Arch Bronconeumol. 2015;51(4):185–192

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Special article

Indications for Active Case Searches and Intravenous Alpha-1 Antitrypsin Treatment for Patients With Alpha-1 Antitrypsin Deficiency Chronic Pulmonary Obstructive Disease: An Update☆

Francisco Casas,[a] Ignacio Blanco,[b] María Teresa Martínez,[c] Ana Bustamante,[d] Marc Miravitlles,[e] Sergio Cadenas,[f] José M. Hernández,[g] Lourdes Lázaro,[h] Esther Rodríguez,[e] Francisco Rodríguez-Frías,[i] María Torres,[j] Beatriz Lara[k,*]

[a] *Unidad de Gestión Clínica de Neumología, Hospital Universitario San Cecilio, Granada, Spain*
[b] *Registro Español de pacientes con déficit de alfa-1 antitripsina, Fundación Española de Pulmón, Respira, SEPAR*
[c] *Servicio de Neumología, Hospital Universitario Doce de Octubre, Madrid, Spain*
[d] *Servicio de Neumología, Hospital de Sierrallana, Torrelavega, Cantabria, Spain*
[e] *Servicio de Neumología, Hospital Universitari Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain*
[f] *Servicio de Neumología, Hospital Clínico Universitario de Salamanca, Salamanca, Spain*
[g] *Servicio de Neumología, Hospital General de la Palma, La Palma, Santa Cruz de Tenerife, Spain*
[h] *Servicio de Neumología, Hospital Universitario de Burgos, Burgos, Spain*
[i] *Servicio de Bioquímica, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[j] *Servicio de Neumología, Complexo Universitario de Vigo, Pontevedra, Spain*
[k] *Servicio de Neumología, Hospital Universitario Arnau de Vilanova, Lleida, Spain*

ARTICLE INFO

Article history:
Received 7 February 2014
Accepted 26 May 2014
Available online 14 January 2015

Keywords:
Alpha-1 antitrypsin deficiency
Diagnoses
Treatment
Spanish Registry of Patients with alpha-1 antitrypsin deficiency

ABSTRACT

The effect of hereditary alpha-1 antitrypsin (AAT) deficiency can manifest clinically in the form of chronic obstructive pulmonary disease (COPD). AAT deficiency (AATD) is defined as a serum concentration lower than 35% of the expected mean value or 50 mg/dl (determined by nephelometry). It is associated in over 95% of cases with Pi*ZZ genotypes, and much less frequently with other genotypes resulting from combinations of Z, S, rare and null alleles. A systematic qualitative review was made of 107 articles, focusing mainly on an active search for AATD in COPD patients and intravenous (iv) treatment with AAT. On the basis of this review, the consultant committee of the Spanish Registry of Patients with AATD recommends that all COPD patients be screened for AATD with the determination of AAT serum concentrations, and when these are low, the evaluation must be completed with phenotyping and, on occasions, genotyping. Patients with severe AATD COPD should receive both the pharmacological and non-pharmacological treatments recommended in the COPD guidelines. There is enough evidence from large observational studies and randomized placebo-controlled clinical trials to show that the administration of iv AAT reduces mortality and slows the progression of emphysema, hence its indication in selected cases that meet the inclusion criteria stipulated in international guidelines.

The administration of periodic infusions of AAT is the only specific treatment for delaying the progression of emphysema associated with AATD.

☆ Please cite this article as: Casas F, Blanco I, Martínez MT, Bustamante A, Miravitlles M, Cadenas S, et al. Actualización sobre indicaciones de búsqueda activa de casos y tratamiento con alfa-1 antitripsina por vía intravenosa en pacientes con enfermedad pulmonar obstructiva crónica asociada a déficit de alfa-1 antitripsina. Arch Bronconeumol. 2015;51:185–192.

* Corresponding author.
E-mail address: beat1135@gmail.com (B. Lara).

Actualización sobre indicaciones de búsqueda activa de casos y tratamiento con alfa-1 antitripsina por vía intravenosa en pacientes con enfermedad pulmonar obstructiva crónica asociada a déficit de alfa-1 antitripsina

Palabras clave:
Déficit de alfa-1 antitripsina
Diagnóstico
Tratamiento
Registro de Pacientes con Déficit de Alfa-1 Antitripsina

R E S U M E N

El déficit hereditario de la alfa-1 antitripsina (AAT) se puede manifestar clínicamente como una enfermedad pulmonar obstructiva crónica (EPOC). Se define por una concentración sérica por debajo del 35% del valor medio esperado, o 50 mg/dL (medida por nefelometría) y está relacionado en más del 95% de los casos, con genotipos Pi*ZZ, y muy infrecuentemente con otros genotipos resultantes de combinaciones entre alelos Z, S, raros y nulos. Se ha realizado una revisión sistemática cualitativa de 107 artículos, centrados principalmente en la búsqueda activa del déficit de AAT (DAAT) en pacientes con EPOC y en el tratamiento con AAT por vía intravenosa (iv). El comité asesor del Registro Español de pacientes con DAAT, sobre la base de esta revisión, considera que se debe descartar el DAAT, mediante la cuantificación de las concentraciones séricas de AAT, en todos los pacientes con EPOC y cuando sean bajas se debe completar el estudio mediante la determinación del fenotipo y, en ocasiones, del genotipo. El tratamiento de los individuos con EPOC asociado a DAAT grave debe incluir el tratamiento farmacológico y no farmacológico recomendado en las normativas de la EPOC. Existe suficiente evidencia, derivada de grandes estudios observacionales y de ensayos clínicos aleatorizados con placebo, que demuestran que el tratamiento con AAT iv disminuye la mortalidad y reduce la velocidad de progresión del enfisema, por lo que está indicado en casos seleccionados que cumplan los criterios de inclusión establecidos en las normativas internacionales.

La terapia con infusiones iv periódicas de AAT es el único tratamiento específico que existe para frenar la progresión del enfisema asociado al DAAT.

