Usefulness of a national registry of alpha-1-antitrypsin deficiency. The Spanish experience

M. Miravitlles*, R. Vidal*, J. C. Barros-Tizón†, A. Bustamante‡, P. P. España§, F. Casas¶, M. T. Martínez*, C. Escudero** and R. Jardi++

*Servei de Pneumologia, Hospital Vall d'Hebron, Barcelona
†Servicio de Neumología, Hospital Xeral-Cies, Vigo
‡Unidad de Neumología, Hospital Sierra Llanas, Torrelavega
§Servicio de Neumología, Hospital de Galdakao
¶Servicio de Neumología, Hospital Granada
*Servicio de Neumología, Hospital 12 de Octubre, Madrid
**Servicio de Neumología, Hospital Central de Asturias, Oviedo
++Servei de Bioquimica, Hospital Vall d'Hebron, Barcelona

Severe alpha-1-antitrypsin (AAT) deficiency, phenotype Pi ZZ, is a rare condition with an estimated prevalence of 1/4500 individuals in Spain. Given this low prevalence, it seems useful to accumulate all the information derived from the care of these patients. In this context, the Spanish Registry of patients with AAT deficiency was founded in 1993; its main objectives were to establish guidelines adapted to our country for the treatment and management of AAT-deficient patients, offer expert support to physicians all over the country treating these patients, and provide technical support on the determination of Pi phenotyping and genotyping of individuals suspected of being AAT-deficient.

From 1993 to January 1998 the number of enrollees increased from 48 to 223, of which 216 were Pi ZZ. Seventy-three per cent were male and only 31.5% were never smokers, mean age was 46 years (SD = 13 years) and mean FEV1 53% predicted (SD = 31%). 83% were index cases who, compared with non-index cases, were older (49 ± 11 vs. 35 ± 13 years, P < 0.001), more likely to have a smoking history (85% vs. 47%, P < 0.01) and displayed more severe impairment in pulmonary function (FEV1% = 40% ± 19% vs. 96% ± 23%, P < 0.001). Augmentation therapy was administered to 129 patients (58%). Treated patients had more severe impairment in pulmonary function than the untreated (FEV1% = 40% ± 21% vs. 72% ± 32%, P < 0.001) and were more likely to be index cases (81% vs. 43%, P < 0.001).

Characteristics of the patients included are similar to those described for other Registries. The Registry has extended knowledge of the disease throughout the country and has established local guidelines for treatment and follow-up. It may be a valid database for future co-operation in international initiatives.

Introduction

Hereditary deficiency of alpha-1-antitrypsin (AAT), the main serum inhibitor of proteolytic enzymes, is associated

Received 24 March 1998 and accepted in revised form 3 June 1998.
The Spanish Registry is a workshop of the área de Insuficiencia Respiratoria y Trastornos del Sueño (IRTS), Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Financial support was obtained from Bayer Q.F., Spain.

Correspondence should be addressed to: M. Miravitlles, Rocafort 173-177, 3º/1ª 08015 Barcelona, Spain.

© 1998 W. B. SAUNDERS COMPANY LTD
frequency 0.023 in Sweden (3) and Denmark (4), than in Mediterranean countries [0.015 in Spain (5)]. With these figures, the estimated number of homozygous Pi ZZ (phenotype inhibitor) individuals ranges from 1/1600 in Scandinavia to 1/4500 in Spain.

Owing to the low prevalence of AAT deficiency, there is a need to accumulate information derived from the study of individuals with the disease. In this respect, the Danish Registry was founded in 1978 and in 1994 included more than 500 individuals (6). However, the greatest interest for the registries came with the availability of an augmentation treatment for the disease. It was realized early on that a clinical trial to ascertain the long-term clinical efficacy of such treatment would be unaffordable (7); consequently, some registries appeared as an alternative to a clinical trial (8,9) by comparing the clinical evolution of a great cohort of patients with and without augmentation therapy (10,11).

The Spanish Registry of patients with AAT deficiency was founded in 1993 (12) but because of the relatively small expected number of individuals to be recruited, the initial purpose of the Registry was not to be an alternative to clinical trials on augmentation therapy. The objectives of the Registry were: (1) to ascertain the frequency and characteristics of AAT deficiency in Spain; (2) to establish guidelines adapted to our country for treatment and management of AAT-deficient patients; (3) to offer expert support to physicians treating these patients all over Spain; (4) to increase interest in this rare disease and attempt to decrease underdiagnosis and delay in recognition of the deficiency; and (5) to offer technical support on the determination of Pi phenotyping and genotyping of individuals suspected of being AAT-deficient.

In this report the experience of the first 5 years of the Registry is described.

Methods

ORGANIZATION OF THE REGISTRY

The Spanish Registry of patients with alpha-1-antitrypsin deficiency (AATD) was founded early in 1993 as a workshop of the IRTS working group (Insuiciencia Respiratoria y Trastornos de Sueiio) of the SEPAR (Sociedad Espafiola de Neumologia y Cirugia Toracica). Organizational components of the Registry include two co-ordinators (M.M. and R.V.), a Steering Committee and 62 participating clinical centres, 61 distributed throughout Spain and one in Andorra. A Clinical Co-ordinating Center houses the central database of the Registry. In this Centre there is also a Central Laboratory (R.J.) which offers support in determining Pi phenotype by isoelectric focusing and genotyping via DNA extraction and amplification; the techniques used have been described extensively in previous works (5,13,14). A list of participants in the Registry is provided in the Appendix.

