The Future of Lung Transplantation in Cystic Fibrosis

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AN INSIGHTFUL session on the future of lung transplantation presented at this year's European Respiratory Society (ERS) Congress explored the insights shared by experts during sessions on lung transplantation, the role of machine learning in cystic fibrosis care, and the future challenges ahead.

IS CYSTIC FIBROSIS STILL AN INDICATION FOR LUNG TRANSPLANTATION?

Clemence Martin from Chochin Hospital, Paris, France, delivered a talk on cystic fibrosis and lung transplantation. Martin presented the results of a 6 month trial conducted in 2019,[1] which used a highly effective triple combination of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators in a population of patients with a single Phe508del allele variant, a frequent deletion in patients with CF. The patients with a pulmonary function between 40–50% and aged ≥12 years old were selected. Results demonstrated, for the first time, a rapid and stable increase in forced expiratory volume (FEV_1) in these patients. This was also associated with a drop in pulmonary exacerbations, hospitalisations, intravenous antibiotic courses, an increase in body weight, and an improvement in quality of life. However, as the patients were selected based on their pulmonary functions, very few would have been considered for lung transplantation.

Martin described an early access programme in France, which began in January 2020. This programme was designed to provide early access to CFTR modulators for patients with advanced CF, prior to full regulatory approval therapy. It was specifically aimed at patients with severe lung disease who had limited treatment options.

> **The introduction of CFTR modulators drastically reduced the number of lung transplantations for CF in France**

The eligibility criteria for the programme were carefully assessed, including the presence of the Phe508del allele variant and FEV_1 pulmonary function below 40%, indicating significant pulmonary impairment. The goal of the programme was to treat these patients early, offering them a chance to improve lung function and overall health by accessing treatment early. Over the course of the programme, patients demonstrated significant improvements in lung function, reduced oxygen needs, fewer hospitalisations, and better quality of life.

These benefits were maintained over the long term, and some patients no longer required lung transplantation at the end of 1 year of treatment.

Martin also described how the introduction of CFTR modulators drastically reduced the number of lung transplantations for CF in France, from 80–100 per year before the COVID-19 pandemic to around eight per year after. Martin emphasised that this drop is largely attributed to the effectiveness

of modulators in stabilising pulmonary function. However, approximately 8–10% of patients, particularly those with rare or non-responsive CF variants, still require transplantation.

Martin continued by describing the French compassionate programme, which expanded access to CFTR modulators for patients with advanced lung disease, regardless of genotype. Although the need for lung transplantation has decreased, patients with CF with impaired lung function may still require transplants in the future. Martin emphasised that this population requires follow-up, and proper early referral for lung transplantation if necessary.

In her concluding remarks, Martin explained that CF may still be an indication for lung transplantation in two groups of patients: those who cannot access elexacaftor/tezacaftor/ivacaftor (ETI) therapy, which is the newest CFTR modulator drug approved for the treatment of patients with CF aged ≥6 years with at least one copy of the F508del mutation (F) in the *CFTR* gene; and those with rare or non-responsive variants, who, despite being initiated on ETI, have advanced lung disease and may still require lung transplantation in the future.

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of patients, particularly those with rare or non-responsive CF variants, still require transplantation

CAN MACHINE LEARNING HELP US IN PHENOTYPING CYSTIC FIBROSIS AND PREDICT PROGNOSIS?

The second talk was delivered by Tamara Vagg, Cystic Fibrosis Centre, Cork, Ireland. Vagg began by introducing machine learning in the context of phenotyping as an emerging tool in CF research, particularly in phenotyping, prognosis, and lung transplantation. Machine learning can be used to identify patterns in data, and cluster patients based on factors such as disease severity and response to treatments while improving its predictions over time based on the information it gathers. However, its success depends on the availability of high-quality data.

Vagg described three key studies in this area that demonstrate its potential. Firstly, a 2021 UK-Canadian study[2] identified four CF phenotypes independent of lung function, linking them to factors like weight, height, hospitalisations, and pathogen growth, with two clusters showing milder disease and two showing more severe cases. The data demonstrated how ML can be used to refine CF phenotyping beyond traditional markers, offering a more comprehensive view of the disease severity.

