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European Alpha-1 Research Collaboration (EARCO) in Portugal: The Future Is Happening

European Alpha-1 Research Collaboration (EARCO) em Portugal: O Futuro Está a Acontecer

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Alpha-1 antitrypsin deficiency (AATD), usually categorized as a rare disease,[1] is a common but under-recognized genetic condition that affects approximately one in 2000 - 5000 individuals of European descent and predisposes them to early-onset emphysema and liver disease. Understanding the clinical characteristics and the natural history of a rare disease may be challenging due to the lack of large cohorts.

Human alpha-1 antitrypsin (AAT) is codified by the *SERPINA1* gene, and the most prevalent deficiency alleles are Pi*S and Pi*Z. It is believed that the Pi*Z mutation has a relatively recent origin in northern Europe, having originated about 2000 years ago, and it has been proposed that the S variant emerged in the Iberian Peninsula about 10 000 – 15 000 years ago.[2]

Portugal has the highest estimated PI*SZ prevalence rate in the world (1:205),[2] with also a high PI*ZZ prevalence rate (1:2191).[1] Multiple rare alleles have been identified in Portugal, but their frequencies in the general population are still unknown.[3] The real burden of the disease is also unknown because there are very few studies on the epidemiology of AATD in Portugal[3,4] and a national registry does not exist.

To address the problem of the lack of prospective, standardized follow-up data, both healthcare professionals and patients have agreed to set up an international registry of patients with AATD. As an initiative of the Clinical Research Collaboration (CRC) of the European Respiratory Society (ERS), the European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO) international registry was created, with the objective of characterizing the different genotypes of AATD and investigating their natural history and the impact of different treatments, including augmentation therapy.[5,6] The core project of EARCO is the international AATD Registry, a collaboration which will offer longitudinal real-world data for patients with AATD. One of the key tasks of EARCO will be harmonizing the data collection and assessing the quality of the data included prospectively.[6] Although the EARCO registry was created as a European initiative, it has extended beyond European boundaries to become a global registry.

The EARCO international registry was launched in February 2020 and by May 2023 there were 80 recruiting centers in 24 countries. In the first publication describing the characteristics of the individuals included in the EARCO registry a total of 1044 individuals were analyzed. The most frequent genotype was PI*ZZ (60.2%), followed by PI*SZ (29.2%), PI*SS (3.9%) and rare variants (6.6%). Among PI*ZZ patients, emphysema was the most frequent lung disease (57.2%) followed by chronic obstructive pulmonary disease (COPD) (57.2%) and bronchiectasis (22%).[7]

Besides all the international initiatives, Portugal was still trailing some steps behind. In 2015 a Portuguese alpha-1 study group was created, as an initiative of the Portuguese Society of Pulmonology (Sociedade Portuguesa de Pneumologia - SPP), composed by dedicated AATD pulmonology specialists and fellows, who contributed to raising awareness of this disease in Portugal and were responsible for the publication and dissemination of the Portuguese consensus document for the management of AATD.[8] This alpha-1 study group also started planning a Portuguese AATD registry and, in 2018, all the legal aspects were solved and the database was prepared and ready for the registration of Portuguese patients. However, in 2018 the EARCO project was already approved and ongoing. Portuguese pulmonologists realized that moving forward on their own would compromise the ability to address and answer the questions associated with a rare disease and that being part of an international AATD registry, aimed at obtaining quality prospective information on the natural history of the

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disease, would be much more profitable.

In October 2020 Portugal joined the EARCO International Registry and, since then, the Portuguese AATD registry consists of the Portuguese investigators, centers and participants included in the EARCO registry. The Portuguese registry has one national coordinator nominated by the SPP, and a steering committee formed by clinicians and researchers with expertise in the disease.

At the end of July 2023, the Portuguese AATD registry included 170 individuals with AATD from 12 centers distributed throughout the country [78 patients with the first follow-up (FU) visit completed and 22 with the second FU]. The distribution of genotypes was PI*ZZ in 65 patients (38%), PI*SZ in 53 patients (31%), PI*SS in 17 patients (10%) and rare or null variants in 35 patients (21%). Compared to EARCO data (7), Portugal seems to have a different distribution of AATD genotypes especially a higher percentage of Pi*SS (10% *vs* 3.9%) and rare variants (21% *vs* 6.6%). We need a higher number of patients included in the Portuguese AATD registry to confirm the possibility of a unique AATD population in Portugal.

The implementation of the EARCO in Portugal was presented in a previous editorial.[9] At that time, the EARCO registry and the Portuguese AATD registry were still preliminary projects without registered patients. But now they are both reality – the long awaited future was happening.

It was the persistence, hard work, enthusiasm, motivation, and resilience of some Portuguese clinicians and researchers dedicated to AATD and the support of our international colleagues that allowed us to overcome all the obstacles and bureaucracy and allowed the development of the Portuguese AATD registry. We did it – we finally have our own AATD registry. The Portuguese AATD registry will be an excellent opportunity to investigate the genetics, epidemiology, natural history, impact of different therapies, and prognosis of Portuguese AATD patients and identify their possible unique characteristics.

In addition to the development of the registry, there are other objectives of EARCO. All the EARCO information and projects can be consulted on the website www.earco.org.

Some EARCO projects have been finished and published with the participation of Portuguese clinicians. One of these projects, about the identification of the research priorities in AATD, concluded that the main research and management priorities identified by healthcare professionals and patients included understanding the natural history of AATD, improving information for physicians, access to specialized reference centers, personalizing the treatment, and having equal opportunities for access to existing therapies.[10] Another project analyzed the opinions and attitudes of pulmonologists about augmentation therapy and concluded that there is high variability in the criteria for augmentation prescribing among European experts that take into consideration several variables not included in the current recommendations described in the guidelines.[11]

Portugal is contributing to the different work packages of EARCO with some Portuguese projects that have been approved and are ongoing, such as 1) the impact of augmentation in patients with AATD with PI*SZ or with null or rare genotypes; 2) AATD associated with the Mmalton variant – characterization and prognosis; and 3) alpha-1 antitrypsin related disease risk for the PI*SS genotype.

The EARCO is working and has been supported by an enthusiastic community of researchers, clinical investigators, patients' representatives, and industry. It has attracted the attention of many young investigators, some of them Portuguese. This is an exciting, worthwhile project that is already generating new knowledge and will likely have a direct impact on patients' quality of life and clinical care,[5] including Portuguese patients. You are invited to be part of it.

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AUTHOR CONTRIBUTIONS

MS: Conception, writing and critical review of the manuscript.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

MS received payment or honoraria from Bial, CSL Behring, Grifols and Astra Zeneca for lectures, presentations, speakers' bureaus, manuscript writing or educational events; participated on a Data Safety Monitoring Board or

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