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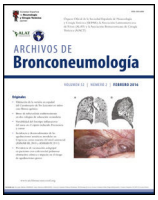

Editorial

Spanish implementation of the new international alpha-1 anitrypsin deficiency international registry: The European Alpha-1 Research Collaboration (EARCO)☆

Implantación en España del nuevo registro internacional de déficit de alfa-1-antitripsina *European Alpha-1-Research Collaboration* (EARCO)

The main function of alpha-1-antitrypsin (AAT) is to protect the lung from the action of proteases. To do this, it behaves as an acute phase reactant and is also endowed with anti-inflammatory activity[1,2]. Alpha-1-antitrypsin deficiency (AATD) is a congenital disease that presents with low serum AAT levels and predisposes patients to the development of pulmonary emphysema[3,4].

AATD is defined as a minority disease, although it is not really that uncommon. In Spain, estimates suggest that there are some 14,000 individuals with severe homozygous deficits (Pi*ZZ)[5], but this figure is far from the number of cases actually diagnosed in our country[6]. The minority nature of AATD and its low diagnostic rate mean that the number of cases seen in each hospital is often very low, making it difficult to gain experience in this disease. For this reason, the *European Respiratory Society* (ERS), in a statement in 2017, recommended that these patients be diagnosed, treated, and followed up in reference centers[7].

Another consequence of the low prevalence of AATD is the difficulty of conducting clinical trials or observational studies with sufficient sample sizes, and many questions on the etiology, pathogenesis, treatment, and natural history of the disease remain unresolved[8–10]. To address this problem, both healthcare professionals and patients have agreed that setting up an international registry of patients with AATD aimed at obtaining prospective information on the natural history of the disease is a priority[7].

To respond to this need, 2017 saw the launch of the *European Alpha-1-Research Collaboration* (EARCO, https://www.earco.eu/registry/), an ERS *Clinical Research Collaboration* (CRC)[11], aimed at establishing a collaborative network of international experts including clinicians, researchers and patients, in collaboration with the *European Lung Foundation* (ELF) and the *European Respiratory Network* (ERN)-*Lung* groups[12]. The main objective and core of this initiative is the EARCO registry, which will begin recruiting patients in 2020. This will be an international, observational registry that will include longitudinal, prospective and standardized data needed to: (a) generate long-term, high-quality clinical data covering an international population of individuals with AATD in all age groups and all stages of disease severity; (b) better understand the natural history and prognosis of AATD in order to develop prognostic tools that support medical decision-making; (c) investigate the impact of augmentation therapy on the progress of emphysema and quality of life and mortality; and (d) learn more about the course of the disease in patients with genotypes other than Pi*ZZ. This will include patients with a diagnosis of severe AATD defined by a serum AAT level <11 μM (50 mg/dl) and/or combinations of ZZ, SZ alleles and heterozygotes or homozygotes composed of combinations of other null or rare deficient variants. The EARCO registry hopes to collect detailed information on 1,000 patients from at least 10 countries during the first year, expanding to 3,000 patients from more than 20 countries during the first 3 years[13].

The Spanish DAAT Registry (REDAAT) has been active since 1992. It now includes data from about 800 individuals and has helped determine the geographical distribution and clinical characteristics of patients[6]. However, the follow-up of registered individuals has been irregular, with only 44% of patients attending a median of only 2 follow-up visits[6], so the information obtained on the natural history of the disease has been very limited[14].

For this reason, the EARCO registry is an opportunity for REDAAT to join this international initiative, use this platform to improve the quantity and quality of the data collected, and ensure long-term prospective follow-up of the individuals included. An important challenge is to ensure that data obtained during the REDAAT years are not lost in this new merger with EARCO, and for this purpose a strategy common to other countries that also have their own registry has been designed. From the moment EARCO is implemented, all individuals diagnosed in Spain who meet the inclusion criteria will be registered directly and uniquely in EARCO, whether they are newly diagnosed or already registered in REDAAT. Historical data from existing registries will not be entered in EARCO; instead, it is a new project that will start from scratch.

Annual monitoring is an essential part of achieving the EARCO goals. For this reason, automatic reminders will be sent to all participating investigators, and an EARCO manager will be appointed who, among other things, will be responsible for ensuring maxi-

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mum compliance with follow-up visits and reviewing the quality of the data entered.

Patients included from Spanish centers will be assigned a pseudonym that will identify their country of origin, and the REDAAT coordinator will be able to access them for review and analysis. Thus, it will be possible to integrate these data with all the historical data that was collected by REDAAT, to ensure that the valuable data obtained during the course of REDAAT will continue to be available for research.

The new European data protection directive has posed a major challenge for the development of disease registries and has greatly complicated all logistics, and required collaboration and data transfer contracts to be set up[15]. For this reason, although no minimum number of cases for participation has been specified, it is logical that inclusion of patients should be concentrated in reference centers or centers with a significant number of cases to compensate the efforts necessary for participation in EARCO. We are convinced that this effort will be worthwhile and that EARCO will become the international reference registry for AATD and the source of future research projects in this "not so rare" disease.

Conflict of interests

Marc Miravitlles has received honoraria for speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis; honoraria for consultancy services from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, TEVA, pH Pharma, Novartis, Sanofi and Grifols, and research funding from GlaxoSmithKline and Grifols.

Miriam Barrecheguren has received honoraria for speaking engagements from Grifols, CSL Behring, Menarini and GlaxoSmithKline, and for consultancy services from GlaxoSmithKline, Novartis and Gebro Pharma.

Francisco Casas has received honoraria for speaking engagements from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Ferrer, Gebro Pharma, GlaxoSmithKline, Esteve Laboratories, Menarini, Novartis, Rovi, Sandoz, TEVA, Zambon, CSL Behring and Grifols.

María Torres-Durán has received honoraria for speaking engagements from Grifols, CSL Behring, Esteve, Ferrer and GlaxoSmithKline, and for consultancy services from Grifols and CSL Behring.

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