ISHLT PEDIATRICS. JUNE 2022
JOURNAL WATCH

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Survival difference between high-risk and low-risk (CFTR) genotypes after lung transplant

Clausen et al. The Journal of Heart and Lung Transplantation, May 2022

STUDY HIGHLIGHTS

Background: There is evidence that cystic fibrosis transmembrane conductor regulator (CFTR) genotypes influence clinical outcomes in cystic fibrosis (CF) patients. It is not known if these genotypes affect lung transplant outcomes.

Method: Retrospective cohort study, combining data from the Organ Procurement and Transplantation Network and the US CF Foundation Patient Registry. This identified 1,830 CF patients older than 12 years who had received a first lung transplant between 2005-2017.

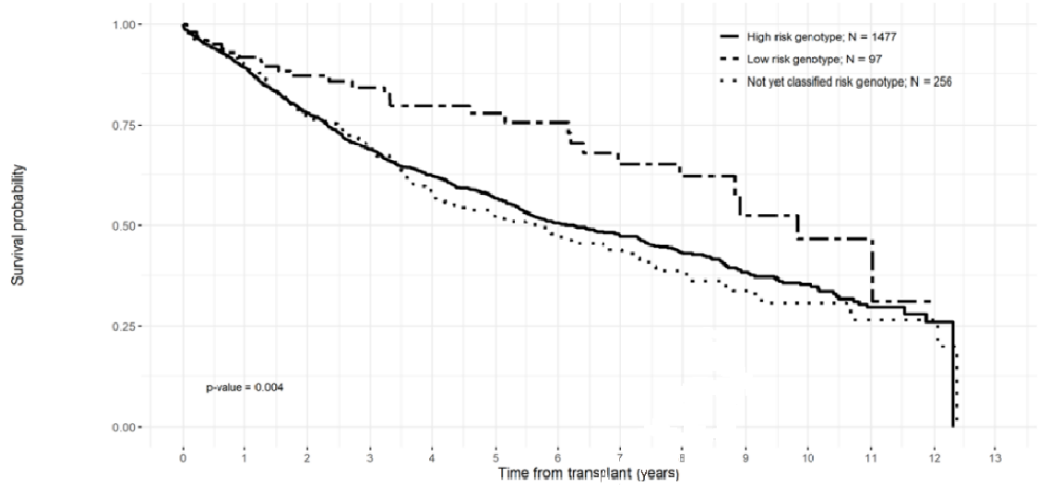
Results:
Median time to graft failure by CFTR genotype:
- Low-risk = 9.83 years
- High-risk = 6.25 years
- Not yet classified = 5.75 years

(other factors associated with graft failure included: age, transplant centre volume, presence of Burkholderia cepacia complex and use of Medicaid insurance)

Conclusions:
- Low-risk CFTR genotypes are associated with better post-transplant graft survival rates

CENTRAL FIGURE

Figure 2 Kaplan-Meier plot showing post-transplant time to graft failure by CFTR genotype. Low-risk CFTR genotype recipients have better graft survival after transplant compared to those with high-risk or not yet classified genotypes. CFTR, cystic fibrosis transmembrane conductance receptor.



Risk factor	Hazard ratios*		P value*
CFTR genotype risk	Low vs High Unclassified vs High	0.57 (0.39, 0.83) 1.08 (0.89, 1.31)	0.004
Age (per 5-year increase)	Age <=35 years Age >35 years	0.79 (0.74, 0.83) 1.04 (0.96, 1.13)	<0.001
Transplant centre volume	Low vs High Medium vs High	1.37 (1.16, 1.60) 1.27 (1.05, 1.54)	<0.001
BMI (per 1 unit increase)	BMI <=18.5 BMI >18.5	0.89 (0.83, 0.96) 1.00 (0.97, 1.03)	0.003
Burkholderia cepacia complex		1.37 (1.14, 1.64)	0.001
Medicaid insurance		1.61 (1.36, 1.91)	<0.001

**Unadjusted figures*

REVIEWER'S COMMENTS

Definitions of high-risk and low-risk CFTR genotypes were based on McKone et al *(CFTR genotype as a predictor of prognosis in cystic fibrosis. Chest. 2006)*

Neither this study, nor a similar review of Canadian registry data from 2015, found an association between graft failure and F508del (the most common CFTR mutation, which is classed as high-risk). This suggests further analysis of what constitutes high- and low-risk genotypes is required.

LIMITATIONS

- Reliance on registry data meant it was not possible to assess for patient adherence to post-transplant treatment regimens
- The study cohort was restricted to the USA and therefore may not be representative of other countries
- The effect of CFTR modulators was not accounted for in the study
- The definition of Medicaid use was based on patient status at the time of transplant

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Ex vivo enzymatic treatment converts blood type A donor lungs into universal blood type lungs

Wang et al. Sci Transl Med, February 2022

STUDY HIGHLIGHTS

Background: Lung transplant requires ABO blood group matching resulting in a lower likelihood of transplant for certain candidates.

Methods: Pre-clinical study assessing ability of enzymes to remove A antigen from human donor lung with EVLP. Additional Ex-vivo plasma perfusion model to simulate ABO incompatible lung transplant with 3 donor lungs v control.

Results: Removal of 100% of A-Ag from red blood cells & 90% from aortae using enzyme treatment. A-Ag depleted by 97% in human lungs treated with enzymes. Reduced vascular expression of A-Ag to 1-2.4% in enzyme treated simulated model with inhibition of antibody binding, completement deposition and antibody mediated injury in treated lungs v control.

