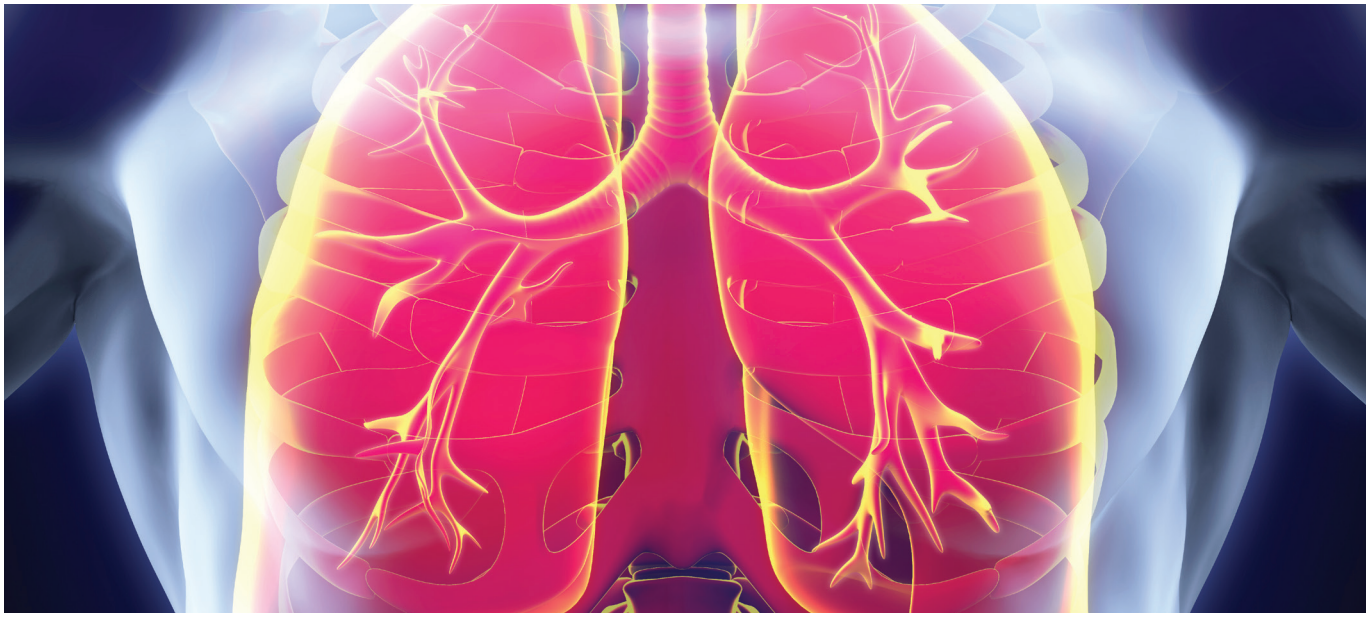
BACK TO THE FUTURE: ALPHA-1-ANTITRYPSIN AND ITS TARGETS. NEW INSIGHTS GAINED DURING THE COVID-19 PANDEMIC

Highlights from the 2021 European Respiratory Society Industry Symposium



Alpha-1-antitrypsin deficiency (AATD) is one of the most common hereditary disorders worldwide and a major genetic risk factor for pulmonary disease.[1–3] Interestingly, **there is a relationship between alpha-1-antitrypsin (AAT) and COVID-19**. COVID-19, a disease of global public health concern, is caused by SARS-CoV-2. It is characterized by acute respiratory distress syndrome, renal failure, shock, arrhythmia-like patterns, severe hypoxemia at initial presentation, cytokinemia, and an AAT acute-phase response. At the phase of viral entry in the cell, the SARS-CoV-2 spike protein is activated by a serine- protease called cellular transmembrane serine protease 2 (TMPRSS2),[4] which is inhibited by AAT,[5] **suggesting a potential role of AAT in the management of COVID-19**.

On September 7, 2021, during the second **virtual European Respiratory Society (ERS) International Congress**, an industry symposium sponsored by Grifols, titled "**Back to the Future: alpha-1-antitrypsin and its targets. New insights gained during the COVID-19 pandemic"**, covered the latest evidence on the role of AAT in patients with COVID-19, the management of patients with AATD during the pandemic, and the latest testing tools for AATD screening. The symposium was led by leading international experts in the field of AATD and was chaired by **Professor Francesco Blasi**, MD.

