HIGHLIGHTS FROM THE 2020 EUROPEAN RESPIRATORY SOCIETY INDUSTRY SYMPOSIUM "MIND THE GAP: EVIDENCE ON THE TREATMENT OF ALPHA$_1$-ANTITRYPSIN DEFICIENCY AND UNMET NEEDS"

Alpha$_1$-antitrypsin (AAT) deficiency is one of the most frequent hereditary disorders in the world and a major genetic risk factor for pulmonary disease.[1-3] Chronic obstructive pulmonary disease (COPD) is the most prevalent clinical disorder associated with this deficiency and the most frequent cause of disability and death in patients with AAT deficiency.[4] Despite recommendations to test for AAT deficiency in all patients with COPD, regardless of age or ethnicity, it remains underdiagnosed and only a small proportion of the population who are estimated to have AAT deficiency are properly diagnosed.[2-4] Early diagnosis allows for counselling for healthier lifestyles, preventive measures, and institution of preventive augmentation therapy at earlier stages of the disease.[3,5] When the clinical picture is consistent with suspected AAT deficiency, the patient should always undergo a genotyping test.[5]

On September 8, 2020, the first virtual European Respiratory Society (ERS) International Congress included an industry symposium on AAT deficiency sponsored by Grifols entitled "Mind the gap: evidence on the treatment of alpha$_1$-antitrypsin deficiency and unmet needs". The symposium elucidated the benefits of augmentation therapy, the value of patient data registries, and the consequences of augmentation therapy withdrawal. Chaired by Dr Claus Vogelmeier MD, PhD, the symposium was conducted by an international faculty of leading experts in the field of AAT deficiency.

The presentations began with Robert A Sandhaus, MD, PhD, who explained that despite the clinical evidence that augmentation therapy improves loss of lung tissue[6] and median survival age, its clinical efficacy has not been accepted in all countries. He then spoke about how the introduction of a disease management program also appears to improve survival and presented the outcomes of a comparison of two groups of patients with AAT deficiency-related lung disease: one from the US who received augmentation therapy, and another from the UK, where augmentation therapy is not available. Augmentation therapy increased overall survival, time to lung transplant,[7] and slowed the decline in

quality of life (SGRQ). It took 6 years of follow-up to demonstrate a significant difference in mortality, which reveals the difficulty in evaluating a condition that progresses slowly. Noteworthy, however, is that the decline in quality of life (as measured by the SGRQ) for the augmentation-treated group compared with the non-treatment group was significantly less at 1 year and clinically less by year 3. Median survival from initial evaluation in those without augmentation therapy was 14 years, and 25 years for those receiving augmentation therapy.

Marc Miravitlles, MD, PhD, moved on to the topic of the future of AAT deficiency registries. In 2017, the ERS had already stated that an AAT deficiency patient registry would enhance knowledge about the evolution of the disease and its optimal management.[8] In this context, a group of experts proposed to the ERS, through its umbrella network, Clinical Research Collaboration (CRC), the creation of the European Alpha-1 Research Collaboration (EARCO). EARCO goals are to increase knowledge and promote clinical research, gather epidemiological data and enable data collection for sufficiently powered clinical trials, promote collaboration between countries and researchers and ensure long-term viability.[9] It was launched in February 2020, collecting different variable data (sociodemographic, clinical, AAT deficiency related, complementary tests, treatment, symptoms and exacerbations) with a yearly follow-up plan. To join the EARCO project, doctors only have to register on its website (www. earco.eu/).

The final speaker, Oliver McElvaney, MD, PhD, talked about pulmonary exacerbations after withdrawal of augmentation therapy. In September 2017, the Irish government decided against reimbursement for patients receiving augmentation therapy; as a consequence, 19 patients had their therapy discontinued, despite having been clinically stable for almost a decade. This unfortunate circumstance offered a unique opportunity to measure the effects of the abrupt cessation of augmentation therapy. In December 2017, 2 of the 19 patients died of respiratory failure in the context of an exacerbation, and the number of exacerbations and hospitalisation were tripled compared to the same time period the year before. These patients also showed a significant increase in inflammatory biomarkers after cessation of augmentation therapy.[10] Following that, the Irish government agreed to reinstitute therapy on a cost-sharing basis. Since reinstitution of augmentation therapy, no more patients have died, their inflammatory biomarkers have gone back down, and their exacerbations profile has followed suit. Dr McElvaney expanded on how, as AAT is an immune modulator, augmentation therapy could be used to modulate the pro-inflammatory response observed in conditions other than AAT deficiency, such as COVID-19.[11]

In conclusion, the industry symposium generated awareness of AAT deficiency, the importance of testing, how augmentation therapy can benefit patients, and illustrated the negative consequences of abrupt discontinuation of augmentation therapy. It also brought attention to the need for continued studies into the use of augmentation therapy and the relevance of AAT deficiency registries.

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