# Development and results of the Spanish registry of patients with alpha-1-antitrypsin deficiency

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**Abstract:** The Spanish registry of alpha-1 antitrypsin deficiency was founded in 1993 and became a member of the International Registry (AIR) in 1999. We describe the updating process following its incorporation into AIR and compare the data collected in the first period (1993–1999) and the second period (1999–2005), during which time patients were included exclusively by internet.

The registry included 301 patients during period 1, 69% males and 46% had a history of smoking. Their mean age was 46 years (SD = 13) and 284 (94%) had the ZZ phenotype, 49% received augmentation therapy. During period 2, 161 new cases were included, 63% of whom were males with a mean age of 44 years (SD = 16). A total of 126 (78%) had the ZZ phenotype. Only 12% received augmentation therapy. A total of 462 different patients were included in both periods. Significant differences were observed in the number of cases with the SZ phenotype and the severity of $FEV_1$ impairment between the two periods.

Implementation of an internet-based collection of data did not result in a lower rate of reporting to the registry. However, data from a significant number of patient included in period 1 could not be actualized in the new data base.

**Keywords:** alpha-1 antitrypsin deficiency, registries, epidemiology, COPD, emphysema

## Introduction

Alpha-1 antitrypsin deficiency (AAT) is a hereditary recessive autosomal disease caused by mutations in the AAT gene. This disease is characterized by abnormally low AAT concentrations in plasma, which, in its homozygote form, carries a high risk of the development of early pulmonary emphysema and, occasionally, liver damage (Carrel et al 1996; Eriksson 1996).

Recent studies in Spain have shown that 1.5% of the general population has the Z allele, thus, of a population of approximately 40 million, 8,000 individuals may be expected to have severe homozygotic PiZZ deficiency (Blanco et al 2006).

Since the end of the 1980s, augmentation therapy with AAT from human plasma has been available for specific treatment of emphysema due to AAT deficiency (Mastrangeli and Crystal1996). The need for consensus criteria for treatment and follow up led to the creation of the Spanish registry of patients with AAT deficiency in 1993, within the working area of respiratory insufficiency and sleep disorders (IRTS) of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) (Vidal et al 1995).

The registry also provides advice on aspects related to the diagnosis, the treatment and the follow up of patients with AAT deficiency and participates in international investigation projects (Vidal et al 1996; Miravitlles et al 1998, 1999).

The low prevalence of AAT deficiency makes the creation of international registries necessary as suggested by the World Health Organization (WHO) in its information bulletin in 1997 (WHO 1997). Only in this way can a large enough population of patients be gathered to perform clinical studies aimed at determining the efficacy of

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new treatments for this disease. Following these guidelines, in 1999 the Spanish registry became a member of the alpha-1 international registry (AIR) which is currently made up of the association of 21 national registries from four continents (Luisetti et al 2002).

The structure of the Spanish registry has undergone different changes during the 13 years of its activity. The most important change was the implementation of a new data collection system through the internet over an official SEPAR website (http://www.separ.es/air) in 2001. This change was accompanied by modifications in the questionnaire in order to adapt it to the format of the AIR questionnaire translated into Spanish. In many cases this change in methodology made the updating of data necessary. This study describes this updating process and compares the data reported in the patients included during the first period (1993–1999) with those obtained during the second period (1999–2005).

## Methods

We carried out a descriptive study of the characteristics of the patients with AAT deficiency included in the Spanish registry during the two periods of activity, period 1 (1993–1999) and period 2 (1999–2005).

The criteria for inclusion in the registry is the presence of severe AAT deficiency defined by AAT plasma concentrations less than 30% of the normal value. In addition, the patients must be carriers of a PiZZ, PiSZ or some other severe phenotypic variant of the deficiency. The criteria for inclusion in the registry have changed: in period 1 only patients over 18 years with a PiZZ phenotype, null or severe deficiency were included while, according to the AIR inclusion criteria, there was no age limit and PiSZ heterozygotes were also accepted in period 2.

During period 1 the information was collected on paper forms sent by post to the SEPAR headquarters to be thereafter distributed to the coordinators who updated the database. A questionnaire was developed in period 2 based on the questionnaire of the AIR registry translated into Spanish and was available in the HTML format and was linked to an Oracle database. The questionnaire is accessible through the SEPAR website (http://www.separ.es/air). The data of the registry were collected following the prevailing legislation on the confidentiality of personal data. The database of the registry has been declared to the Spanish agency of data protection. The registry page is of restricted access and each participating physician must first be registered and obtain a user name and password. The candidates to be registered are manually identified as physicians by those responsible for the registry prior to authorization of access. Data confidentiality is ensured by identifying each patient with a 3 digit number and the name of the corresponding physician, thus, each physician only has access to the data of his/her own patients and is only able to identify his/her patients.