The second study, a one French from 2022[3] predicted patient responses to lumacafor/ivacaftor after 1 year by analysing CT scans and identified three clusters based on lung abnormalities, age, and MRSA colonisation, as well as other factors. Interestingly, the youngest group in this study has the best treatment response.

This shows how ML can help predict patient-specific responses to CFTR modulators, allowing clinicians to personalise treatment based on predicted outcomes.

Lastly, a 2020 US study,[4] used microbiome data to predict lung function decline and demonstrated that analysing the whole microbiome provided better insights than just focusing on pathogens. This suggests that ML can deepen our understanding of how the microbiome influences disease progression, potentially leading to new therapeutic approaches in the treatment of CF.

Vagg went on to describe a study that suggested ML could aid in diagnosing post-transplant complications and refine immunosuppressive regimens. ML also has the potential to improve waiting list optimisation, and organ allocation, and predict patient graft survival. However, most current research is limited and does not really explore these applications in CF lung transplantation. "This gap presents a challenge but also a huge opportunity," concluded Vagg.

Much like the advanced CFTR modulators described earlier, ML can be a useful tool in reshaping CF care, especially in areas like prognosis and lung transplantation. Expanding research and improving data quality will be key to unlocking its full potential.

CURRENT STATUS AND FUTURE CHALLENGES

Alberto Benazzo, Department of Thoracic Surgery, Medical University of Vienna, Austria, began with a brief history of CF, as it is important to understand the history of the disease to develop better treatments. The first lung transplantation in patients with CF occurred in the late 1980s marking lung transplantation as the standard of care for patients with an advanced stage of lung disease. The steep rise in CF transplantation rates was then stabilised by the introduction of a multidisciplinary approach, which improved the management of this disease in patients.

Early challenges in managing this disease included managing infections, malnutrition, and severe respiratory conditions. The development of extracorporeal membrane oxygenation devices and CO_2 removal devices allowed patients to receive transplants safely, even when critically ill. As a result of all these efforts, patients with CF now experience some of the best transplant outcomes, in all underlying conditions, as shown by the data from international registries and single centres like the Toronto Transplant Group.

The introduction of CFTR modulators in 2019 changed the landscape for the disease. Two studies[1,5] investigated the efficacy of triple therapy CFTR modulators in people with cystic fibrosis, with a F508del mutation, and demonstrated excellent results, this led to a dramatic decrease in the number of lung transplants and mortality.

These developments pose some questions for the future, one of them being whether lung transplantation will simply be postponed in patients with CF. Benazzo mentioned that further postponement of lung transplantation will come with a higher burden of concomitant diseases like complications of diabetes mellitus, cardiovascular disease, osteoporosis, and cancer. Another question is whether lung transplant patients will be eligible for ETI, specifically patients with mutations that are not approved for CFTR modulators. Benazzo described a case from his centre, a 17-year-old patient with an N1303k mutation and a heterozygous carrier for alveolar microlithiasis, and CF-related comorbidities. The patient was initially on antibiotic therapy every 10 weeks. A healing attempt was initiated with ETI, whereby her weight and lung function improved, and she was never listed for a lung transplant.

According to Benazzo, the case of this patient and descriptions in several studies like the Burgel et al.[6] demonstrate that patients with mutations that are not FDA-approved for CFTR can still benefit from this specific treatment. However, some cases that present severe haemoptysis or with rare mutations may still necessitate transplants.