Introduction

Hereditary alpha-1 antitrypsin (AAT) deficiency can manifest clinically in the form of chronic obstructive pulmonary disease (COPD) (typically as panacinar pulmonary emphysema), liver cirrhosis at any age and, less commonly, as panniculitis, systemic vasculitis and other diseases.[1] Severe AAT deficiency (AATD) is defined as a serum AAT level lower than 35% of the expected mean value or less than 50 mg/dl (determined by nephelometry). It is associated with Pi*ZZ genotypes in over 95% of cases, and much less frequently with other genotypes resulting from combinations of Z, S, rare and null alleles.[2]

Since the detection of severe AATD cases involves genetic counseling, the study of first-degree relatives and, in selected cases, the administration of regular intravenous (IV) AAT infusions, in 2006, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), in collaboration with the Spanish Registry of Patients with AATD (REDAAT) advisory committee, published guidelines on the diagnosis and treatment of AATD, the basic concepts of which remain valid today.[3] However, several subsequent studies[4–7] have provided new data supporting the importance of detecting AATD in individuals with COPD and the use of replacement therapy in patients with COPD and severe AATD,[8–13] all of which justify this update.

Methodology

The authors performed a literature search of articles published between 1985 and 2013 in the MEDLINE, EMBASE and Cochrane Library databases, using the keywords: "alpha-1 antitrypsin deficiency", "COPD", "asthma", "bronchiectasis", "augmentation therapy" and "replacement therapy". Meta-analyses and systematic reviews by other authors, based on quality of scientific evidence, as well as some articles cited in those selected previously and not detected in the databases, were also included for analysis.

A total of 289 abstracts were obtained using the terms "alpha-1 antitrypsin deficiency" and "COPD"; 154 using "alpha-1 antitrypsin deficiency" and "asthma"; 87 using "alpha-1 antitrypsin deficiency" and "bronchiectasis"; 129 using "alpha-1 antitrypsin deficiency" and "augmentation therapy"; and 71 using "alpha-1 antitrypsin deficiency" and "replacement therapy".

After 3 general meetings and 1 final single-subject meeting, we performed a qualitative systematic analysis of the articles selected in order to draw up this document. After deleting duplicates found in the various searches, and using the information provided in the abstract of the articles selected (or the full text when this was not sufficiently explicit), 107 articles[1–107] were chosen by consensus. Most were focused on the active search for AATD in COPD patients and on replacement therapy in patients with severe AATD-associated COPD. The authors individually assessed the manuscripts considered potentially useful, and rated them according to GRADE System criteria for grading the quality of evidence and strength of recommendations, Regulations for Writing SEPAR Guidelines[108,109] and American College of Chest Physicians Task Force[110] criteria, amended by the Canadian Thoracic Society COPD Clinical Assembly Alpha-1 Antitrypsin Deficiency Expert Working Group.[13] After reviewing the results, the conclusions described below were agreed among the members of the advisory committee.

Results

The results of the qualitative systematic analysis are summarized in Tables 1 and 2. It should be noted that the REDAAT working group detected major shortcomings in the literature, which highlight the need for future high quality studies to address several of the issues raised. Even so, analysis of the 4 papers selected[49,54,71,93] and a recent high-quality meta-analysis[13] focusing on research of AATD in COPD suggest that AATD should be ruled out by measuring serum AAT concentrations in all patients with COPD, and when these are low, the study should be completed by phenotyping and, occasionally, genotyping (consistent recommendation with high quality evidence, which confirms the recommendations proposed in the 2006 guidelines).[3]

The working group, based on the level of evidence provided by 13 specific studies on IV AAT treatment,[4,5,10,12,13,37,40,42,46,53,55,83,96] considers that replacement therapy is indicated in patients

Table 1
Summary of REDAAT Recommendations on ATTD Screening in COPD, Bronchiectasis and Bronchial Asthma, and on the Use of Replacement Therapy.

Strength of recommendation	REDAAT recommendations	Quality of evidence
Consistent recommendation	The working group recommends determination of plasma AAT concentrations in all subjects with COPD[a]	High quality evidence
Consistent recommendation	This working group does not recommend routine determination of AAT concentrations in patients with bronchiectasis. Testing should be on a case-by-case basis[b]	Low quality evidence
Consistent recommendation	This working group does not recommend routine determination of AAT concentrations in asthmatic patients. Testing should be on a case-by-case basis[b]	Low quality evidence
Consistent recommendation	IV AAT replacement therapy is indicated in patients who are never-smokers or former smokers with COPD associated with severe AAT deficiency[d], whose FEV_1 is less than 80% of predicted, and who are correctly treated (pharmacological and non-pharmacological treatment of COPD), in whom respiratory functional decline and/or emphysema progression has been documented[c]	Moderate quality evidence

AAT: alpha-1 antitrypsin; IV: intravenous; AATD: alpha-1 antitrypsin deficiency; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in the first second; REDAAT: Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency.

[a] Consistent recommendation, high quality evidence. Can be applied to most patients in most circumstances.

[b] Consistent recommendation, low quality evidence. May change when other tests are available.

[c] Consistent recommendation, moderate quality evidence. May change when other tests are available.

[d] Severe deficiency is defined as serum AAT concentrations ≤50 mg/dl, measured by nephelometry. It is generally associated with PIZZ phenotypes and combinations of rare and null alleles, with each other or with Z and S. AATD is not considered severe when it is associated with the MZ phenotypes or most SZ phenotypes, except for those with AAT concentrations ≤50 mg/dl.

with severe AATD (defined as an AAT concentration ≤50 mg/dl, measured by nephelometry), never-smokers or former smokers, diagnosed with COPD and lung function decline (FEV_1 <80% of predicted value), with documented loss of lung function or emphysema progression, despite optimal pharmacological and non-pharmacological treatment of COPD. Replacement therapy is not indicated in Pi*MZ heterozygotes or in most Pi*SZ individuals, except in rare cases of SZ heterozygotes with serum AAT concentrations less than or equal to 50 mg/dl who meet the other criteria listed in Tables 3 and 4 (consistent recommendation with moderate quality evidence, and in accordance with SEPAR guidelines).[3] Replacement therapy is not indicated for liver disease caused by AATD.

With regard to the results of 3 studies[6,33,48] on the prevalence of AATD in patients with bronchiectasis and 1 meta-analysis,[13] the REDAAT working group does not recommend routine determination of AAT concentrations in patients with bronchiectasis. This practice should be determined on a case-by-case basis (consistent recommendation with low quality evidence).

Considering the results of 5 studies on the prevalence of AATD in asthmatic patients[7,49,54,56,70] and 1 meta-analysis,[13] the authors do not recommend routine measurement of AAT concentrations in these patients. This practice should be determined on a case-by-case basis (consistent recommendation with low quality evidence).

