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Ongoing research in Europe: Alpha One International Registry (AIR) objectives and development

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ABSTRACT: In 1997, the World Health Organization recommended establishing an international registry of α_1-antitrypsin deficiency. The objective of the present article is to describe the organisation of an international network of registries, the Alpha One International Registry (AIR), and the processes of enrolling and entering data.

By the end of 2005, the registry included individuals from 21 countries (from four continents). The inclusion criterion was either phenotypes PiZZ, PiSZ or other severely deficient variants. Demographic and clinical information have been collected by a standardised questionnaire, translated for each country. Data are transferred to the AIR database at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden, either by e-mail or *via* two web-enabled questionnaires in HTML. All data are merged and checked for consistency and missing values.

Collection of data started in 1999 and, by September 2005, data on 2,150 individual patients (1,180 male) had been submitted. Of these, 1,855 (84%) have phenotype PiZ, 181 (8%) PiSZ and 114 (5%) other rare Pi phenotypes. The mean age at inclusion was 49.8 yrs (SD=13.3) and the majority were index cases (64.1%).

The Alpha One International Registry is the largest specific α_1-antitrypsin deficiency registry, fulfilling a major World Health Organization recommendation. The success related to the convergence of national registries into a common database creating a unique registry beyond geographic boundaries and encompassing α_1-antitrypsin deficiency from various ethnic groups.

KEYWORDS: Augmentation therapy, chronic obstructive pulmonary disease, emphysema, epidemiology, prevalence, registries

Although often regarded as a rare disorder, α_1-antitrypsin deficiency (α_1-ATD) is the most common of inherited deficiency states in the Western hemisphere, an apparent contradiction explained by widespread underdiagnosis. The condition was first identified in 1963 and is known to predispose to severe panlobular emphysema, cirrhosis, liver carcinoma and, less commonly, vasculitis and panniculitis [1]. The present understanding of its genetic basis and the availability of simple screening and diagnostic tests offer a largely neglected opportunity to identify those with the deficiency who have developed severe pulmonary or hepatic disease. However, they also permit identification of deficient and undetected family members prior to the onset of disease, at a time when preventive measures can be most effective.

The major handicap to understanding and designing interventions is the relative infrequency (one in 1,600 to one in 2,000 in Europe) of the disorder, which has precluded the recruitment and study of sufficient patients for meaningful, adequately powered studies [2]. In 1997, the World Health Organization (WHO) published state-of-the-art documentation [3] following a meeting of experts, and identified questions that remained to be answered. A key recommendation was the establishment of national and international registries to enable data collection, collaborative research and, most specifically, a patient resource for the design and conduct of suitably powered clinical trials. This latter process required the novel design of collection methods for centralisation of data and an unprecedented international collaboration. The

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Alpha One International Registry (AIR) was initiated to comply with the WHO recommendation to establish an international registry of α_1-ATD, characterised in as standardised a way as possible by employing a common database. The main objectives of the registry were as follows: 1) to establish an international database of patients and their demographic details; 2) to promote basic and clinical research into α_1-ATD and to coordinate the activity; 3) to collect, assess and disseminate information concerning all aspects of α_1-ATD; and 4) to encourage support and awareness of α_1-ATD. The present article describes the methods and format of this unique database.

METHOD

Organisation of the registry

AIR was founded in 1997 and included an initial group of European countries (the UK, Germany, Denmark, Sweden, the Netherlands, Italy, Spain and Switzerland), along with New Zealand, South Africa, Canada and a part of the USA. Other countries have since joined, including Denmark, Austria, Belgium, Australia, Poland, Finland, Latvia, Lithuania, Argentina and Brazil. By 2005, the registry included 21 countries from four continents.

The constituent parts of the registry are the general members, the council and the coordinating committee. Each national registry is represented on the council by one national delegate. This national delegate ensures the liaison between the national registry and AIR. The coordinating committee directs and conducts the general activities of AIR, and comprises a chairman, secretary, treasurer and two other members, all elected by the council.

AIR organises at least two annual administrative meetings, as well as a scientific meeting every 2 yrs to provide an update on research progress related to α_1-ATD [4].

Collection of data

All data in the registry are collected according to national and international rules of confidentiality of personal data and following approval by the corresponding Independent Review Boards. Confidentiality of the data is assured by coding the included patients with an identification number consisting of a six-digit field (four digits for the national registry number and two corresponding to each national telephone code).

The sole inclusion criterion for the registry is the presence of phenotype PiZZ, PiSZ or other severely deficient variants (serum α_1-antitrypsin (α_1-AT) concentrations <11 μM). From the beginning of the registry until 2005, only individuals aged >18 yrs were included, although from 2005 this age limit has been rescinded.

