational exposure to irritants, certain high-risk occupations, the presence of wheezing, respiratory infections (especially pneumonias), and a body mass index of less than 20. There is also a genetic factor that gives rise to an accumulation of index cases in certain families. The life expectancy of PiZZ nonsmokers who are nonindex cases and present no other risk factors may be similar to that of the general population.[1,32]

Medium AAT Deficiency: Risk Associated With Heterozygosis and Other Phenotypes

The S and Z alleles are more often associated with intermediate AAT deficiency. The MS and MZ phenotypes, which are present in Caucasian populations at a rate of 10% and 3% respectively,[33] more often give rise to intermediate AAT deficiency. There is, however, still a great deal of debate about whether these phenotypes actually confer greater susceptibility to emphysema and COPD than MM phenotypes.[34] Although most studies have failed to demonstrate a greater prevalence of respiratory symptoms or COPD in nonsmokers with a PiMZ phenotype, 2 studies carried out in the general population did show that the phenotype is associated with a faster decline in FEV_1 than that found in MM individuals.[35,36] Case–control studies indicate a higher prevalence of type PiMZ individuals among patients with COPD as compared to control groups, and data from the NHLBI Lung Health Study reveal a more rapid decline in FEV_1 among smokers with an MZ phenotype, who have a higher risk for COPD.[36,37] The SS phenotype, which produces AAT levels 60% of those associated with normal variants, has not been associated with COPD.[38] SZ heterozygotes, who have AAT levels around 40% of normal, are rare (<1%) and present a higher prevalence of COPD if they are smokers. However, the degree of functional impairment in these patients tends to be lower than in PiZZ individuals.[39,40] Table 1 shows the range of AAT levels for each phenotype and the associated risk for emphysema.

Clinical Diagnosis

Suspected Diagnosis

AAT deficiency should be suspected in the presence of several clinical presentations. The classic presentation is that of a young adult, smoker or nonsmoker, with progressive dyspnea and full-blown emphysema, but other patients are diagnosed when they are much older after years of COPD with emphysema. Still others are asymptomatic and are diagnosed in the course of family studies or screening programs or because of hepatic abnormalities in infancy.

Despite the fact that AAT deficiency is the most common hereditary disease diagnosed in adults, there is a generalized lack of knowledge in the medical community about this disorder. Physicians forget to order serum AAT levels for many COPD patients and lack information about how to diagnose the condition or how or where to refer patients for confirmation of the diagnosis. Two of the reasons for this situation are that the age of onset of disease varies considerably and that the deficiency is found in only 1% to 2% of emphysema cases. As a result, this genetic abnormality is grossly underdiagnosed all over the world. In Spain, on average 10 years elapse between the diagnosis of COPD and the subsequent diagnosis of AAT deficiency.[41] In the United States of America this gap was found to be 7.2 years, and 43% of patients reported seeing 3 physicians and 12% more than 6 physicians before the diagnosis was established.[42]

Data from the Spanish national registry reveals that around 500 patients with a ZZ phenotype have been diagnosed in this country. This figure represents 4% of the 12 000 cases estimated to exist in Spain.[10,43] Similar percentages have been diagnosed in the USA and the United Kingdom, and only in Denmark have 28% of the estimated total number of cases been diagnosed.

Early diagnosis of this genetic abnormality is important because it allows clinicians to implement early and intensive interventions to help smokers to quit (since tobacco cessation is a determining factor in the prognosis of this disease), to treat the symptoms of emphysema and exacerbations, and to undertake family studies to ensure early diagnosis of other cases and provide genetic advice. Augmentation therapy can also be started when indicated.

Clinical Presentation and Diagnostic Tests

Adults with this condition often present with early onset of the typical symptoms of COPD: cough, expectoration, dyspnea, and frequent exacerbations.

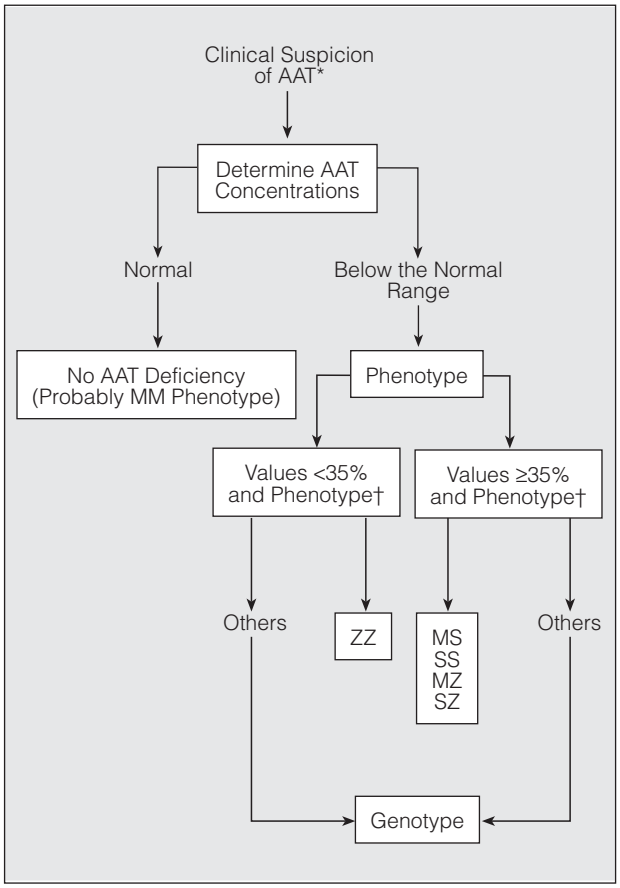

Figure 2. Diagnostic algorithm for α_1-antitrypsin (AAT) deficiency. *See Table 4. †Percentage with respect to lower limit of reference.