Discussion

The results shown support the recommendation to rule out AATD in all patients with COPD. This was proposed by the World Health Organization as far back as 1997,[35] and was subsequently included in various guidelines, including those of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and SEPAR.[1,3] Furthermore, although there are insufficient studies to precisely establish a strength of recommendation, the authors also advise ruling out AATD in first-degree relatives of the index case, even if they are asymptomatic, due to the high probability that some may be carriers of severe mutations and may benefit from genetic counseling and preventive measures (the most important being to avoid inhaling cigarette smoke and other pollutants).[1,3]

With respect to other obstructive airways diseases, the REDAAT working group agrees with other authors[13] in not recommending routine determination of AAT levels to rule out severe deficiency in patients with either bronchiectasis or asthma, leaving the decision to request this test in specific cases at the discretion of the attending physician, e.g. in patients with emphysema lesions associated with the aforementioned conditions.

Quantitative serum AAT measurement, most often by nephelometry, is the basis for diagnosing AATD. When the AAT concentration is lower than the reference range, the study should be completed by phenotyping (protein or allele variants). The combination of both techniques is sufficient to clarify most cases of AATD. Isoelectric focusing is the most widely used method to identify allelic variants, and can characterize up to 30 AAT deficiency variants.

Since each phenotype has its own range of AAT values, in cases in which the AAT concentration is not consistent with the phenotype, the presence of null or rare deficient alleles should be suspected, and consequently, the genotype should be determined.[95] AAT gene sequencing by real time polymerase chain reaction (PCR) is the reference method for clarifying these discordant cases (Fig. 1).[3,95]

The dried blood spot samples used in screening programs indicate the presence or absence of the alleles studied, but cannot exclude the presence of other deficiency alleles. Genotyping must therefore be performed in cases in which the AAT concentration is not consistent with the phenotype. Dried blood spot samples can currently be genotyped using PCR sequencing. These methods are reliable, but each laboratory must report the method used and its possible limitations.

With respect to treatment, the REDAAT working group considers that:

- Treatment of individuals with severe AATD-associated COPD should include the pharmacological and non-pharmacological treatment recommended in COPD guidelines.[111]
- There is sufficient evidence available (although of moderate quality[4,5,10,12,13,37,40,42,46,53,55,83,96]) to recommend replacement therapy in individuals with COPD associated with severe AATD (serum AAT concentrations ≤50 mg/dl), never-smokers or former smokers, whose FEV_1 is less than 80% of predicted and who have loss of lung function or emphysema progression, despite standard COPD treatment.
- Regular AAT replacement therapy is the only specific treatment to slow the progression of AATD-associated emphysema. Its efficacy has been demonstrated in randomized, double-blind,

Table 2
Summary of Studies Evaluating Augmentation Therapy.

Authors	Dose	Type of study	Results measure	Results	Level of evidence
Non-randomized studies					
Seersholm et al.[37] (1997)	60 mg/kg/7 days	Observational study with control group (n=295)	FEV_1 decline	Reduction in FEV_1 decline in the treatment group (56 vs 75 ml/year; *P*=.02). Greater benefit in patients with FEV_1 31%–65%	C2
American AAT Deficiency Registry Study Group[40] (1998)	33% weekly doses; 43% fortnightly and 24% monthly	Observational study with control group (n=1129)	FEV_1 decline Mortality	Reduction in mortality (OR=0.64; *P*=.02) The FEV_1 decline is slower in patients receiving IV replacement therapy with FEV_1 35%–49% (66 vs 93 ml/year; *P*=.03)	C2
Wencker et al.[53] (2001)	60 mg/kg/7 days	Observational cohort with no control group (n=96)	FEV_1 decline	The rate of FEV_1 decline was slower during the treatment period (49.2 vs 34.2 ml/year, *P*=.019) and was slower in patients with FEV_1 >65% (256 vs 53 ml/year, *P*=.001)	C2
Tonelli et al.[83] (2009)		Observational study with control group (n=164)	FEV_1 decline Mortality	Gain in FEV_1 of 10.6 ± 21.4 ml/year vs loss of 36.96 ± 12.1 ml/year; *P*=.05) No differences in mortality	C2
Ma et al.[42] (2013)	60 mg/kg/7 days	Observational cohort study with control group (n=100)	Plasma desmosine and isodesmosine	A significant reduction in desmosine and isodesmosine levels in the patient cohort on IV AAT replacement therapy vs untreated patients (*P*<.0001), with values similar to the normal population	C1
Ma et al.[42] (2013)	60 mg/kg/7 days	Observational study with no control group (n=10)	Desmosine and isodesmosine in bronchoalveolar lavage and plasma	Significant reduction in desmosine and isodesmosine levels in bronchoalveolar lavage (*P*=.0273) and in plasma at 12 (*P*=.0038) and 24 weeks (0.0038) after receiving IV replacement therapy	C2
Randomized studies					
Dirksen et al.[4] (2009)	60 mg/kg/7 days	Randomized, double-blind, placebo-controlled study (n=77) (COPD with FEV_1 = 25%–80%)	Lung function, quality of life, exacerbations and loss of CT lung density	Reduction in loss of CT lung density in treated patients (*P*=.049) No differences in FEV_1 or DLCO No differences in frequency of exacerbations, but less severe in the treatment group	B1
Meta-analyses					
Chapman et al.[12] (2009)		Meta-analysis of studies in patients on replacement therapy vs controls in the Canadian Registry (n=1509)	FEV_1 decline	Reduction in FEV_1 decline in patients on IV replacement therapy by 26% (17.9 ml/year). Effect due to subgroup of subjects with FEV_1 30%–65%	B1
Gøtzsche and Johansen[10] (2010)	60 mg/kg/7 days	Cochrane meta-analysis of 2 randomized, placebo-controlled studies (n=140)	Decline in FEV1, DLCO and loss of CT lung density Exacerbations	The lung density loss was less in patients on IV replacement therapy (*P*=.03) No differences in lung function No difference in exacerbations	B2
Stockley et al.[5] (2010)	60 mg/kg/7 days	Comprehensive analysis of lung density (n=119)	Decline in lung density and FEV_1	Less lung density loss in treated patients (1.73 vs 2.74 g/l, *P*=.006) No differences in FEV_1 decline	A1
Marciniuk et al.[13] (2012)		Meta-analysis of all studies in patients on IV replacement therapy vs controls	All parameters	Reduction in CT lung density loss and reduction in mortality	B1
Studies in exacerbations					
Lieberman[46] (2000)	55% weekly doses, 37% fortnightly and 8% monthly	Observational (internet survey) (n=89)	Frequency of exacerbations	Reduction in the frequency of exacerbations from 3–5/year to 0–1/year after starting IV replacement therapy	C2
Stockley et al.[55] (2002)	60 mg/kg/7 days	Descriptive study (n=12)	Inflammatory markers in sputum	Significant reduction in LTB4 in sputum following treatment	C2
Barros-Tizón et al.[96] (2012)	180 mg/kg/21 days	Retrospective study (pre–post IV replacement therapy)	Frequency and severity of exacerbations and hospitalization costs	Reduction in the number and severity of exacerbations and hospitalization-derived costs	C1