The questionnaire (available from the present authors by request) consists of standard demographic information (including age and sex), current and previous smoking history to calculate pack-yrs, a pulmonary history with the main symptoms, respiratory medication, the α_1-AT phenotype, reasons for α_1-ATD assessment, information on augmentation therapy, lung function (including pre- and post-bronchodilator spirometry, lung volumes and carbon monoxide gas transfer) and liver function tests (γ-glutamyl transferase, alanine transferase and aspartate transferase), comorbidities, whether the patient has undergone lung and/or liver transplantation and specific health-related quality of life measured by the St. George's Respiratory Questionnaire, social status and other diagnoses classified by the International Classification of Diseases code. The patients are followed up annually and information is collected to document changes in characteristics of the disease, treatment, smoking habits and lung and liver function. The original English-language version of the questionnaire has been translated and adapted into the appropriate language for each country.

Transmission and validation of data

The database and data manager are located at the Dept of Respiratory Medicine, University Hospital, Malmö, Sweden. Data from the national registries are transferred periodically to the AIR database. Initially, the questionnaire was incorporated in a Microsoft Access sheet and each national delegate collected their own data and submitted it to the data manager by encrypted e-mail or by delivery of electronic media. All data were downloaded into a unique database and were checked by the national coordinator for consistency. The database manager then reviewed the data submitted and checked with the national coordinator if data was missing or calculated lung function appeared at variance. At the present time, data from Germany, Italy, Sweden and Canada are still periodically transferred to the central database using this process.

Each national coordinator is able to review their own entries. An update of the data from all countries is presented at each AIR meeting and searched to answer specific queries raised by the council. The database cannot be accessed by a third party.

As early as 1999 it was recognised that some countries would experience great difficulty in centralising the collection of data in a single centre. Spain developed a web-enabled questionnaire in HTML, which was the interface for a database in Oracle, hosted at the web page of the National Society of Chest Physicians (SEPAR). By using a username and a password every physician in the country caring for an α_1-ATD individual was able to access the web page and complete the questionnaire online. The national delegate has a special user access and can check the quality of data whilst preserving the confidentiality. The Oracle database is adapted to the format text delimited as requested by the central data manager and submitted (encrypted) twice a year from 2001, to the central database in Malmö. The same web-enabled questionnaire in Spanish has been used from 2003 by the Argentinean registry, and the Portuguese translation has been used by the Brazilian registry from 2005.

Another web-enabled database was developed in the Netherlands in 2000, and is available in the UK, Switzerland, the USA, New Zealand, Australia, South Africa, Austria, Belgium and Poland. Data collected in these countries are submitted to the Netherlands and then periodically to the central database in Sweden.

All data downloaded to the central database are merged in a single database and checked for consistency and missing values by the data manager. Queries are sent to the national representatives for completion and resolution.

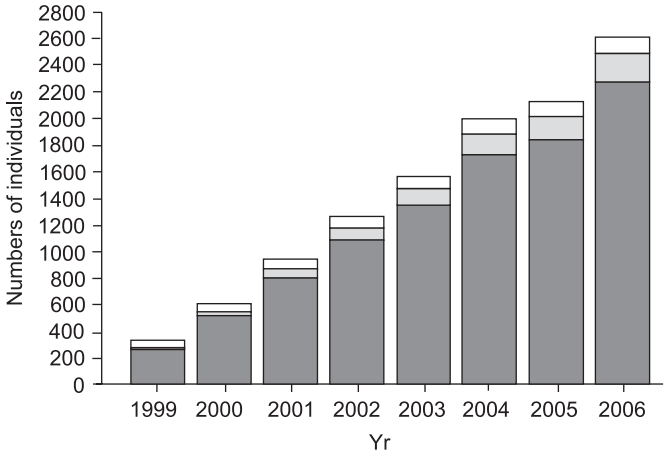

FIGURE 1. Cumulative increase of the Alpha One International Registry. By March 2006, a total of 2,627 α_1-antitrypsin (AT)-deficient individuals (2,285 PiZZ, 218 PiSZ, and 124 other rare α_1-AT-deficient phenotypes) were included in the register. □: Pi "other"; ▒: PiSZ; ■: PiZZ.