However, the primary symptom is progressive dyspnea. Some 60% of ZZ nonsmokers develop the initial symptoms by 40 years of age and 90% by 50 years of age, although onset is earlier among smokers. Consequently, in many cases it is difficult to differentiate between COPD secondary to AAT deficiency and COPD related to other causes if the clinician fails to order AAT tests.

Chest radiography and computed tomography reveal a predominantly basal panlobular emphysema. Large bullae are uncommon. Bronchiectasis is found in around 25% of patients, a percentage similar to that found in COPD case series.[44] While respiratory function varies, most patients present with an obstructive pattern and a more pronounced decline in FEV_1 and ratio of FEV_1 to forced vital capacity than would be expected solely on the basis of the smoking history. Other characteristic findings are increased residual volume, hyperinflation, and impaired diffusion. Some patients have a positive bronchodilator response, which is sometimes associated with the clinical signs and symptoms of asthma. Airway hyperreactivity associated with the ZZ phenotype is indicative of a poor prognosis in these patients.

During COPD exacerbations, values of the inflammatory markers interleukin-8 and leukotriene B4 have been observed to be higher in AAT-deficient individuals than in other patients. This finding could explain why the former experience frequent exacerbations that can be more prolonged and severe.[45]

The first symptoms that develop in some homozygous ZZ patients are liver function disorders in early life. These infants develop cholestasis of varying degrees of severity associated with jaundice and elevated liver enzyme levels. Some cases may progress to cirrhosis and eventually liver failure, which is fatal unless the patient receives a liver transplant. This liver disorder is caused by an accumulation of the Z variant of AAT in hepatocytes, although it is not known why only a small proportion of homozygous subjects develop the disease. Liver function is normal in most adult patients.

Another less common clinical form is panniculitis, which takes the form of generalized, painful, and erythematous subcutaneous nodules that may ulcerate. Figure 2 shows the diagnostic algorithm that should be used to confirm diagnosis when AAT deficiency is suspected.

TABLE 4
Candidates for Measurement of AAT Levels*

1. Patients with chronic obstructive pulmonary disease
2. Adults with bronchiectasis
3. Patients with partially reversible adult asthma
4. Blood relatives of individuals with known AAT deficiency
5. Dyspnea and chronic cough in many members of the same family
6. Liver disease of unknown cause
7. Reduction in the α_1 protein peak in the proteinogram

*AAT indicates α_1-antitrypsin.

Family Genetic Studies and Population Screening

When the clinical picture is consistent with suspected AAT deficiency, the patient should always undergo genetic testing. The primary candidates for AAT deficiency are nonsmokers who are not asthmatic presenting with dyspnea and abnormal lung function results and smokers under 40 years of age with impaired lung function. However, the application of these criteria alone would not diagnose many other patients with a more atypical presentation. For this reason, in a consensus statement published in 1997, the World Health Organization recommended that AAT levels should be measured at least once for all COPD patients. This recommendation was also included in the ATS/ERS standards document.[1,46] Once-in-a-lifetime measurement of serum AAT concentrations is, therefore, always indicated for patients who present, in addition to COPD, any of the diseases included in Table 4. Phenotyping is indicated in patients with low AAT levels, and genotype sequencing should only be carried out when a discrepancy is found between AAT levels and the phenotype (Table 5).

Before undertaking population genetic studies, the benefits and potential disadvantages should be weighed. Benefits include early diagnosis, preventative measures, genetic advice, and specific treatments. The potential

disadvantages for the patient are psychological, social, and occupational. The high cost and scientifically exacting nature of these tests is also a drawback.

There are 2 possible reasons for determining serum AAT levels and phenotype in healthy subjects.

1. Predispositional testing. Predisposed subjects would be persons with no specific symptoms who, nonetheless, are at high risk for this genetic abnormality, primarily blood relatives of diagnosed individuals. Children of heterozygous parents with one Z allele each have a 25% chance of having the homozygous PiZZ phenotype. Children with one homozygous ZZ parent and one heterozygous parent will all be either PiZZ or carriers of a Z allele. When these patients present liver symptoms or emphysema a diagnosis should be established without delay. Moreover, all blood relatives of homozygous ZZ or heterozygous MZ or SZ subjects, or carriers of rare defective alleles should also be tested.[47]

2. General population screening. Population screening studies are carried out to determine the prevalence of this deficiency in different populations. Screening of neonates or of the general population should only be undertaken to obtain epidemiological data in a specific population or geographic area when the following conditions apply: a high prevalence is suspected, the condition is underdiagnosed, and smoking is highly prevalent.