The Steering Committee provides scientific direction for the Registry and consists of representatives from some of the participating clinical centres and the two co-ordinators.

An annual conference of representatives from the participating clinical centres is held to comment on the situation of the database, characteristics of the patients enrolled and the specific problems derived from the care and treatment of these patients, and the guidelines for treatment and follow-up are updated.

ELIGIBILITY CRITERIA

To be eligible for inclusion in the Registry, an individual must have serum AAT below 35% of normal values (<50 mg dl–1 or <11 μM) and phenotype Pi ZZ or other severe deficient variants. For patients receiving augmentation therapy, serum AAT levels must have been determined before the first dose, or after therapy has been suspended for 4 weeks. Patients with phenotype Pi SZ are not included in the Registry unless they have serum levels of AAT <11 μM and are administered augmentation therapy on the decision of the corresponding physician.

The Registry collects information at 6-month intervals on demographic data, medical history, pulmonary function measurements which include prebronchodilator and postbronchodilator FEV1 and FVC, and information on the use and frequency of augmentation therapy as well as the possible incidence of adverse side-effects.

Lung function measurements (spirometry) were performed in the respective participating clinical centres and reported by the referring physician. All participating centres performed measurements according to European recommendations (15). The percentage of the reference values was calculated using Mediterranean population reference values (16). In this report the postbronchodilator FEV1 was used in all calculations.

Family study after the diagnosis of an index case was recommended by the Registry, but the Registry itself did not perform the investigation, which depended on the criteria of each participating centre.

DATA MANAGEMENT

Standardized data forms were used to record data at each clinical centre. The forms were mailed to the SEPAR office, from where they were sent to the Co-ordinating Centre. Forms were logged and entered into a microcomputer-based data management system. Exploratory analysis to detect missing or out-of-range values was performed for purging of the database. Characteristics of the patients included in the Registry in January 1998 are described in the present paper.

Statistical analysis was performed using the Statistical Analysis System software (SAS-Institute, Cary, NC, U.S.A.). The Student’s t-test was used for comparisons between means and the chi-square test was used to study the relationship between categoric variables. A difference of P<0.05 was considered significant.

Results

Two hundred and twenty-three individuals had been included in the Registry from 1993, of whom four died
Demographic, clinical and functional characteristics of enrollees are shown in Table 1. There is a predominance of men (73%), ex-smokers (62.5%) and individuals included because of pulmonary symptoms (83%), while those diagnosed by family screening represent 14%.

Comparison between index cases, i.e. those identified through chest symptoms, and non-index cases is shown in Table 2.

Criteria established by the Registry to initiate augmentation therapy with intravenous AAT (Prolastina®; Bayer Pharmaceutical; West Haven, CT, U.S.A.) are depicted in Table 3. Decisions to treat with augmentation therapy were always left to the discretion of the enrollees’ attending physicians. Frequency and dosage of augmentation therapy recommended by the Registry was 180 mg kg⁻¹ every 3 weeks. A total of 129 (58%) patients were receiving augmentation therapy at the time of enrolment or initiated the treatment the year after enrolment; their characteristics and comparison with those not receiving augmentation therapy are shown in Table 4. Administration frequency of augmentation therapy was: weekly four patients (3%), every 2 weeks 16 (12%), every 3 weeks 99 (77%), monthly 3 (2.3%) and not stated seven (5.4%). Regarding functional impairment, 65% (84/129) of patients with FEV₁<30% were receiving augmentation therapy, 67% (29/43) of those with FEV₁ between 30% and 49%, 63% (11/17) of those with FEV₁ between 50% and 69%, and 15% (5/34) of those with FEV₁ ≥ 70%.

Of the four patients who died, three had an FEV₁<30% predicted; two of these died of pulmonary emphysema and the other of acute peritonitis due to diverticulitis. The remaining patient had an FEV₁ of 60% predicted and died of disseminated stomach cancer.
TABLE 1. Demographic, clinical and functional characteristics of individuals with AAT deficiency at enrolment

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>163</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>39 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascertainment*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>145</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>25</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Smoking status†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>42</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>83</td>
<td>62.5</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Augmentation therapy</td>
<td>129</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>1726 (1200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>53 (31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentages refer to 175 enrollees for whom this information is available.
†Percentages refer to 133 enrollees for whom this information is available.