AAT: alpha-1 antitrypsin; IV: intravenous; AATD: alpha-1 antitrypsin deficiency; DLCO: carbon monoxide diffusing capacity; FEV_1: forced expiratory volume in the first second; LTB4: leukotriene B4; CT: computed tomography.

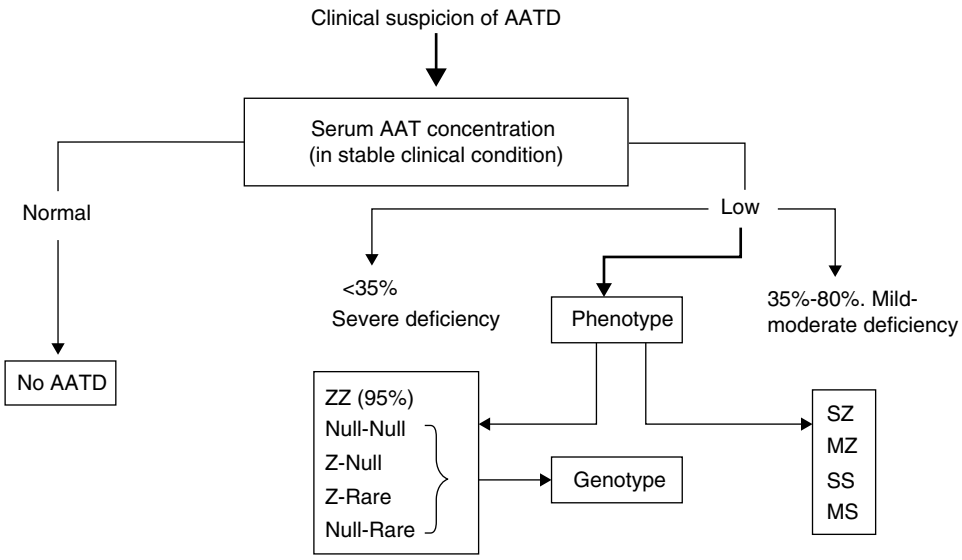

Fig. 1. Diagnostic algorithm for AAT deficiency (AATD).
Taken from Vidal et al.[3]

placebo-controlled studies, with analysis of the decline in lung density as the primary outcome measure.

Table 3 specifies the REDAAT requirements for replacement therapy. Table 4 provides more detail on the procedure to be followed before commencing treatment. Table 2 lists the main studies

Table 3
REDAAT Criteria for IV AAT Therapy.[a]

1. Aged 18 years or over
2. AATD demonstrated by serum concentrations ≤50 mg/dl
3. Never-smokers or ex-smokers for at least the last 6 months
4. Pulmonary emphysema demonstrated by lung function tests and/or chest HRCT
5. COPD with FEV_1 <80% of predicted,[b] who are receiving optimal pharmacological and non-pharmacological treatment
6. Do not have immunoglobulin A deficiency
7. Prepared to receive regular treatment at a day hospital

AAT: alpha-1 antitrypsin; IV: intravenous; AATD: alpha-1 antitrypsin deficiency; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in the first second; REDAAT: high resolution computed tomography.

[a] All criteria must be met.

[b] Intravenous AAT therapy should not be discontinued in a patient who has already been treated if their lung function deteriorates and/or their FEV_1 falls below 25%.

Table 4
Procedure to be Followed Prior to Commencing IV AAT Replacement Therapy.

Informed consent[a]
Additional tests
Determination of serum immunoglobulins
Complete liver function tests
Serology for hepatitis-B virus and human immunodeficiency virus
Lung function tests: spirometry, lung volumes and carbon monoxide diffusing capacity
Arterial blood gases: if peripheral oxygen saturation is less than 92%
Chest HRCT scan
Hepatitis B vaccination

AAT: alpha-1 antitrypsin; IV: intravenous; HRCT: high resolution computed tomography.

[a] Available on the website of the (http://www.redaat.es/presentacion.php) and the Andalusia Regional Government Health website, in the area on Informed Consent for Respiratory Medicine procedures (http://www.juntadeandalucia.es/salud/sites/csalud/contenidos/Informacion_General/p_3_p_11_procedimiento_consentimiento_informado/neumologia?perfil=org).

on its efficacy or effectiveness in patients with COPD and severe AAT, and the quality of evidence.

The efficacy of replacement therapy is defined on the basis of biochemical and clinical criteria. Biochemical efficacy has been demonstrated, as IV AAT administration increases serum values above those considered protective, increases its concentration in alveolar fluid, and neutralizes neutrophil elastase.[18,19] It has been agreed that the serum AAT value that protects the lung against free neutrophil elastase should be greater than or equal to 50 mg/dl (if determined by nephelometry), 80 mg/dl (if measured by radial immunodiffusion) or 11 μM/l (if the NHLBI standard from the US Registry is used). This widely disseminated and applied laboratory criterion is based on studies by Wewers et al. (1987)[18] and Turino et al. (1996).[34] The former[18] shows the biochemical efficacy of AAT replacement therapy (*moderate quality evidence*) but is insufficient to establish a protective cut-off value. The latter[34] describes the clinical characteristics of 59 SZ subjects, of whom 52% were receiving or had received IV AAT treatment, and has been used to justify the biochemical criteria for patient selection for AAT replacement therapy. However, the quality of scientific evidence is very low, and its findings cannot be extrapolated to the other SZ subjects. Similar arguments are applicable to another descriptive study in 25 SZ subjects.[17]

Various studies have shown the clinical efficacy of replacement therapy,[4,10,12,13,37,40,42,46,53,55,83,96] the most important being the study by Dirksen et al.,[4] a randomized, double-blind, placebo-controlled trial in which the primary endpoint was loss of lung density measured by computed tomography (CT). This showed a significantly lower annual loss of lung density in subjects who received AAT replacement therapy compared to those who did not. There were no differences in lung function, exacerbations and quality of life (St. George's questionnaire) between groups. A subsequent analysis by Stockley et al.,[5] combining data from these 2 trials, confirmed lung tissue loss was lower in subjects treated with IV AAT vs placebo (P=.006).