RESULTS

The number of patients for whom data has been submitted to the central database is shown in figure 1. Collection of data began in 1999 and by September 2005, data from 2,150 α_1-AT-deficient individuals (1,180 male, 968 female) had been submitted (in two subjects the sex was not reported). Of these subjects, 1,855 (84%) have phenotype PiZ, 181 (8%) phenotype PiSZ, and 114 (5%) have other rare Pi phenotypes with severe α_1-ATD. A total of 45 (2%) subjects have been excluded at present, as the Pi phenotype has yet to be reported, and 16 subjects have been excluded because of an inappropriate Pi phenotype (PiMZ, PiSS, *etc.*). Table 1 shows the number of subjects by country and the year when each country included its first patient (updated March 2006). The mean age of the subjects was 49.8 yrs (range 0–100 yrs; SD 13.3 yrs) at inclusion, although the age has yet to be submitted for 17 of the patients. The initial reasons for the α_1-AT analyses are shown in table 2. Table 3 compares the characteristics of patients in the AIR with those of patients in two large North American databases: the National Heart, Lung, and Blood Institute (NHLBI) Registry and the Alpha One Foundation Research Network Registry (AOF-RNR).

TABLE 1 The number of patients included in the Alpha One International Registry by country, last updated March 2006

Country	Subjects n	First patient included yr
Total	2627	1997
Australia	18	1997
Germany	340	1997
Italy	172	1997
The Netherlands	290	1997
The Republic of South Africa	12	1997
UK	552	1997
Sweden	343	1997
Canada	184	1999
New Zealand	151	1999
USA	25	2000
Spain	277	2001
Austria	98	2002
Switzerland	64	2002
Belgium	27	2003
Argentina	15	2004
Denmark	54	2006
Poland	3	2006
Brazil	2	2006

TABLE 2 The initial reasons for α_1-antitrypsin analysis

Reason	n	%
Total	2121	100
Lung disease	1379	64.1
Liver disease	101	4.7
Other disease	85	4.0
Family screening	412	19.2
Population screening	24	1.1
Other	120	5.6
Information missing	29	1.3

DISCUSSION

In the present paper, the successful implementation of a major recommendation made by the 1996 WHO workshop on α_1-ATD is described [3]. Registries of individuals fulfilling careful diagnostic and assessment criteria, and enrolled on a national basis under the supervision of an expert database manager make available populations in whom understanding of this rare disease (*i.e.* disorders, such as α_1-AT, characterised by a prevalence of <5 out of 10,000 subjects) can be furthered. The success of AIR has been the convergence of national registries into a common database combining agreed information, thus creating a unique registry beyond geographical boundaries and encompassing α_1-ATD from varying ethnic groups. This is of particular relevance, since it has recently been shown that α_1-ATD is not confined to Northern European populations and their descendants alone but is a disorder with a worldwide distribution [5, 6]. The development of a shared questionnaire, the adoption of a minimum requirement to ensure a quality control, and the electronic transfer of data, either by encrypted e-mail shipment of Access sheets or by a secure web-enabled database, greatly contributed to the success of AIR data validation, dissemination and rapid growth.

With 2,627 subjects enrolled (last updated March 2006; fig. 1), AIR is the largest and most comprehensive registry for α_1-ATD (PiZ phenotype). Two other large registries for α_1-ATD exist; both are located in North America. The NHLBI Registry for individuals with severe α_1-ATD completed recruitment in 1996 and included 1,129 subjects, with the main goal of characterising the natural history of α_1-ATD, and with the rate of lung function decline and survival as major aims [7]. The AOF-RNR is a separate registry; participating subjects have expressed a willingness to be approached for participation in studies, including randomised clinical trials [8]. A board of

TABLE 3 Characteristics of α_1-antitrypsin deficiency (α_1-ATD) subjects included in the Alpha One International Registry (AIR), the National Heart, Lung, and Blood Institute (NHLBI) registry, and the Alpha One Foundation Research Network Registry (AOF-RNR)

	AIR	NHLBI	AOF-RNR
Subjects n	2143	1129	712
Male %	55	55.5	53
Mean age yrs	49.8	46.1	49.3
Ascertainment %			
Lung/liver disease	68.8	72.3	NA
Family screening	19.2	19.8	NA
α_1-ATD phenotype %			
PI*ZZ	86.2	97.3	70.7
PI*SZ	8.5	1.0	2.1
Rare α_1-ATD alleles	5.3	1.7	NA
Smoking status %			
Never	30	20.1	24.1
Former	60	71.6	73.3
Current	10	8.3	2.1

NA: not available.