Such testing should only be carried out under the auspices of registries or scientific societies. The study design should be supervised by experts, and all participants should be properly informed both before and after the results are known.[1,48]

Once AAT concentrations have been determined, phenotyping should be performed in subjects whose AAT levels are below a predetermined level.

Whenever a subject is diagnosed as AAT deficient in the course of a family study or population screening program and has a concordant phenotype, chest radiography, lung function tests, and liver function tests should be carried out. Blood relatives of the AAT-deficient individual should also be tested. All cases diagnosed should be included in the National Registry.

It should always remembered that there is an important difference—in both clinical expression and prognosis—between index cases (patients diagnosed as a result of clinical suspicion) and nonindex cases (those discovered in the course of family studies or general population screening). The latter are usually asymptomatic, and their long-term prognosis is more favorable, particularly if preventative health measures are implemented.[49]

Laboratory Testing

Laboratory diagnosis of this condition is based on the quantitative measurement of AAT levels in serum and identification of an AAT phenotype. Molecular analysis of the AAT gene or genotype is the gold standard for identifying rare allelic variants. AAT concentrations are measured in total blood using ethylenediaminetetraacetic acid as an anticoagulant.

TABLE 5
Candidates for Determination of Phenotype and Genotype

Phenotype
1. Individuals with lower than normal AAT levels
2. Blood relatives of patients with AAT deficiency
3. Partners of individuals with phenotypes having 1 or 2 Z alleles before having children
Genotype
1. Discrepancy between low α_1-antitrypsin levels and a theoretically normal phenotype

TABLE 6
Standards for Obtaining Specimens for Phenotyping and Measurement of α_1-Antitrypsin*

Extract 5 mL of blood without anticoagulant
Centrifuge and separate serum
Divide serum into 500-µL aliquots (plastic tubes)
The analysis should, if possible, be performed on fresh serum specimens
If the specimens are not analyzed immediately, they can be stored for a maximum of 1 week at 4º-8ºC or frozen at –20ºC
Avoid repeated thawing and refreezing
Specimens sent to the Registry's central laboratory should be frozen in hermetically sealed plastic tubes

*Note: The storage conditions influence the result, in particular with respect to the identification of PiZ α_1-antitrypsin, which may degrade.

Measurement of AAT Serum Concentrations

The method most often used for measuring serum AAT levels is kinetic immune nephelometry. This assay is based on the formation of insoluble immune complexes when the protein is mixed with the anti-AAT antibodies. When, in the course of this process, an intense beam of light is passed through the sample, the beam is dispersed by the precipitating particles and the intensity of the scattered light is proportional to the quantity of the antigen present in the serum sample. Whenever possible, the serum samples analyzed should be fresh or frozen at –20ºC, and repeated freezing and thawing should be avoided (Table 6).

In order to facilitate proper interpretation of the results, each laboratory should have previously determined normal AAT levels in serum samples obtained from a healthy population. The reference values for AAT concentration in serum samples from healthy adults range from 103 to 200 mg/dL.[50] AAT levels in children are lower than those in the adult population. The results of quantitative measurements may also be expressed in micromolar units; the conversion to µM is made by multiplying the concentration in mg/dL by 0.1923.

Measurement of serum AAT levels is the key technique for diagnosing this hereditary deficiency. Values under 35% of normal are indicative of a possible homozygous PiZZ phenotype.

TABLE 7
Standards for Obtaining Specimens for the Determination of the α_1-Antitrypsin Genotype

Extract 1 mL of blood using ethylenediaminetetraacetic acid as an anticoagulant
Do not centrifuge
Divide the blood into 500-µL aliquots (plastic tubes)
Specimens can be stored at room temperature or at 4º-8ºC. When not processed immediately, they should be stored at 4º-8ºC or frozen at –20ºC.
Specimens sent to the Registry's central laboratory should be frozen in hermetically sealed plastic tubes

When interpreting the results of an isolated qualitative measurement, it is important to bear in mind that AAT is an acute-phase reactant and that infectious or inflammatory processes can distort the results by producing normal or high levels in patients with a moderate deficiency. High AAT concentrations have also been reported during pregnancy and after consumption of oral contraceptives. Consequently, the diagnosis of AAT deficiency should be based on both measurement of AAT levels and identification of the patient's phenotype.

Determination of AAT Phenotypes

The high degree of polymorphism of the AAT gene explains the high number of protein variants or phenotypes. These variants are mostly due to the mutation of a single base in the DNA chain, which is expressed by the substitution of one amino acid for another and by the alteration of the protein charge.

The method most widely used to identify protein variants is isoelectric focusing. This technique uses electrophoresis to separate the proteins by their isoelectric point in an acrylamide/bisacrylamide gel at a pH of 4.2 to 4.5. Whenever possible, the serum samples analyzed should be fresh or frozen at –20ºC, and repeated freezing and thawing should be avoided. Storage conditions are crucial since they influence the results and particularly the identification of PiZ phenotype AAT, which has very labile antigens that make it susceptible to degradation.