A meta-analysis conducted by Chapman et al. on 5 studies with a total of 1509 patients found that AAT replacement therapy significantly reduced annual decline in FEV_1, especially in patients with an FEV_1 between 30% and 65% of predicted.[12]

In another meta-analysis, Gøtzsche and Johansen[10] concluded that AAT replacement therapy cannot be recommended, based on its lack of efficacy and high cost. However, this analysis has been

widely criticized by the scientific community and patient associations, such as the Alpha-One Foundation, for its partiality. It bases its conclusions on 2 studies with a total of 140 patients and downplays the importance of measuring loss of CT lung density, when this loss is a central feature in the natural history of these patients. Furthermore, it excludes the results of some observational studies that support the clinical efficacy of AAT replacement therapy, and which have been the basis for its indication in ATS, ERS and American College of Physicians guidelines, including the multicenter prospective cohort study conducted in 1129 patients with AATD in the American Registry. This study showed a 36% reduction in mortality (Relative Risk = 0.64) and a significant reduction in the FEV_1 decline in the subgroup of patients with FEV_1 values between 35% and 49%.[40]

Finally, a recent, extremely thorough meta-analysis by the Canadian Thoracic Society[13] recommends replacement therapy in patients with COPD and FEV_1 between 25% and 80%, never-smokers or former smokers, with documented AATD (11 μmol/l), who are receiving optimal pharmacological and non-pharmacological treatment (including rehabilitation), because of the benefits that it provides (less loss of lung density, demonstrated by CT densitometry, and reduction in mortality).

In conclusion, severe AAT deficiency is a rare genetic condition that principally manifests clinically as pulmonary emphysema. There is sufficient evidence to recommend AAT replacement therapy (Table 2) in patients who meet certain conditions (Table 3).

This working group is of the opinion that further studies are warranted to better determine the mechanisms that lead to the development of COPD in subjects with AATD, and to determine, with stronger evidence, the AAT level needed to protect the lung from the elastolytic action of elastase, in stable conditions and in the case of exacerbation, as well as the dose of AAT required to reach these protective levels. Finally, the authors believe that better and more cost-effective means for producing and administering AAT must be found.

Funding

The authors have not received any funding for this article.

Conflict of Interest

The Spanish Lung Foundation (Respira) received donations from Laboratorios Grifols for sponsoring activities by the Spanish Registry for Patients with Alpha-1 Antitrypsin Deficiency.

Ana Bustamante received honoraria for lecturing from Grifols, Astra, Boheringer-Ingelheim, Pfizer, Chiesi, and Almirall.

Francisco Casas received honoraria for scientific advice and/or for lecturing from Almirall, AstraZeneca, Boehringer Ingelheim, Grupo Ferrer, GlaxoSmithKline, Grifols, Laboratorios Esteve, Pfizer, Novartis and Takeda.

José María Hernández received honoraria from Grifols for scientific advice and for lecturing.

Lourdes Lázaro received honoraria from Grifols for lecturing.

Beatriz Lara received honoraria for lecturing from Boehringer Ingelheim, Pfizer, Grifols and Novartis.

Marc Miravitlles received honoraria for scientific advice and/or for lecturing from Almirall, AstraZeneca, Bayer Schering Boehringer Ingelheim, Grupo Ferrer, GlaxoSmithKline, Grifols, Laboratorios Esteve, Pfizer, Novartis and Nycomed.

María Torres received honoraria from Grifols for scientific advice.

Acknowledgements

The REDAAT Committee would like to thank Doctors Rafael Vidal, Rosendo Jardí, Juan Carlos Barros-Tizón, Pedro Pablo España and Carlos Escudero for their contribution to the work of the Registry over the years.

References

1. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818–900.
2. Stoller JK, Aboussouan LS. A review of α1-antitrypsin deficiency. Am J Respir Crit Care Med. 2012;185:246–59.
3. Vidal R, Blanco I, Casas F, Jardí R, Miravitlles M, Comité del Registro Nacional de Pacientes con Déficit de Alfa-1-Antitripsina. Normativa SEPAR: diagnóstico y tratamiento del déficit de alfa-1-antitripsina. Arch Bronconeumol. 2006;42:645–59.
4. Dirksen A, Piitulainen E, Parr DG, Deng C, Wencker M, Shaker SB, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. Eur Respir J. 2009;33:1345–53.
5. Stockley RA, Parr DG, Piitulainen E, Stolk J, Stoel BC, Dirksen A. Therapeutic efficacy of α-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. Respir Res. 2010;11:136–44.
6. Parr DG, Guest PG, Reynolds JH, Dowson LJ, Stockley RA. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2007;176:1215–21.
7. Eden E, Holbrook JT, Brantly ML, Turino GM, Wise RA. Prevalence of alpha-1 antitrypsin deficiency in poorly controlled asthma – results from the ALA-ACRC low-dose theophylline trial. J Asthma. 2007;44:605–8.
8. Mascalchi M, Diciotti S, Sverzellati N, Camiciottoli G, Ciccotosto C, Falaschi F, et al. Low agreement of visual rating for detailed quantification of pulmonary emphysema in whole-lung CT. Acta Radiol. 2012;53:53–60.
9. Hogarth DK, Rachelefsky G. Screening and familial testing of patients for alpha 1-antitrypsin deficiency. Chest. 2008;133:981–8.
10. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. 2010:CD007851 (7).
11. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy: systematic review. Dan Med Bull. 2010;57:A4175.
12. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. COPD. 2009;6:177–84.
13. Marciniuk DD, Hernandez P, Balter M, Bourbeau J, Chapman KR, Ford GT, et al., Canadian Thoracic Society COPD Clinical Assembly Alpha-1 Antitrypsin Deficiency Expert Working Group. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2012;19:109–16.
14. Gadek JE, Klein HG, Holland PV, Crystal RG. Replacement therapy of alpha 1-antitrypsin deficiency. Reversal of protease–antiprotease imbalance within the alveolar structures of PiZ subjects. J Clin Invest. 1981;68:1158–65.
15. From the NIH: intravenous replacement therapy for patients with severe alpha 1-antitrypsin deficiency. JAMA. 1982;248:1693.
16. Gadek JE, Crystal RG. Experience with replacement therapy in the destructive lung disease associated with severe alpha-1-antitrypsin deficiency. Am Rev Respir Dis. 1983;127:S45–6.
17. Hutchison DC, Tobin MJ, Cook PJ. Alpha 1 antitrypsin deficiency: clinical and physiological features in heterozygotes of Pi type SZ. A survey by the British Thoracic Association. Br J Dis Chest. 1983;77:28–34.
18. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. N Engl J Med. 1987;316:1055–62.
19. Hubbard RC, Sellers S, Czerski D, Stephens L, Crystal RG. Biochemical efficacy and safety of monthly augmentation therapy for alpha 1-antitrypsin deficiency. JAMA. 1988;260:1259–64.
20. Schmidt EW, Rasche B, Ulmer WT, Konietzko N, Becker M, Fallise JP, et al. Replacement therapy for alpha-1-protease inhibitor deficiency in PiZ subjects with chronic obstructive lung disease. Am J Med. 1988;84:63–9.
21. Eriksson S. Replacement therapy in alpha 1-antitrypsin deficiency. J Intern Med. 1989;225:69–72.
22. Eriksson S, Wu MC. Aspects of treatment in alpha 1-antitrypsin deficiency: insights derived from a Swedish PiZZ series. Eur Respir J Suppl. 1990;9:39s–43s.
23. Vidal R, Miravitlles M, de Gracia X, Gallego B, Morell F. Replacement therapy of emphysema caused by alpha 1-antitrypsin deficiency. Med Clin (Barc). 1991;96:180–2.
24. Hay JW, Robin ED. Cost-effectiveness of alpha-1 antitrypsin replacement therapy in treatment of congenital chronic obstructive pulmonary disease. Am J Public Health. 1991;81:427–33.
25. Barker AF. Alpha 1-antitrypsin-deficiency-related emphysema. J Am Board Fam Pract. 1992;5:489–93.
26. Ad Hoc Committee on alpha-1 antitrypsin replacement therapy of the Standards Committee, Canadian Thoracic Society. Current status