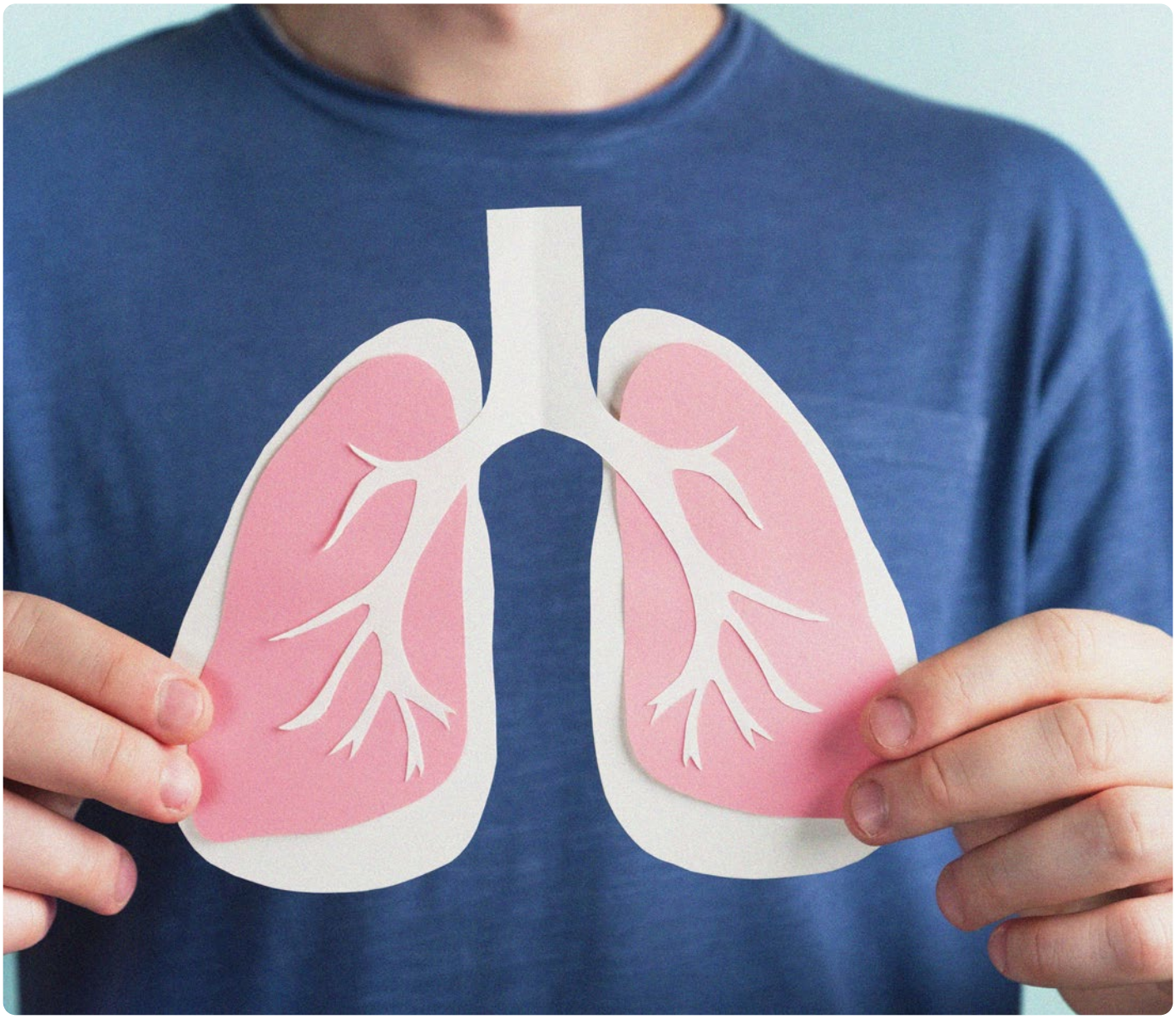
In conclusion, CF lung transplantation has achieved excellent outcomes throughout years of multidisciplinary work, but the advent of CFTR modulators poses a new challenge in determining which patients will require transplants in the future.

CONCLUSION

The evolution of care, marked by novel therapies and technology, is transforming the landscape of lung transplantation.

While the need for transplants has decreased significantly due to improved patient outcomes, ongoing research and innovations will be essential in identifying which patients with CF still require lung transplantation. As CF care continues to evolve, maintaining expertise in high-volume transplant centres and leveraging emerging tools like machine learning will be key to improving care and ensuring successful outcomes for all patients.

“The advent of CFTR modulators poses a new challenge in determining which patients will require transplants in the future”



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