Discussion

Since its foundation in 1993, the Spanish Registry has included a total of 223 patients, of whom four have died and four received a lung transplant up to January 1998. Most of the enrollees are males in the fourth or fifth decade of life with a history of cigarette smoking and pulmonary symptoms and lung function tests consistent with emphysema. More than one half of the enrollees are receiving augmentation therapy, with the patients treated being older, more likely to have smoked and with severe pulmonary function impairment with a mean FEV₁ of only 40% predicted. Only 17% of cases have been diagnosed despite not having respiratory symptoms (non-index cases) and the majority were identified through family screening of an index case. This description is similar to that of the NHLBI Registry in the U.S.A. (10) where non-index cases represent 28% of enrollees, but clearly below the Danish Registry where cases diagnosed through family screening constitute almost one half of the enrollees (6).

A recent study in Barcelona observed a gene frequency of the Z allele to be 0.015 (5). If this frequency were valid for the whole country, the expected number of individuals homozygous for Pi ZZ in Spain would be approximately 8400. The number of patients registered is 0.58/100 000, ranging from 0 in three regions or 0.08/100 000 in Valencia to 3/100 000 in Cantabria and Asturias, and represents globally 2.6% of the total deficient individuals expected. This percentage lies between that of the NHLBI Registry (10) and other Registries with a longer tradition such as the Danish one, where approximately 28% of the estimated number of patients in the 30–59 year age category are registered (6).

TABLE 2. Comparison between index and non-index cases

<table>
<thead>
<tr>
<th></th>
<th>Index n=145</th>
<th>Non-index n=30</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>78</td>
<td>60</td>
<td>0.21*</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3</td>
<td>0</td>
<td>n.s.*</td>
</tr>
<tr>
<td>Lung transplant (%)</td>
<td>3</td>
<td>0</td>
<td>n.s.*</td>
</tr>
<tr>
<td>Non-smokers (%)</td>
<td>15</td>
<td>53</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Pack-year (smokers and ex-smokers)</td>
<td>29 ± 17</td>
<td>16 ± 13</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 11</td>
<td>35 ± 13</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Augmentation therapy (%)</td>
<td>78</td>
<td>16</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>1242 ± 699</td>
<td>3358 ± 1232</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>40 ± 19</td>
<td>96 ± 23</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
*Chi-square test.
†Student's t-test.
The differences observed in some areas are not likely to be due to differences in gene frequencies (5,17,18) or cigarette smoking habits, but to differences in diagnostic rates due to the existence or not of medical groups interested in the deficiency in different areas. It is well documented that some non-smoking, non-index deficient individuals will never develop significant emphysema and thus will not be detected (6,19,20), but even today many patients with early onset emphysema due to the deficiency are misdiagnosed for many years as having smoking-related disease, until the final diagnosis of the deficiency is (if ever) established. In a national series, mean delay in diagnosis was 10 years (range=3-22 yr) although mean age at diagnosis was only 46 yr and mean FEV₁ 0.80 1 (21).

The criteria established by the Registry for initiating augmentation therapy are very restrictive. Patients must refrain from smoking for at least 1 year and present pulmonary function impairment consistent with emphysema; those with FEV₁ > 50% predicted must show an annual decline of more than 150 ml. The reasons for adopting these restrictive criteria are lack of definitive evidence of the clinical efficacy of the therapy, and lack of information on which patients are going to benefit more from the treatment, together with the fact that the treatment is very expensive and of limited availability (22) and its use should be, in our opinion, restricted to patients with well-defined characteristics in the setting of experimental trials or under the supervision of national or international registries. Nevertheless, the decision to treat is left to the corresponding physicians and in our series, at least five patients on augmentation therapy did not fulfill all criteria and, conversely, eight patients who did meet the criteria were not receiving augmentation therapy for different reasons, including the limited availability of the product.

Most of the patients on augmentation therapy were receiving AAT on an every-3-weeks schedule following the recommendations of the Registry. This dosage was adopted because in Spain almost all patients are treated in a hospital-based administration programme, some are still employed, and others depend on their relatives to attend the hospital. For these reasons, the weekly or every-2-weeks schedules are difficult to accept for most patients. The biochemical efficacy of augmentation therapy in terms of obtaining serum AAT levels above those considered protective (80 mg dl⁻¹ or 11 μM) and enhanced antineutrophil elastase activity in both serum and BAL fluid throughout the period between doses has only been proven for the weekly administration (23,24). The efficacy of other administration regimens is under debate; some authors have found good serum AAT levels with a 2 weeks' interval (25) while others suggest that this interval is too long (26).

The Registry recommended a dose of 180 mg kg⁻¹ every 3 weeks, a regimen already reported in another recent study (28).

Two considerations must be made at this point: first, we are only considering biochemical efficacy, and although some promising data exist on the clinical efficacy of the treatment (8,11,21,28-30), definitive evidence is lacking. Furthermore, it is not known to what extent the fact that serum AAT levels are below 80 mg dl⁻¹ during the last few days of each cycle of treatment implies a worse outcome of therapy; second, the approach of a standard dose for every patient may be too simple: patients with purulent bronchitis or frequent infectious exacerbations may need higher doses of AAT to compensate for the highest neutrophil elastase burden (31). Consequently, the Registry recommended a dose of 180 mg kg⁻¹ every 3 weeks, a regimen already reported in another recent study (28).

Values are mean ± SD.

*Chi-square test.
†Student's t-test.


Appendix