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The European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO). A new ERS Clinical Research Collaboration to promote research in alpha-1 antitrypsin deficiency.

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Alpha-1 antitrypsin deficiency (AATD) is a common but under-recognized genetic condition that affects approximately 1 in 2000 to 1 in 5000 individuals and predisposes to early-onset emphysema and liver disease (1). Alpha-1 antitrypsin (AAT) is mainly produced in the liver, and its main function is to protect the lung against the proteolytic damage, especially from neutrophil elastase (2). To date, more than 100 variant alleles of the AAT gene have been described, but the Z allele is the most prevalent and responsible for severe AATD leading to lung and liver disease (3).

Rational

Although great improvements have been made in the understanding of the pathophysiology of AATD in recent years, many questions remain unanswered, and the disease poses several important challenges: 1) A large proportion ($\approx 90\%$) of individuals affected remain undiagnosed and therefore have no access to appropriate care and treatment. 2) Augmentation therapy is the only specific treatment for lung diseases associated with AATD and has been shown to slow down, but not stop, the progression of emphysema, as assessed by CT densitometry (4). However, its impact on FEV₁, quality of life, exacerbations and

mortality has not been definitively established. Consequently, augmentation therapy is not reimbursed in many European countries (3,5). 3) Although the vast majority of patients with severe deficiency share the same genetic disorder (ZZ genotype), the prevalence and severity of liver and respiratory disease vary markedly (6). Genetic cofactors have been suspected, but the majority have yet to be identified. 4) The natural history and prognosis of AATD patients is not well known, and there is a lack of prognostic tools to support medical decisions, for example early referral for lung transplantation (7). 5) Most studies on AATD have focused on the ZZ population. The impact of other genotypes such as SZ or rare deficient variants on outcomes is less well known (8,9). The answer to these questions requires the access to large cohorts of patients and cannot be addressed adequately even at the country level.

Acronym

The European Alpha-1 Clinical Research Collaboration (EARCO) is a Clinical Research Collaboration (CRC) (10) of the Assembly 5 airway diseases: asthma and COPD of the European Respiratory Society (ERS) and aims to establish a collaborative effort that brings together multiple stakeholders including researchers, healthcare providers, patients and industry with the aim of advancing understanding through clinical and scientific research and improving the quality of life of patients with the disease. This pan-European initiative will enable a group of experienced and new researchers across Europe to answer fundamental questions about epidemiology, genetics, physiopathology, clinical management and prognosis of lung disease associated with AATD.

Aims of EARCO: The International Registry

The first objective of EARCO is to design and implement a prospective, international registry of patients with AATD in order to understand the natural history of the disease and investigate the impact of different therapies, including augmentation therapy, on the course of the disease. Alpha-1 antitrypsin deficiency is considered a rare disease and the European Commission recommends the development of reference centres for rare diseases. These reference centres must establish a registry of their activity and collect information of the natural history of the patients prospectively (11). These data can be shared at national and international levels and be the foundation of the registries of AATD. The development of registries is crucial as the only way for the successful accumulation of knowledge about the clinical characteristics, evolution, natural history and response to treatment of patients with rare diseases, such as AATD (3).

The European Lung Foundation (ELF) actively participated in the elaboration of the recent ERS statement on diagnosis and treatment of pulmonary disease in AATD (3). Among the most frequent issues raised by patients was the need of a global registry, more information about comorbidities, natural history of the disease and about risk factors for progression and poor prognosis of lung disease. This unmet need was shared by the authors of the statement, and one of the conclusions was that “The systematic collection of data concerning clinical characteristics and natural history of patients with AATD in national and international registries will enhance knowledge about the evolution of this disease and its optimal management” (3). Therefore, the EARCO registry is the response to this unmet need; it will work in close collaboration with the European Reference Network for rare lung diseases (ERN-LUNG) (12) and the ERN-LIVER and the registry of the Alpha-1 Liver Group. In doing this it will consider the

recommendations of the European Medicines Agency about the methodology for the development of registries for regulatory purposes (13).