Phenotype determination is required to confirm the diagnosis of AAT deficiency and is indicated in patients whose AAT levels are below the normal range or close to the lower limit. Individuals with low normal levels may have an MS, SS, or MZ phenotype. As has been mentioned with respect to reference values for normal AAT levels, reference values for the AAT concentrations corresponding to each of the major phenotypes must also be established. It is likewise essential to ascertain which phenotypes are prevalent in the area where testing is being carried out. Table 1 shows the results on the relationship between AAT concentrations and phenotypes. AAT serum concentrations are highest in individuals with a PiMM or PiMS phenotype, and there is no overlap between the AAT levels of PiMM, PiMS, and PiSS (only slightly deficient) phenotypes and those associated with PiSZ and PiZZ phenotypes. The only overlap is between the AAT concentration of the PiSZ and PiZZ type deficient phenotypes.

Determination of the AAT Genotype

Molecular analysis of the AAT gene is the gold standard for identifying rare allelic variants associated with hereditary AAT deficiency and characterizing new variants.[51-53] It is likewise the most appropriate method for identifying null variants. Genotyping is also useful where there is a discrepancy between a patient's AAT levels and his or her phenotype such as, for example, a subject who has an AAT deficiency despite having a normal PiMM phenotype. This would probably be due to the presence of an AAT protein variant with an isoelectric point similar to that of the PiMM variant, which is, therefore, impossible to classify by phenotyping.

Genotyping is performed using samples of total blood and ethylenediaminetetraacetate as an anticoagulant. The samples can be stored at 4ºC for 48 hours after extraction, or frozen at –20ºC if not processed immediately (Table 7). The method most often used consists in the amplification of DNA extracted from mononuclear cells by polymerase chain reaction (PCR) followed by cycle sequencing of the PCR products. This determination requires a complete study of the DNA sequences of the 4 exons of the AAT gene in addition to those of the corresponding intron sequences.[54]

Other Determinations

Determination of the Neutrophil Elastase Inhibitory Capacity of AAT

Elastase inhibitory activity correlates with AAT concentrations; the higher the levels of circulating AAT, the greater the inhibitory effect. However, antielastase capacity may be poor in certain patients with normal or raised AAT levels because not all the protein is active. These cases are associated with AAT that is oxidized, degraded, or has scant capacity to bind neutrophils.

Determination of antielastase activity is indicated primarily in the study of COPD patients with apparently normal AAT levels suspected of having AAT deficiency. The aim in such cases, in light of the discrepancy between observed AAT level and clinical course, is to ascertain whether the increase in AAT levels during COPD exacerbations is proportional to the antielastase activity, and in general to assess the repercussions of AAT deficiency on the severity of pulmonary disease.

Elastase inhibitory capacity is evaluated by incubating serum samples with an excess of elastase and quantifying residual elastase; the lower the concentration of residual elastase detected, the greater the antielastase activity.

Assessment of Liver Function

Liver function is assessed in patients with AAT deficiency by analyzing alanine aminotransferase,

aspartate aminotransferase, bilirubin, and albumin, as well as by coagulation tests.

Diagnosis of AAT Deficiency by Serum Proteinogram Analysis

Diagnosis of this deficiency through the observation of a reduced or absent α_1-globulin band on a serum proteinogram is no longer used. This method, which was not very sensitive or specific, always required confirmation of the result by quantitative and qualitative analysis of AAT levels.[55]

Screening for AAT Deficiency Using Dried Blood Spot Specimens on Paper

Dried blood spot specimens on paper are particularly useful for diagnosing and screening for genetic diseases. The procedure for obtaining blood samples is minimally invasive and specimens are easy to store and transport to the central reference laboratory.

The determination is made in capillary blood obtained by sterile puncture in the soft pad of the fingertip. The drops of blood are applied to disks of filter paper which are then left to dry at room temperature before being sent by surface mail to a central laboratory for analysis (Table 8).[56]

The established protocols usually measure AAT levels by kinetic nephelometry[57] and the most common deficient S and Z genotypes using real time PCR.[54] It should be remembered that measurement in dried blood is a screening method and that all cases diagnosed as AAT-deficient should then be studied in serum samples by AAT measurement and phenotyping.[48]

TABLE 8
Standards for Obtaining Dried Blood Spot Specimens

Wash and dry the patient's hands. Clean the patient's fingertip with sterile gauze impregnated with alcohol, and allow to dry for 15 seconds before puncturing soft tip with a lancet
When the blood begins to flow, allow drops to fall onto each of the 3 circles printed on the filter paper such that the blood fills the circle thoroughly soaking through the paper (the circular stain should be visible on the reverse side). It is also very important to dry the specimens at room temperature before placing the filter paper in the impermeable envelope and sending the specimens as soon as possible to the central laboratory by surface mail
Adherence to these recommendations ensures that the specimens will be in optimum condition for laboratory analysis, both for the purposes of α_1-antitrypsin quantification and for genotyping