of alpha-1-antitrypsin replacement therapy: recommendations for the management of patients with severe hereditary deficiency. Ad Hoc Committee on Alpha-1-Antitrypsin Replacement Therapy of the Standards Committee, Canadian Thoracic Society. CMAJ. 1992;146:841–4.
27. Burdon J, Cook L, Holmes P, Janus E, Watts S. Alpha-1-antitrypsin replacement therapy – an early Australian experience. Aust N Z J Med. 1992;22:498–9.
28. Cammarata SK, Stone CL, Carey JL, Eichenhorn MS. Failure to achieve adequate serum levels with monthly replacement therapy in alpha 1-antitrypsin deficiency. Chest. 1994;106:651–2.
29. Miravitlles M, Vidal R, Torrella M, Bofill JM, Cotrina M, de Gracia J. Evaluation of replacement therapy in emphysema caused by alpha 1-antitrypsin deficiency. Arch Bronconeumol. 1994;30:479–84.
30. Bhagat R, Swystun VA, Cockcroft DW. Clinical trials needed for alpha 1-antitrypsin replacement therapy. Chest. 1995;108:586–7.
31. Manresa F. The evolution of the replacement treatment of emphysema due to alpha 1-antitrypsin deficiency. Arch Bronconeumol. 1995;31:371–2.
32. Gadek JE, Pacht ER. Pathogenesis of hereditary emphysema and replacement therapy for alpha 1-antitrypsin deficiency. Insight into the more common forms of emphysema. Chest. 1996;110:248s–50s.
33. King MA, Stone JA, Diaz PT, Mueller CF, Becker WJ, Gadek JE. Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. Radiology. 1996;199:137–41.
34. Turino GM, Barker AF, Brantly ML, Cohen AB, Connelly RP, Crystal RG, et al., Alpha 1-Antitrypsin Deficiency Registry Study Group. Clinical features of individuals with PI*SZ phenotype of alpha 1-antitrypsin deficiency. Am J Respir Crit Care Med. 1996;154:1718–25.
35. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. Bull World Health Organ. 1997;75:397–415.
36. Hutchison DC, Hughes MD. Alpha-1-antitrypsin replacement therapy: will its efficacy ever be proved. Eur Respir J. 1997;10:2191–3.
37. Seersholm N, Wencker M, Banik N, Viskum K, Dirksen A, Kok-Jensen A, et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. Eur Respir J. 1997;10:2260–3.
38. Miravitlles M. ¿ Deberíamos administrar tratamiento sustitutivo a los pacientes con déficit de alfa-1 antitripsina? Arch Bronconeumol. 1998;34:109–11.
39. Miravitlles M, Vidal R, Barros-Tizón JC, Bustamante A, España PP, Casas F, et al. Usefulness of a national registry of alpha-1-antitrypsin deficiency. The Spanish experience. Respir Med. 1998;92:1181–7.
40. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med. 1998;158:49–59.
41. Wencker M, Banik N, Buhl R, Seidel R, Konietzko N. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)-alpha1-AT-study group. Eur Respir J. 1998;11:428–33.
42. Ma S, Lin YY, He J, Rouhani FN, Brantly M, Turino GM. Alpha-1 antitrypsin augmentation therapy and biomarkers of elastin degradation. COPD. 2013;10:473–81.
43. Köhnlein T, Klein H, Welte T. Alpha 1-protease inhibitor deficiency. Diagnosis, follow-up and therapy options. Med Klin (Munich). 1999;94:371–6.
44. Stoller JK, Brantly M, Fleming LE, Bean JA, Walsh J. Formation and current results of a patient-organized registry for alpha(1)-antitrypsin deficiency. Chest. 2000;118:843–8.
45. Schluchter MD, Stoller JK, Barker AF, Buist AS, Crystal RG, Donohue JF, et al. Feasibility of a clinical trial of augmentation therapy for alpha(1)-antitrypsin deficiency. The Alpha 1-Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med. 2000;161:796–801.
46. Lieberman J. Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: a new hypothesis with supporting data. Chest. 2000;118:1480–5.
47. Alkins SA, O'Malley P. Should health-care systems pay for replacement therapy in patients with alpha(1)-antitrypsin deficiency? A critical review and cost-effectiveness analysis. Chest. 2000;117:875–80.
48. Cuvelier A, Muir JF, Hellot MF, Benhamou D, Martin JP, Bénichou J, et al. Distribution of alpha(1)-antitrypsin alleles in patients with bronchiectasis. Chest. 2000;117:415–9.
49. Seersholm N, Wilcke JT, Kok-Jensen A, Dirksen A. Risk of hospital admission for obstructive pulmonary disease in alpha(1)-antitrypsin heterozygotes of phenotype PiMZ. Am J Respir Crit Care Med. 2000;161:81–4.
50. Abboud RT, Ford GT, Chapman KR, Standards Committee of the Canadian Thoracic Society. Alpha1-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. Can Respir J. 2001;8:81–8.
51. Dowson LJ, Guest PJ, Hill SL, Holder RL, Stockley RA. High-resolution computed tomography scanning in alpha1-antitrypsin deficiency: relationship to lung function and health status. Eur Respir J. 2001;17:1097–104.
52. Sansom ME, Ferry BL, Sherrell ZP, Chapel HM. A preliminary assessment of alpha-1 antitrypsin S and Z deficiency allele frequencies in common variable immunodeficiency patients with and without bronchiectasis. Clin Exp Immunol. 2002;130:489–94.
53. Wencker M, Fuhrmann B, Banik N, Konietzko N. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen. Longitudinal follow-up of patients with alpha (1)-protease inhibitor deficiency before and during therapy with IV alpha(1)-protease inhibitor. Chest. 2001;119:737–44.
54. Wencker M, Marx A, Konietzko N, Schaefer B, Campbell EJ. Screening for alpha1-Pi deficiency in patients with lung diseases. Eur Respir J. 2002;20:319–24.