Relationship with other AATD registries

The EARCO registry is modelled in part on the Alpha One International Registry (A.I.R.) group established in 1997, which included representatives from 14 European countries (14). The AIR group was successful in stimulating international collaborative research and organising and developing clinical trials; however, no real-life, longitudinal data were systematically collected (15). The EARCO registry will also take advantage of the existing AATD registries that have been developed at the national level. Several countries have established registries in which AATD patients are included and followed-up (16-22). However, these registries differ in terms of inclusion criteria, data collected and follow-up. One of the key tasks of EARCO will be harmonising the data collection and assessing the quality of the data included prospectively. Moreover, EARCO will include all data fields that were previously used by national European registries in order to allow the future combined analysis of longitudinal data of EARCO and previous data collected by each country at a national level.

Other research projects

In addition to the development of the registry, there are other initial objectives of EARCO for the next three years, as depicted in Table 1. Among these objectives, it is of great importance to build a network of patients' representatives, researchers and clinical investigators to identify informed research needs and establish an agenda for AATD research and attract young investigators to the area of clinical management and research of AATD for the future. In this respect, two surveys are being conducted, one for patients and the second for healthcare providers, similar

to those conducted by the EMBARC CRC for bronchiectasis (23), particularly in order to understand the key research needs in the field of AATD in Europe.

Irrespective of the results of those surveys, it is clear that the EARCO registry by itself will not provide an answer to all the research questions in the field of AATD, but it can be the backbone of different research initiatives, some of which are already ongoing (Table 1). Other initial projects of EARCO are the evaluation of laboratory diagnostic methods of AATD in Europe and a survey on the initiation of augmentation therapy in Europe.

Developing reliable standards for laboratory diagnosis of AATD is crucial. There are different diagnostic algorithms in reference laboratories in Europe (24) that are usually adapted to the demands of the countries or to the needs of target population to whom turn the diagnosis. Although all algorithms can provide an accurate diagnosis, it is important to establish an external quality control program that can be also used for new laboratories in order to reassure reliable test results (25). The detection of a severe ZZ deficient individual may be relatively straight forward, but rare variants and heterozygotes with intermediate serum levels of AAT may remain undiagnosed if not properly assessed. The quality control program of laboratory diagnosis will set the standards for the correct diagnosis of the condition across Europe (26).

Regarding augmentation therapy, the ERS statement summarised the inequalities of access to augmentation therapy in different European countries (3); but even in countries where augmentation is available and reimbursed there are differences in prescribing habits (27). Although severe emphysema at a young age is the most characteristic clinical manifestation of AATD, the clinical expression and severity of the disease is very heterogeneous (28) and some individuals with severe

deficiency may have normal or near normal lung function for prolonged periods of time or even their life-time (29); therefore, the decision as to when to initiate augmentation therapy is often complex. An ongoing international survey will provide insights into the current practice of augmentation therapy in those European countries where it is available.

Joining EARCO

Over the next 3 years, EARCO will set up the new European-based AATD registry and establish the roadmap for clinical and translational research in the field. It will also make a substantial contribution in advocacy and education in AATD and we open a call to all ERS members to be part of that. EARCO can be contacted through the group members, the national representatives, or directly through our website (<https://www.ersnet.org/research/earco-european-alpha-1-research-collaboration>). The collaboration of all stakeholders, and in particular the inclusion of patients as active participants in the development of EARCO makes it highly likely that EARCO will generate new knowledge with direct impact into our patients' quality of life and clinical care.

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Table 1. Objectives and initial projects of EARCO

Objectives of EARCO
<p>1. To build a network of patients, researchers and clinical experts in AATD to guide future clinical and research priorities in Europe.</p> <p>2. To create the EARCO prospective registry with a quality control system, a European AATD registry to facilitate patient recruitment for research and quality improvement initiatives across healthcare systems.</p> <p>3. To establish a consensus among patients and physicians on the main clinical and translational research priorities in the field of AATD.</p> <p>5. To support and encourage early career researchers in the field of AATD through involvement in network activities.</p> <p>6. To increase the number and quality of clinical trials performed in AATD across Europe.</p>
Initial projects of EARCO
<p>1. Development of the EARCO international Registry</p> <p>2. Survey for patients and healthcare providers of unmet needs in research in AATD.</p> <p>3. Quality control program of laboratory diagnosis of AATD in Europe</p> <p>4. Survey on the initiation and indications of augmentation therapy in Europe</p>

Figures

Figure 1. EARCO organisation