The Importance of Registries: the Spanish Registry and the International Registry for AAT Deficiency

Patient registries were set up because of the low prevalence of AAT deficiency and the need to gather information on large groups of patients. The Danish registry, which was set up in 1978, included over 500 individuals by 1994. In Sweden, a country that pioneered the study of this disease, the registry was set up in 1991 and by December 1994 included 665 persons. Interest in registries increased with the availability of augmentation therapy because it was decided at an early stage that it would be impossible to carry out clinical trials on the long-term efficacy of this treatment. In this context, registries were set up as an alternative to such trials in order to facilitate comparison of the evolution of large cohorts who had or had not received augmentation therapy. The main registries set up with this aim in view were the German national registry (which was established in 1989 and by 1995 had compiled data on 443 patients in 23 health-care facilities) and the NHLBI registry (which was set up in 1988 and by October 1992 had registered 1129 patients from 37 health-care facilities in the USA and Canada).[25]

The Spanish registry was set up in 1993[58] and, in view of the small number of patients it was expected to recruit, the initial aims were as follows: *a)* to gather data on the characteristics and frequency of AAT deficiency in Spain; *b)* to establish guidelines adapted to Spain on the treatment and follow-up of patients with this deficiency; *c)* to provide information to the physicians who treat those patients in Spain; *d)* to improve understanding of and interest in this "not so rare" disease and to reduce underdiagnosis and delayed recognition of the disorder; and *e)* to provide technical support for the determination of the Pi phenotype and, when indicated, the genotype of individuals with suspected AAT deficiency.

The International Registry for AAT Deficiency (AIR) was set up in 1997 as a European initiative under the auspices of the European Respiratory Society. The scope of the registry is, however, international and, in addition to European countries, such as the United Kingdom, Sweden, Denmark, the Netherlands, Spain, Italy, Switzerland, and Germany, it also includes representatives from New Zealand, Australia, South Africa, Argentina, Brazil, and Canada.[59] In the future, this registry may form the basis of more comprehensive programs designed to gain a better understanding of the natural history of AAT deficiency and it will perhaps give rise to definitive clinical trials on the efficacy of augmentation therapy. Clearly, initiatives such as these national and international registries are the only way we can recruit a sufficient number of patients and broaden our understanding of this disorder.[60]

Patients with AAT deficiency (PiZZ, rare deficient variants, and PiSZ) can be registered through the SEPAR web site (www.separ.es/air). The Spanish registry of patients with AAT deficiency is located within the Assembly on Respiratory Failure and Sleep Disorders and can be accessed through the Assemblies tab (Áreas de Trabajo, Sueño – ventilación mecánica – CRC). This web page provides general information about the Spanish registry and its coordinators, the people responsible for each autonomous community in Spain, and access to the registry's central laboratory and its publications. The page also includes links to other medical web pages and patient support associations.

Figure 3. Front page of the Spanish registry of patients with α_1-antitrypsin deficiency. Available from: http://db.separ.es/air

Users must be logged on in order to access the registry database. The first step is to register and apply for a key code. Within a few days, the applicant will receive a user name and key that will allow personal access to the registry (Table 9 and Figure 3).

The tests that should be carried out on a regular basis are shown in Table 10. Every 6 months, physicians should access the database and update the data on their registered patients by completing the electronic follow-up forms.

TABLE 9
Patients Who Should Be Registered

ZZ
SZ
Rarer defective variants

Augmentation Therapy

Fundamental Aspects of Augmentation Therapy
Biochemical Effectiveness

Medical treatment of patients with emphysema associated with AAT deficiency should include the same pharmacological and nonpharmacological measures as those used to manage AAT-replete COPD patients.[61,62] A purified preparation of AAT derived from donor plasma has been available for intravenous administration since 1987. It has been shown that the infused preparation maintains its enzymatic activity in both plasma and bronchoalveolar lavage. Moreover, since a direct correlation exists between plasma concentrations of AAT and its pulmonary activity, treatment can be monitored by measuring minimum plasma concentrations at steady state (C_{min}), also called trough concentrations. C_{min} are the concentrations obtained after a steady state has been

TABLE 10
Management of Patients Receiving α_1-Antitrypsin Augmentation Therapy

Test	Timing
Spirometry + bronchodilator test	Quarterly
Static lung volumes	Annual
Carbon monoxide transfer factor	Annual
Arterial blood gas analysis and exercise testing	Depends on the clinical picture and the results of other tests
Liver function	Annual
Chest radiograph	6-monthly or when new symptoms appear
High-resolution computed tomographic scan of the thorax	As part of the initial diagnostic study and repeated only if the clinical picture justifies repetition
Hepatitis C virus, hepatitis B virus, and human immunodeficiency virus serology	As there is no evidence of transmission of viral agents, routine use of these tests is not recommended

reached and before the subsequent infusion.[63] On the basis of data from epidemiological studies, it has been concluded that a C_{min} of 0.8 g/L as determined by radial immunodiffusion or 0.5 g/L as determined by nephelometry is a level that can provide adequate protection for the lungs comparable to that enjoyed by normal nonsmokers.[1] As the half-life of infused AAT is between 4 and 5 days, the regimens initially tested were based on weekly infusions.[63] The dosage regimen recommended in the manufacturer's prescribing information sheet is still 60 mg/kg/week. However, given the obvious disadvantages of weekly administration for a lifetime treatment, infusions every 14, 21, and 28 days have also been tried. Table 11 shows the biochemical results obtained with these different administration regimens.