55. Stockley RA, Bayley DL, Unsal I, Dowson LJ. The effect of augmentation therapy on bronchial inflammation in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2002;165:1494–8.
56. Miravitlles M, Vilà S, Torrella M, Balcells E, Rodríguez-Frías F, de la Roza C, et al. Influence of deficient alpha1-anti-trypsin phenotypes on clinical characteristics and severity of asthma in adults. Respir Med. 2002;96:186–92.
57. Stoller JK, Fallat R, Schluchter MD, O'Brien RG, Connor JT, Gross N, et al. Augmentation therapy with alpha1-antitrypsin: patterns of use and adverse events. Chest. 2003;123:1425–34.
58. Dawkins PA, Dowson LJ, Guest PJ, Stockley RA. Predictors of mortality in alpha1-antitrypsin deficiency. Thorax. 2003;58:1020–6.
59. Mullins CD, Wang J, Stoller JK. Major components of the direct medical costs of alpha1-antitrypsin deficiency. Chest. 2003;124:826–31.
60. Gildea TR, Shermock KM, Singer ME, Stoller JK. Cost-effectiveness analysis of augmentation therapy for severe alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2003;167:1387–92.
61. Hersh CP, Dahl M, Ly NP, Berkey CS, Nordestgaard BG, Silverman EK. Chronic obstructive pulmonary disease in alpha1-antitrypsin PI MZ heterozygotes: a meta-analysis. Thorax. 2004;59:843–9.
62. Ranes J, Stoller JK. A review of alpha-1 antitrypsin deficiency. Semin Respir Crit Care Med. 2005;26:154–66.
63. Abboud RT, Ford GT, Chapman KR. Emphysema in alpha1-antitrypsin deficiency: does replacement therapy affect outcome? Treat Respir Med. 2005;4:1–8.
64. Shermock KM, Gildea TR, Singer M, Stoller JK. Cost-effectiveness of population screening for alpha-1 antitrypsin deficiency: a decision analysis. COPD. 2005;2:411–8.
65. Stocks JM, Brantly M, Pollock D, Barker A, Kueppers F, Strange C, et al. Multicenter study: the biochemical efficacy, safety and tolerability of a new alpha1-proteinase inhibitor, Zemaira. COPD. 2006;3:17–23.
66. Soy D, de la Roza C, Lara B, Esquinas C, Torres A, Miravitlles M. Alpha-1-antitrypsin deficiency: optimal therapeutic regimen based on population pharmacokinetics. Thorax. 2006;61:1059–64.
67. Vidal R, Padullés N, Sala F, Jardí R, Rodríguez F, Montoro JB. Pharmacokinetics of alpha1-antitrypsin replacement therapy in severe congenital emphysema. Arch Bronconeumol. 2006;42:553–6.
68. Strange C, Stoller JK, Sandhaus RA, Dickson R, Turino G. Results of a survey of patients with alpha-1 antitrypsin deficiency. Respiration. 2006;73:185–90.
69. Abusriwil H, Stockley RA. Alpha-1-antitrypsin replacement therapy: current status. Curr Opin Pulm Med. 2006;12:125–31.
70. Van Veen IH, ten Brinke A, van der Linden AC, Rabe KF, Bel EH. Deficient alpha-1-antitrypsin phenotypes and persistent airflow limitation in severe asthma. Respir Med. 2006;100:1534–9.
71. De Serres FJ, Blanco I, Fernández-Bustillo E. Estimating the risk for alpha-1 antitrypsin deficiency among COPD patients: evidence supporting targeted screening. COPD. 2006;3:133–9.
72. Hericks AJ, Bhat A. An overview of alpha-1 antitrypsin deficiency. Mol Med. 2007;104:255–9.
73. Mordwinkin NM, Louie SG. Aralast: an alpha 1-protease inhibitor for the treatment of alpha-antitrypsin deficiency. Expert Opin Pharmacother. 2007;8:2609–14.
74. Lara B, de la Roza C, Vilà S, Vidal R, Miravitlles M. Development and results of the Spanish registry of patients with alpha-1-antitrypsin deficiency. Int J Chron Obstruct Pulmon Dis. 2007;2:393–8.
75. Wood AM, Stockley RA. Alpha one antitrypsin deficiency: from gene to treatment. Respiration. 2007;74:481–92.
76. Russi EW. Alpha-1 antitrypsin: now available, but do we need it. Swiss Med Wkly. 2008;138:191–6.
77. Aboussouan LS, Stoller JK. Detection of alpha-1 antitrypsin deficiency: a review. Respir Med. 2009;103:335–41.
78. Petrache I, Hajjar J, Campos M. Safety and efficacy of alpha-1-antitrypsin augmentation therapy in the treatment of patients with alpha-1-antitrypsin deficiency. Biologics. 2009;3:193–204.
79. Sandhaus RA. Augmentation therapy in alpha-1 antitrypsin deficiency. COPD. 2009;6:147–8.
80. Silverman EK, Sandhaus RA. Alpha1-antitrypsin deficiency. N Engl J Med. 2009;360:2749–57.
81. Stoller JK, Fallat R, Schluchter MD, O'Brien RG, Connor JT, Gross N, et al. Augmentation therapy with alpha1-antitrypsin: patterns of use and adverse events. Chest. 2009;136 5 Suppl.:e30.
82. Kalsheker NA. Alpha1-antitrypsin deficiency: best clinical practice. J Clin Pathol. 2009;62:865–9.
83. Tonelli AR, Rouhani F, Li N, Schreck P, Brantly ML. Alpha-1-antitrypsin augmentation therapy in deficient individuals enrolled in the Alpha-1 Foundation DNA and Tissue Bank. Int J Chron Obstruct Pulmon Dis. 2009;4:443–52.
84. Dawkins PA, Dawkins CL, Wood AM, Nightingale PG, Stockley JA, Stockley RA. Rate of progression of lung function impairment in alpha1-antitrypsin deficiency. Eur Respir J. 2009;33:1338–44.
85. McCarthy C, Dimitrov BD. Augmentation therapy for alpha-1 antitrypsin deficiency – not enough evidence to support its use yet! COPD. 2010;7:234.
86. Kaplan A, Cosentino L. Alpha1-antitrypsin deficiency: forgotten etiology. Can Fam Physician. 2010;56:19–24.