The new questionnaire includes demographic data, smoking history, respiratory symptoms, phenotype and reasons for AAT determination. It also collects data on respiratory function (FVC and $FEV_1$ pre- and post-bronchodilator, CV and DLCO) and quality of life according to the score of the St. George's respiratory questionnaire. Other questions refer to augmentation therapy, associated diseases, and lung and liver transplantation. One specific section is designed to register data on clinical and functional evolution each semester.

The information collected in the new questionnaire was, in part, different and more extensive than that reported during the first period, thereby requiring progressive updating by direct contact with the physicians who registered the patients in period 1 and who did not have patients registered in period 2. On compiling the maximum data possible, a comparative analysis was made between the patients from periods 1 and 2 to determine the common variables in the questionnaires used in the two periods.

## Statistical analysis

The baseline characteristics of the patients included in periods 1 and 2 are presented. Patients included in period 1 were divided into updated and not updated according to whether they had been newly registered in period 2 through the on-line database. The comparisons betweens the two groups were performed with the Chi-square test for qualitative variables and the Student's-t test for quantitative variables, with $p < 0.05$ being considered significant.

## Results

A total of 301 individuals were registered in period 1, 69% of whom were males with a mean age of 46 years (SD = 13 years) and 46% had a history of smoking (Table1). The ZZ phenotype was reported in 284 patients (94%) and 49% had received augmentation therapy at some time during their evolution.

In period 2, 161 new cases were included (Table 1). Of these 63% were males with a mean age of 44 years (SD = 16 years). Ten individuals were younger than 18 years, 7 boys and 3 girls with a mean age of 12 years (range: 2 to 17 years). A total of 126 had the ZZ phenotype while the remaining patients were of the PiSZ phenotype. Only 12% received augmentation therapy ($p < 0.05$ compared to period 1). Compared to period 1, significant differences were

**Table 1** Characteristics of patients registered in the two registry periods: period 1 (1993–1999) and period 2 (2001–2005)

| Characteristics | Period 1 (n = 301) | Period 2 (n = 161) |
|---|---|---|
| Sex, males (%) | 69% | 63% |
| Age, years (SD) | 46 (13) | 44 (16) |
| Active or ex-smoker (%) | 46% | 68% |
| Phenotype (%) | | |
| ZZ | 284 (94%) | 122 (76%) |
| SZ | 4 (1.3%) | 27 (17%) |
| Others | 13 (4.3%) | 7 (4.3%) |
| Augmentation therapy (%) | 49% | 12% |
| $FEV_1$, L (SD) | 1.7 (1.1) | 2.1 (1.2)* |

*$p < 0.05$ compared with period 1.

observed in the proportion of cases with the SZ phenotype and in pulmonary function measured by $FEV_1$, which was found to be lower in period 1 (1.7 liters (SD = 1,1 L) versus 2.1 L (SD = 1.2 L); p = 0.01.

Following the contacts established with the participating physicians the data of 130 (43%) out of the 301 patients included in period 1 were updated. The characteristics of both groups are shown in Table 2. No statistically significant differences were observed between the initial updated data of the patients compared with those in whom new information could not be obtained.

A total of 462 different individuals were included in both periods. The sum of the patients included in period 2 plus those updated from period 1 provides a total of 291 patients with complete data as of January 2006 (Table 3). It is of note that 29% of the patients were not smokers and that 18% of the cases were detected on a family study. The percentage of subjects identified through family screening increased from 11% in period 1 to 21% in period 2. The mean $FEV_1$ was 1.94 L (SD = 1.2 L) and 33% were taking or had received augmentation therapy at the time of inclusion in the registry.