Clinical Efficacy

Only 1 randomized double-blind clinical trial has compared treatment with human AAT and placebo; the dosage regimen studied was 250 mg/kg/28 days. That trial, which studied 58 patients treated for 3 years, revealed no significant differences in the evolution of lung function, but the patients who received AAT presented an annual loss of lung density as measured by computed tomography of 1.50 g/L compared to a 2.57 g/L loss observed in patients receiving placebo (*P*=.07).[64]

All other data in the literature concerning the effectiveness of augmentation therapy relate to comparative cohort studies. These studies have revealed a significant reduction in the decline in FEV_1 in patients with an FEV_1 between 30% and 60% of the predicted value.[65,66] Moreover, data from the NHLBI in the USA on 1048 patients followed for between 3.5 and 7 years reveal a significant 36% reduction in mortality among patients receiving augmentation therapy continuously or intermittently as compared to patients not receiving such therapy (*P*=.02).[25]

An interesting effect of augmentation therapy is that it may possibly afford protection against bronchial infections, an important consideration given the high prevalence of bronchiectasis in this population.[67] The results of one observational study suggest that patients receiving augmentation therapy experience fewer exacerbations.[68] This finding may be related to restoration of the protease/antiprotease imbalance and reduction of inflammation in the airways of patients receiving augmentation therapy.[69]

It is difficult to observe the effect of augmentation therapy in patients with severe disease (FEV_1 <30%) because such patients often die or undergo lung transplantation before a sufficiently long follow-up period has elapsed. Neither is it possible to evaluate the effect of this treatment in patients with mild disease (FEV_1 >60%), as bias enters owing to confounding by indication. The few patients who receive treatment at such an early stage are index cases with particularly serious symptoms or patients experiencing accelerated loss of lung function, while the patients in the control group who are not receiving treatment tend to be nonindex cases who are not receiving treatment precisely

TABLE 11
Biochemical Efficacy of Infused AAT Using Various Intravenous Treatment Regimens*

Author	N	Serum AAT, Mean (SD), mg/dL†	Methods	Dosage	Results‡
Wewers et al[63]	21	30 (1)	RID	60 mg/kg/7 days	C_{min} =126 mg/dL (SD=1) with increased antielastase activity in serum and BAL
Schwaiblmair et al[77]	20	43 (4)	RID	60 mg/kg/7 days	C_{min} >100 mg/dL for 36 months >3000 doses
Schmidt et al[78]	20	18 (3.2)	RID	60 mg/kg/7 days	At 6 months all patients had a C_{min} >80 mg/dL
Wencker et al[66]	443	33 (22)	NP	60 mg/kg/7days >58 000 infusions	C_{min} always >80 mg/dL, mean 95 mg/dL
Barker et al[79]	21	67 (15)	NP	120 dmg/kg /14 days	After 9 doses, C_{min} >80 mg/dL until day 8 and >70 mg/dL until day 10 in all patients. C_{min} >70 mg/dL on day 14 in only 1 case
Miravitlles et al[41]	6	25 (4)	NP	240 mg/kg/28 days >250 infusions	In 3 cases C_{min} between 45 and 46 mg/dL. Another 3 patients had C_{min} between 35 and 36 mg/dL
Hubbard et al[70]	9	35 (10)	RID	250 mg/kg/28 days	After 1 dose, C_{min} >80 mg/dL for 21 days. After 12 months C_{min} >80 mg/dL for 25 days. Mean (SD) C_{min} at 28 days 67 (10) mg/dL
Dirksen et al[64]	26	32 (8)	NP	250 mg/kg/28 days	C_{min} >80 mg/dL 23-24 days
De la Roza et al[74]	7 (PK)	24 (1)	NP	Various regimens	Cmin >50 mg/dL with doses of 50 and 60 mg/kg/7 days and 120 mg/kg/14 days. Doses of 250 mg/kg/28 days produced C_{min} >50 mg/dL for only 22 days. Doses of 180 mg/kg/21 days can maintain C_{min} >50 mg/dL for 85% of the time
Vidal et al[75]	7 (PK)	36 (3)	NP	Various regimens	Regimens of 60 mg/kg/week and 120 mg/kg/14 days produced C_{min} >50 mg/dL in 100% of patients. Doses of 180 mg/kg/ 21 days produced C_{min} >50 mg/dL in 76% of patients

*AAT indicates α_1-antitrypsin; BAL, bronchoalveolar lavage; C_{min}, minimum concentration at steady state; RID, radial immunodiffusion; NP, nephelometry; PK, pharmacokinetic model of infused AAT.
†All the concentrations referred to are trough levels before the subsequent dose.
‡The protective threshold value is considered to be 80 g/L as measured by radial immunodiffusion and 50 g/L by nephelometry[1].

because they are asymptomatic or have stable lung function.[25,66]

Data from the main studies that have evaluated the efficacy or effectiveness of augmentation therapy are shown in Table 12.