87. Banauch GI, Brantly M, Izbicki G, Hall C, Shanske A, Chavko R, et al. Accelerated spirometric decline in New York City firefighters with a1-antitrypsin deficiency. Chest. 2010;138:1116–24.
88. Stockley RA. Emerging drugs for alpha-1-antitrypsin deficiency. Expert Opin Emerg Drugs. 2010;15:685–94.
89. Tonelli AR, Brantly ML. Augmentation therapy in alpha-1 antitrypsin deficiency: advances and controversies. Ther Adv Respir Dis. 2010;4:289–312.
90. Lara B. COPD and alpha-1-antitrypsin deficiency. Arch Bronconeumol. 2010;46:2–8.
91. Sandhaus RA. Alpha-1 antitrypsin deficiency: whom to test, whom to treat. Semin Respir Crit Care Med. 2010;31:343–7.
92. Sørheim IC, Bakke P, Gulsvik A, Pillai SG, Johannessen A, Gaarder PI, et al. α1-Antitrypsin protease inhibitor MZ heterozygosity is associated with airflow obstruction in two large cohorts. Chest. 2010;138:1125–32.
93. Kueppers F. The role of augmentation therapy in alpha-1 antitrypsin deficiency. Curr Med Res Opin. 2011;27:579–88.
94. Dickens JA, Lomas DA. Why has it been so difficult to prove the efficacy of alpha-1-antitrypsin replacement therapy Insights from the study of disease pathogenesis. Drug Des Dev Ther. 2011;5:391–405.
95. Rodriguez-Frías F, Miravitlles M, Vidal R, Camos S, Jardí R. Rare alpha-1-antitrypsin variants: are they really so rare. Ther Adv Respir Dis. 2012;6:79–85.
96. Barros-Tizón JC, Torres ML, Blanco I, Martínez MT, Investigators of the rEXA study group. Reduction of severe exacerbations and hospitalization-derived costs in alpha-1-antitrypsin-deficient patients treated with alpha-1-antitrypsin augmentation therapy. Ther Adv Respir Dis. 2012;6:67–78.
97. Miravitlles M. Alpha-1-antitrypsin and other proteinase inhibitors. Curr Opin Pharmacol. 2012;12:309–14.
98. Schmid ST, Koepke J, Dresel M, Hattesohl A, Frenzel E, Perez J, et al. The effects of weekly augmentation therapy in patients with PiZZ α1-antitrypsin deficiency. Int J Chron Obstruct Pulmon Dis. 2012;7:687–96.
99. Mohanka M, Khemasuwan D, Stoller JK. A review of augmentation therapy for alpha-1 antitrypsin deficiency. Expert Opin Biol Ther. 2012;12:685–700.
100. Sclar DA, Evans MA, Robison LM, Skaer TL. α1-Proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to α1-antitrypsin deficiency: number and costs of years of life gained. Clin Drug Invest. 2012;32:353–60.
101. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. COPD. 2013;10:26–34.
102. Stockley RA, Dirksen A, Stolk J. Alpha-1 antitrypsin deficiency: the European experience. COPD. 2013;10:50–3.
103. Wewers MD, Crystal RG. Alpha-1 antitrypsin augmentation therapy. COPD. 2013;10:64–7.
104. Strange C. Airway disease in alpha-1 antitrypsin deficiency. COPD. 2013;10:68–73.
105. Campos MA, Kueppers F, Stocks JM, Strange C, Chen J, Griffin R, et al. Safety and pharmacokinetics of 120 mg/kg versus 60 mg/kg weekly intravenous infusions of alpha-1 proteinase inhibitor in alpha-1 antitrypsin deficiency: a multicenter, randomized, double-blind, crossover Study (SPARK). COPD. 2013;10:687–95.
106. Monk R, Graves M, Williams P, Strange C. Inhaled alpha 1-antitrypsin: gauging patient interest in a new treatment. COPD. 2013;10:411–5.
107. Stockley RA, Miravitlles M, Vogelmeier C. Augmentation therapy for alpha-1 antitrypsin deficiency: towards a personalised approach. Orphanet J Rare Dis. 2013;8:149.
108. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al., ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med. 2006;174:605–14.
109. Alonso-Coello P, Rigau D, Juliana Sanabria A, Plaza V, Miravitlles M, Martínez L. Calidad y fuerza: el sistema GRADE para la formulación de recomendaciones en las guías de práctica clínica. Arch Bronconeumol. 2013;49:261–7.
110. Guyatt G, Gutterman D, Baumann MH, Adrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American Colleg Chest Physicians Task Force. Chest. 2006;129:178–81.
111. Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Guía Española de la EPOC (GesEPOC). Tratamiento farmacológico de la EPOC estable. Arch Bronconeumol. 2012;48:247–57.