**Table 2** Characteristics of the patients in period 1 according to the updating of the registry online

| Characteristics | Updated (n = 130) | Not updated (n = 171) |
|---|---|---|
| Sex, males (%) | 63% | 74% |
| Age, Years (SD) | 45 (14) | 45 (15) |
| Smoker (active or ex) | 76 (59%) | 62 (36%) |
| Reason determination | | |
| Lung disease | 92 (71%) | 105 (61%) |
| Live disease | 4 (3%) | 1 (0.6%) |
| Family study | 20 (15%) | 12 (7%) |
| Not reported | 14 (11%) | 53 (31%) |
| Phenotype (%) | | |
| ZZ | 122 (94%) | 162 (95%) |
| SZ | 1 (0.8%) | 3 (2%) |
| Others | 7 (5.4%) | 2 (4%) |
| Augmentation therapy | 49% | 49% |
| $FEV_1$, L (SD) | 1.70 (1.1) | 1.68 (1.1) |
| $FEV_1$ % (SD) | 54.7 (31.4) | 53.2 (30.4) |
| Lung transplantation | 3 (2%) | 3 (2%) |

$p > 0.05$ in all comparisons

## Discussion

Registries of patients with infrequent diseases are considered of great utility to improve the knowledge on their natural history and are an essential strategy to develop clinical studies with new therapies. This need has been demonstrated in the document by the WHO on AAT deficiency in 1997 (WHO 1997). The AIR was founded on the basis of this document by uniting the different existing national registries. Following its foundation, new countries have initiated their own national registry and have also become members thereby constituting

**Table 3** Characteristics of the patients in the Spanish Registry of AAT Deficiency (n = 291). Includes those updated from period 1 (n = 130) plus those newly registered in period 2 (n = 161)

| Characteristics | N = 291 |
|---|---|
| Sex, males (%) | 63.5% |
| Age, years (SD) | 51 (14.9%) |
| Smokers | |
| Non smoker | 85 (29%) |
| Active smoker | 26 (9%) |
| Ex-smoker | 175 (60%) |
| Not reported | 5 (1.7%) |
| Packs-year | 26.5 (17.7) |
| Respiratory symptoms | |
| Non productive cough | 8 (3%) |
| Productive cough | 41 (14%) |
| Resting dyspnea | 10 (3.4%) |
| Effort dyspnea | 144 (49%) |
| Dyspnea attacks | 20 (7%) |
| No symptoms | 68 (23%) |
| Reason for AAT determination | |
| Lung disease | 201 (59%) |
| Liver disease | 22 (7.5%) |
| Family screening | 53 (18%) |
| Population screening | 1 (0.3%) |
| Others | 10 (3.4%) |
| Not reported | 4 (1.3%) |
| Phenotype | |
| ZZ | 247 (85%) |
| SZ | 27 (9%) |
| Others | 13 (4%) |
| Not reported | 4 (1%) |
| Augmentation therapy | 97 (33%) |
| $FEV_1$, L (SD) | 1.94 (1.2) |
| FVC, L (SD) | 3.23 (1.2) |
| Transplantation | |
| Lung | 8 (3%) |
| Liver | 2 (0.7%) |

the greatest registry of patients with AAT deficiency worldwide (Luisetti et al 2002).

To participate in the AIR the Spanish registry has had to adapt its questionnaire to the new format which includes a greater number of variables and has taken the opportunity to develop an application of on line data registry through the SEPAR website which allows any physician who diagnoses a case to include this information by computer. The data are encrypted and coded and are incorporated each semester in the AIR. The headquarters of the AIR database is in Malmo (Sweden) and currently includes more than 2,000 patients from 21 countries. The questionnaire was initially made up of a document in the microsoft access format. Spain was the first country to develop a questionnaire in the HTML format which could be filled out on line to thereby facilitate the participation of physicians throughout the country. This strategy has been useful to thereafter adapt the questionnaire to the national registries of Argentina and Brazil. The change in the structure of the registry which was necessary and was performed in 1999–2000 represented a loss of information since some physicians did not update the data of their patients registered previously with the paper questionnaire.

The other large registries of patients with AAT deficiency are from the United States. The registry of the National Heart and Lung and Blood Institute (NHLBI) of the USA included 1,129 patients and had the objective of studying the natural history of the disease over five years (McElvaney et al 1997). The registry was completed and the results have been published (The alpha-1-antitrypsin deficiency registry study group 1998). The second is the Alpha One Foundation Research Network Registry (AOF-FNR) also from the USA and is based on patients who register themselves to be able to participate in studies and clinical trials. According to the data published, this registry included a total of 1,204 individuals in the year 2000 (Stoller et al 2000). Despite the differences between these registries, the characteristics of the patients included are similar in certain points: the disease was diagnosed in the 4th to 5th decade of life and males and index cases predominate over those detected in screening programs or family studies. In all the cases the delay in diagnosis and the low number of patients registered are constant compared to the reference population (Stoller et al 2005).