Safety

Intravenous infusion of human AAT for the chronic treatment of emphysema caused by AAT deficiency has been shown to be very safe. This treatment was first administered in 1987, and no acute reactions were observed.[63] It should be noted that no adverse reactions to protein overload have been observed after long-term regular monthly administration of high doses of AAT.[41,64,70] In the largest database of adverse effects (the NHLBI Registry) the frequency of such effects was 0.02 per patient per month, but only 9% of these were considered serious and only 1.7% required emergency department attention or led to hospitalization. Up to 85% of patients reported no adverse effects. The most common adverse effects were headache (47%), dizziness (17%), nausea (9%), and dyspnea (9%). No cases have been reported of transmission of human immunodeficiency virus, prion diseases, or hepatitis A, B, C, or delta. Patients who received weekly infusions reported a higher frequency of both adverse effects and adverse effects considered to be serious.[71]

Products Available for Intravenous Administration

In Spain, there are currently 2 AAT preparations derived from human plasma available for intravenous administration:

– Prolastin (QF Bayer, S.A.), which is supplied in powder form for reconstitution in 50 ml vials. After reconstitution, each vial contains at least 20 mg/mL providing a total of 1000 mg of AAT.

– Trypsone (Instituto Grifols, S.A.), which is supplied in powder form for reconstitution in 25 or 50 mL vials. After reconstitution, each vial contains at least 20 mg/mL providing a total of 500 mg or 1000 mg of AAT respectively.

In the only trial carried out to date, Trypsone achieved a C_{min} in serum equivalent to the levels obtained with Prolastin. The antielastase capacity of the AAT levels in bronchoalveolar lavage was also equivalent for both preparations.[72]

Treatment is administered in the day hospital sections of hospitals. The product for infusion must be prepared by the hospital pharmacy after the patient has arrived and must be infused as soon as possible because the period of activity after reconstitution is between 3 and 4 hours. The continuous perfusion rate should be under 0.08 mL/kg/min.

Treatment Criteria

Augmentation therapy is only indicated in patients with pulmonary emphysema secondary to AAT deficiency. It has no effect on liver disease associated with this deficiency. The possible benefits of this therapy in the management of other less common manifestations of AAT deficiency, such as panniculitis, are not documented.

Augmentation therapy should only be prescribed to patients with severe AAT deficiency, a PiZZ phenotype,

TABLE 12
Efficacy or Clinical Effectiveness of AAT Augmentation Therapy*

Author	Dose	Design	Outcome Measure	Results
Wencker et al[66]	60 mg/kg/7 days	Observational cohort with no control group	Decline in FEV_1	In patients with FEV_1 <30%, decline of 35.6 mL/year; with FEV_1 =30%-65%, decline of 64 mL/year
Seersholm et al[65]	60 mg/kg/7 days	Observational cohort with control group	Decline in FEV_1	In patients with FEV_1 =31%-65%, therapy slowed down the decline in FEV_1 by 21 mL/year
Schwaiblmair et al[77]	60 mg/kg/7 days	Observational cohort with no control group	Decline in FEV_1	Decline in FEV_1 of 35.6 mL/year for 36 months, lower than historical controls
NHLBI Registry[25]	33%, weekly doses; 43%, every 14 days; and 24%, monthly	Observational cohort with and untreated control group	Decline in FEV_1 and survival	In patients with FEV_1 =35%-49%, treatment slowed down the decline in FEV_1 by 27 mL/year: relative risk of death with treatment, 0.64
Dirksen et al[64]	250 mg/kg/28 days	Double-blind randomized controlled trial	Decline in FEV_1 and pulmonary density as measured by CT	Loss of pulmonary tissue 2.6 g/L/year with placebo and 1.5 g/L/year with therapy (P=.07)
Gottlieb et al[80]	60 mg/kg/7 days	Descriptive	Urine desmosine	Treatment did not reduce urinary excretion of desmosine
Lieberman[68]	55% weekly doses, 37% every 2 weeks, and 8% monthly	Observational (surveys conducted via the Internet)	Frequency of bronchial infections	The number of bronchial infections went from 3-5 per year before treatment to 0-1 per year after treatment
Wencker[66]	60 mg/kg/7 days	Observational (pre-and post-treatment)	Decline in FEV_1	The decline in FEV_1 went from 49.2 mL/year before treatment to 34.2 mL/year after treatment
Stockley[69]	60 mg/kg/7 days	Descriptive	Inflammatory markers in sputum	After treatment LTB4 was significantly reduced and IL-8 was reduced but not significantly

*Adapted from Stoller.[81] AAT indicates α_1-antitrypsin; FEV_1, forced expiratory volume in 1 second; NHLBI, National Heart, Lung, and Blood Institute; CT, computed tomography; LTB4, leukotriene B4; and IL-8, interleukin.[8]

or a rare deficient variant, and functional evidence of pulmonary emphysema.[32] In nonindex cases (those in which the deficiency is diagnosed through family screening rather than as a result of respiratory symptoms), accelerated loss of lung function for at least 1 year should be demonstrated.