The presentations began with P**rofessor Noel G. McElvaney**, MD, PhD, who characterized AAT in patients with severe COVID-19 (severe defined as being in an intensive care unit and intubated/ventilated) and its potential role in managing the disease. Professor McElvaney showed that despite increased active AAT serum levels in these patients, the high levels of neutrophil elastases (NE) overwhelmed AAT binding and NE inactivation.[6] Importantly, Professor McElvaney highlighted that patients with severe COVID-19 had increased levels of interleukin (IL)-6:AAT ratio, suggesting a defective ability of the liver to release AAT into the circulation in these patients.[6] **Therefore, the IL-6:AAT ratio could be used as a prognosis factor, with a higher IL-6:AAT ratio leading to a worse disease prognosis**. Interestingly, in the tracheal aspirates of patients with severe COVID-19, while NE was high, the AAT present had a lower molecular weight than normal (<52 kDa), similar to that seen in cystic fibrosis.

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Evidence from a case study (N=1) of a patient with both cystic fibrosis and COVID-19 treated with intravenous plasma-purified AAT (Prolastin, Grifols) showed that the cytokine profile and the NE activity in plasma and airway improved from baseline during the first week of treatment, with a large decrease observed following 4 weeks of treatment.[7] A randomized, multicenter, double-blind, placebo-controlled trial (Eudra CT: 2020-001391-15) investigating the effects of intravenous AAT in patients with acute respiratory distress syndrome secondary to COVID-19 infection has just completed the data analysis, and results should be published shortly.

Dr Christian F. Clarenbach, MD, explained his experience managing patients with AATD during the COVID-19 pandemic in Switzerland, the challenges he encountered, and how these were addressed. Lockdown restrictions had a large impact on general hospital care and were the greatest challenge. In the particular case of patients with chronic obstructive pulmonary disease (COPD) and AATD, a major decrease in patient hospital attendance to receive augmentation therapies was observed. Thus, home care services were put in place to allow for continued administration of patient augmentation therapy. In addition, on March 13, 2020, the World Health Organization advised against the routine use of systemic corticosteroids in the clinical management of severe viral pneumonia if COVID-19 was suspected.[8] This caused uncertainty amongst physicians on whether treatments for COPD and AATD were suitable during the COVID-19 pandemic. Nevertheless, the decision was made to reassure patients to comply with their established action plans, which was later supported by evidence.[9]

Keeping patients with COPD and AATD active was integral to therapy during the lockdown. An action plan was established involving physiotherapists phoning patients to follow up, monitor, and encourage physical activity with video tutorials. The use of a device application called "MyHealth"* with functions (ie, step-tracker) that promoted healthy habits was also initiated. This was coupled with a pre-existing initiative called "Telehealthcare" developed in collaboration with IBM Research in Zurich. It involves a series of wearable devices and a phone app to track and improve physical activity, medication adherence, COPD management, and smoking cessation. Data on the efficacy of implementing these strategies to increase physical activity were not provided.

Dr Clarenbach then discussed the relationship of COPD and AATD with COVID-19. Patients with COPD have a 5-fold increased risk of developing severe COVID-19 [95% confidence interval 2.49-13.00] compared with healthy controls, as reported in a meta-analysis.[10] In a study conducted by the European Alpha-1 Research Collaboration (EARCO) consortium, patients with AATD (PiZZ, PiSZ, or rare severe variants) with COVID-19 were identified by investigator via clinical contact and patient-group awareness. In total, 57 of the patients with AATD were infected with COVID-19 and 21 of them required hospital admission.[11] Data from an Italian AATD registry (N=209) showed that while there was a higher incidence of COVID-19 in this cohort (3.8%), the death rate was similar to the general population.

The final speaker, **Professor José Luis López-Campos**, MD, PhD, talked about the latest testing methodology for AATD screening. He highlighted the **current existing problem of AATD: underdiagnosis**. To address this, **Progenika Biopharma**, **a Grifols company**, **has developed the A1AT Genotyping Test**. This is a next-generation genetic test that has two main advantages:

1. Analysis of the 14 most prevalent mutations associated with AATD[13]
2. Non-invasive and easy saliva sample collection method via buccal swab[14]

Furthermore, the sampling collection method has proven to be COVID-19-safe.[15] Compared with traditional phenotyping, the Progenika test can be used as a screening tool and quickly provides results (6 days for analysis + shipping time depending on the country of origin).

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Professor López-Campos strongly believes that should the A1AT Genotyping Test be made available in clinics, it would increase the number of AATD diagnoses.

In conclusion, the industry symposium provided evidence that **AAT therapy could be a potential treatment for patients with severe COVID-19**. Currently, studies investigating this are underway, and data should be available soon. The symposium also reviewed the challenges faced when managing patients with AATD during the COVID-19 pandemic including the option for home-based treatment, and presented the **A1AT Genotyping Test, a non-invasive, easy, and COVID-19-safe screening tool by Progenika with the potential to increase AATD diagnosis amongst patients with COPD**.

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