The initial population of the Spanish registry was also fundamentally made up of middle-aged males with a history of smoking and the ZZ phenotype in most cases as well as an important deterioration in respiratory function. The new cases are of similar age, although their pulmonary function is not as altered. The number of patients detected in family studies has also increased. These data are positive since they demonstrate a trend towards earlier diagnosis of the disease. This trend has not been observed in other countries such as the USA where there is a high diagnostic delay which has remained high during the last decades (Stoller et al 2005). It is therefore important to alert physicians attending patients with COPD to the need for determining plasma concentrations of AAT in their patients at least once (ATS/ERS Statement 2003; Miravitlles 2004). Although the diagnosis of the deficiency is not difficult and its detection is a type A recommendation in the guidelines (ATS/ERS Statement 2003), all the studies undertaken have demonstrated that it is not performed early and underdiagnosis is a constant (ATS/ERS Statement 2003; Campos et al 2005; Stoller et al 2005). The Spanish registry has carried out a screening campaign for the deficiency in patients with COPD with the dried blood spots (Costa et al 2000; Rodriguez et al 2002) which has allowed the analysis of more than 2,000 samples and the diagnosis of 8 individuals with a severe deficiency (De la Roza et al 2005; De la Roza et al 2006). Taking into account the expected number of patients with COPD in Spain (Sobradillo et al 2000), it can be said that there must be 5,000 patients with COPD due to a severe AAT deficiency. These numbers are somewhat lower than the number of homozygote PiZZ individuals expected on epidemiological calculations derived from studies analyzing the genic frequency in the population (Blanco et al 2006). These differences are, in part, due to the penetration of the gene, that is, the variability in the development of COPD in homozygotic carriers according to different factors such as smoking or other genetic determinants of risk (Rodriguez et al 2005) which condition the fact that not all the PiZZ individuals develop emphysema at a similar age or with a similar severity. Nonetheless, the most optimistic estimations suggest that the Spanish registry only includes 6% of the probably existent cases in Spain. In view of these results, the new SEPAR guidelines on treatment of AAT deficiency insist on the need for performing the determination of seric AAT in all patients with COPD (Vidal et al 2006).

Throughout the history of the registry the age of diagnosis has remained at a mean of between 44 and 46 years, despite the inclusion of children, most of whom were relatives of index cases with pulmonary emphysema or who had liver disease, in period 2. The fact that the registry is organized and directed by SEPAR without active participation of pediatricians or gastroenterologists probably explains the

reason why the mean age did not decrease. Indeed, there is a greater number of patients with the SZ deficiency due to their not being initially included in the registry and what is even more relevant is that the number of new cases receiving augmentation therapy has significantly decreased from 49% in period 1 to 12% in period 2. The most probable cause for these differences is the scarce availability of treatment for the patients, especially from 1999 to 2003 (Horowitz 1996; Miravitlles et al 1999). It is possible that the current number of patients receiving augmentation therapy is higher than that reported in the questionnaires since some patients may have started treatment after having been registered as not being treated.

Of the 301 patients registered up to 1999, 170 were not included in the new database, despite the efforts to contact the physicians responsible for these cases. The reasons for this may be diverse. Some patients may have been lost to follow up on interrupting their visits to the physician or changing their physician. Deaths not reported to the registry may also be possible. On other occasions the physicians responsible could not be contacted because of a change in work place. Our results did not show any characteristic to differentiate updated from non updated patients, thereby suggesting that neither clinical nor demographic characteristics justify the lack of updating of some patients.

A total of 462 different patients have been registered during the time the registry has existed. Of these patients, the current database contains information on 291 individuals, 120 of whom were registered during the first period and were later updated and 161 included in period 2. A total of 171 patients were not newly registered after belonging to the initial registry. The most common profile of the patients is a male smoker in whom the main symptoms include effort dyspnea and COPD, with a $FEV_1$ of around 1.5 liters. The most frequent phenotype is the PiZ, although PiSZ heterozygotes are also currently registered. The cases of severe deficiency by alleles other than Z and S are exceptional, with two new variants described in Spain being of note (Ybarcelona and Mvall d'hebron) (Jardi et al 2000; Miravitlles et al 2003). The inclusion of patients in the registry is the only valid strategy to know the characteristics of these patients and their needs in Spain as well as to participate in clinical studies aimed at establishing better treatment or even a cure for this genetic disease.

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## Appendix

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