This therapy is not indicated in heterozygous PiMZ or PiSZ patients. Owing to the fact that blood derivatives may contain traces of IgA, and that patients with IgA deficiency may have circulating anti-IgA antibodies, the presence of IgA deficiency must be ruled out before augmentation therapy is started. The treatment criteria are shown in Table 13.

Routine vaccination against hepatitis A and B before treatment is not recommended at this time (Table 14).[1]

TABLE 13
Criteria for Starting Augmentation Therapy. Patients Must Fulfill All of the Criteria*

1. Over 18 years of age
2. α_1-antitrypsin deficiency demonstrated by the presence of serum concentrations less than 35% of normal
3. PiZZ defective phenotype or rare defective variants
4. Nonsmoker at least during the previous 6 months
5. Pulmonary emphysema demonstrated by symptoms and FEV_1/FVC <70% and FEV_1 <80%
6. In nonindex cases, accelerated loss of lung function during a minimum of 1 year should be demonstrated in patients with an FEV_1 of 70%–80%
7. IgA deficiency must be ruled out
8. Patients must be willing to undergo treatment on a regular basis at the day hospital

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; and Ig, immunoglobulin.

TABLE 14
Tests Required Before Augmentation Therapy is Started

Immunoglobulins
Lung function testing
High resolution computed tomography
Complete liver function analysis

TABLE 15
Recommended Dosage Regimens for Augmentation Therapy

1. 120 mg/kg/14 days
2. 180 mg/kg/21 days
3. 60 mg/kg/7 days*
4. 50 mg/kg/7 days

*Regimen recommended in the manufacturer's prescribing information.

Recommended Dosage and Administration

No single dosage regimen exists for AAT augmentation therapy. The prescribing information sheets for the products currently available recommend—in the absence of any other medical indication—a dosage of 60 mg/kg/week because this is the most well documented regimen and the one that was studied first. However, the safety and efficacy of other regimens have been demonstrated in several studies. In total, 67% of patients in the USA whose data is on the NHLBI registry have been administered therapy at intervals other than 1 week. In light of these data together with the difficulties most patients have with a lifetime weekly regimen and the demonstration that monthly administration produced very low C_{min} values,[41,64,70] the general recommendation of the Spanish Registry is a dosage of 180 mg/kg/21 days.[32,41] This is the regimen that has been used in most Spanish hospitals over the last 10 years.[73]

Today, new pharmacokinetic studies have provided data on the behavior of AAT infused at different intervals, and this has made it possible to establish a wider variety of dosage regimens.[74,75] These new regimens are shown in Table 15.

Administration of 50 mg/kg/7 days and 120 mg/kg/14 days have been shown to produce C_{min} values above the threshold protective level in over 90% of patients. Administration of 180 mg/kg/21 days produces protective C_{min} values for approximately 85% of the interval between doses. In the absence of conclusive studies on the relationship between clinical efficacy and pharmacokinetic measurements, dosage regimens must be chosen on a patient-by-patient basis and will be the result of a compromise between biochemical efficacy, the patient's expectations and availability, and the possibilities of the hospital.

Measurement of C_{min} values is not recommended because the interpretation of the findings is complex and subsequent adjustment of the dosage regimen would require an individual pharmacokinetic study. When it is suspected that a dose adjustment is needed, the necessary study should be undertaken by a facility with experience in pharmacokinetics.

Other Treatments

Recommendations for the management of patients with emphysema secondary to AAT deficiency are similar to those that apply to patients with COPD who have normal AAT levels. These patients should receive routine treatment with inhaled bronchodilators supplemented, when indicated, by inhaled corticosteroids. Annual influenza and pneumococcal vaccination is recommended because it has been demonstrated that these patients have a good specific antibody response.[67]

Exacerbations are characterized in AAT deficient patients by an excess of elastase activity, much more marked than in AAT-replete COPD patients.[45] For this reason, exacerbations must be treated energetically and as early as possible by increasing the bronchodilator dosage, administering short courses of oral corticosteroids, and prescribing antibiotics when changes are observed in the quantity or characteristics of sputum.

Supplemental oxygen should be considered when the case fulfills the conventional criteria for this treatment. Pulmonary rehabilitation should be offered to patients with functional impairment.

Lung transplantation is an option that can be offered to selected patients with severe disease. The results of

lung volume reduction surgery in patients with AAT deficiency have been inconclusive, and they are not considered to be ideal candidates for this intervention owing to the morphological characteristics of their pulmonary impairment.[76]

As a general rule, a quarterly visit to the treating physician and simple spirometry is recommended. Static lung volumes and carbon monoxide transfer should be measured once a year. Arterial blood gas analysis and chest computed tomography should be performed when justified by clinical changes (Table 10).

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