physicians/investigators and patient advocates ensures data quality control; by 2001, the AOF-RNR included 1,204 individuals, although the phenotype is self-reported and hence contains unconfirmed PiZ patients. Besides differences concerning structure and enrolment mechanisms, a major, intuitive difference between AIR and the two Northern American α_1-ATD registries is geography. AIR enrolees are mostly Europeans (1,745; 81% of the total included). Taking into account that 204 α_1-ATD subjects in the AIR are from the USA and Canada (and therefore they might be also present in both NHLBI and AOF registries), AIR includes a cohort of $\geqslant$90% α_1-ATD subjects that differs from that of the two Northern American registries. However, comparing some characteristics of the α_1-ATD series in AIR (current results) with the published ones in the NHLBI series [7] and in the AOF registry [8], there is a general concordance of basic characteristic data (table 3). The disorder is usually diagnosed within the fifth decade of life and there is a slight preponderance of male subjects. The rate of ascertainment for family screening (more recently referred to as predispositional testing) [9] is similar between AIR and the NHLBI registry (19.2 and 19.8%, respectively). The main difference between the two registries is the distribution of α_1-ATD phenotypes. AIR included a lower percentage of PI*Z subjects than the NHLBI registry (86.2 *versus* 97.3%, respectively). Furthermore, the PI*SZ and rare genotypes are eight- and three-fold higher in AIR, respectively. This might reflect the different epidemiology of S and rare α_1-ATD variants in the European countries [2, 5, 6, 10, 11] or different inclusion criteria. Comparison with the AOF-RNR is, however, uncertain with reference to phenotype, since the AOF-RNR registry includes mainly self-reported deficiency patients and includes intermediate (PI*MZ) and undetermined phenotypes, whereas those in AIR are confirmed. Finally, the smoking habit is similar among all three registries, although the lower rate of active smoking in the AOF-RNR may reflect the higher rate of awareness about smoking cessation in the self-reported patients. Detailed analysis of these and other characteristics of the α_1-ATD subjects in AIR will be the subject of future publications.

There are some features of the AIR development that exceed those of a simple registry for a rare disease. First, AIR has facilitated collaboration between clinicians from 21 different countries in four continents, 18 of which have already entered patients to the registry (table 1). Existing national registries for α_1-ATD, such as those in Sweden, the UK, Spain [12] and the Netherlands, joined other registries, such as that in Italy, that were established to join the AIR on its formation. More recently, registries have joined as they have been formed in response to the AIR. Thus, AIR has played a central role in raising awareness of α_1-ATD in countries with medium-to-low prevalence of the disorder. Secondly, AIR and its scientific initiatives, such as the international conferences [4], have not only gathered clinicians concerned with α_1-ATD but have also encouraged a number of scientists, including geneticists, epidemiologists, biochemists and pathologists, as well as representatives of patient support groups, public health and pharmaceutical companies, to collaborate with a common goal. It is clear that such synergy is critical for significant advances in and a better understanding of α_1-ATD, its pathogenesis, its current management and the development of novel therapeutic strategies, with a patient database needed to successfully deliver clinical trials (in this uncommon condition). In this respect, two such trials are currently underway: EXACTLIE (Exacerbations and Computer Tomography in Laurell's syndrome as Investigative Endpoints), which is a 2-yr, placebo-controlled intravenous augmentation study and REPAIR (Retinoids for Emphysema Patients and Alpha-1-antitrypsin International Registry), a 12-month trial of a retinoic acid receptor-γ agonist. In addition, the consortium has been successful in obtaining two European Union grants (AIR genetics and SPREAD (grant number RNDV07773). Finally, data gathered *via* AIR and, in particular, in the UK and Canadian registries has led to a new study confirming a beneficial effect of augmentation therapy for emphysema arising from α_1-ATD and to a meta-analysis of this and published studies of α_1-ATD [13, 14].

In conclusion, a major international collaboration is described herein that has provided a common database to advance in understanding and treatment of α_1-antitrypsin deficiency.

APPENDIX: ALPHA ONE INTERNATIONAL REGISTRY (AIR) GROUP

Structure of AIR

AIR Chairman: J. Stolk (the Netherlands).

Past chairmen: N. Konietzko (Germany) and R.A. Stockley (UK).

Council: M. Luisetti (Italy), M. Miravitlles (Spain), E. Piitulainen (Sweden), P. Fernandez (UK), K.R. Chapman (Canada), A. Dirksen (Denmark), J. Houtsebaut (Belgium), J. Jardim (Brazil), G. Menga (Argentina), C. Vogelmeier (Germany), J. Zielinski (Poland), G. Ainslie (South Africa), E.W. Russi (Switzerland), E.

Campbell (USA), M. Epton (New Zealand), K. Schmid (Austria), A. Krams (Latvia), M. Zolubas (Lithuania), S. Saarelainen (Finland) and J. Burdon (Australia).

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