CENTRAL FIGURE

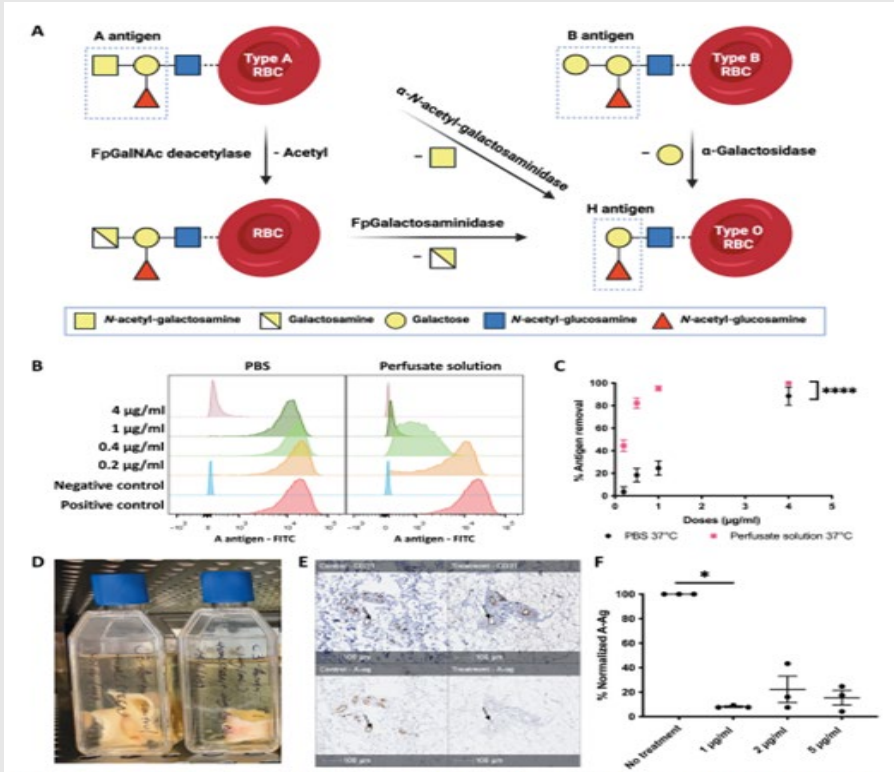

Fig. 1. Azymes removed A-Ag from human ABO-A1 RBCs and aortae in the presence of perfusate solution. (**A**) Concept of enzymatic removal of ABO antigen. The dashed boxes show basic ABH antigens on red blood cells (RBCs) [modified from Rahfeld *et al.* (*8*)]. Enzymatic reactions by respective enzymes remove the terminal α-*N*-acetyl-galactosamine or α-galactose monosaccharide and turn A/B red cells to an O type. This study examines the paired enzymatic actions by FpGalNAc deacetylase and FpGalactosaminidase (Azymes) to remove A antigen (A-Ag) from organs. Sugars are shown using the Consortium for Functional Glycomics (CFG) notation (*30*). (**B**) The histograms show A-Ag expression on RBCs treated with Azymes at the indicated doses in either PBS or perfusate solution. RBCs were treated for 30 min at 37°C. The positive control is untreated ABO-A RBCs, and the negative control is group ABO-O RBCs. Cells were stained with fluorescein isothiocyanate (FITC)–conjugated anti-A antibody. (**C**) The degree of antigen removal was quantified on the basis of percent changes in MFI relative to baseline. For each dose group, $n = 5$ RBC treatments were conducted. (**D**) The image shows static incubation of aortae in perfusate solution. Samples were incubated without (control) or with Azymes (treatment) at 37°C for 4 hours. (**E**) Representative images of immunohistochemical staining of aortae are shown, zoomed in the adventitial side. Positive staining is denoted by brown color and arrows. A-Ag staining colocalized with CD31 staining, which indicates endothelial cells, in control aortae, but was reduced

REVIEWER'S COMMENTS

- Potentially beneficial strategy to overcome ABO compatibility in lung transplantation, yielding greater potential access to transplantation for blood group O candidates.
- In simulated ABO incompatible lung transplant enzyme treatment prevented hyperacute injury.

LIMITATIONS

- Pre-clinical ex-vivo study, in vitro physiology & results may differ.
- Lack of post-transplant clinical data due to pre-clinical nature of study.

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Sustained effectiveness of elexacaftor-tezacaftor-ivacaftor in lung transplant candidates with cystic fibrosis

Martin et al. Journal of Cystic Fibrosis, February 2022

STUDY HIGHLIGHTS

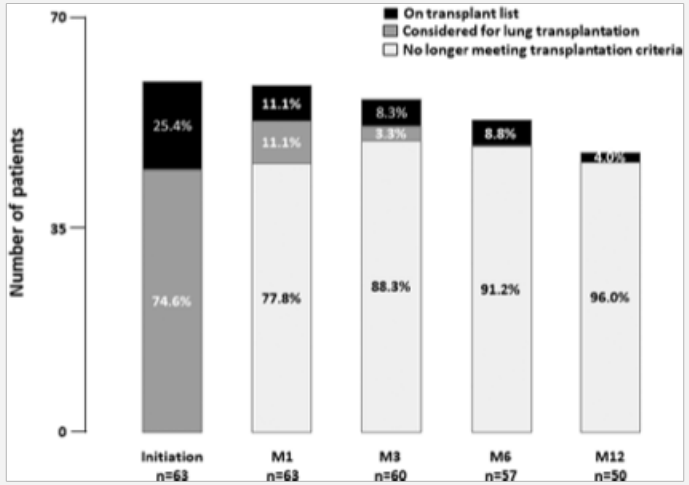
Objective: describe the **evolution of Cystic Fibrosis (CF) patient status toward lung transplantation** 12 months after the initiation of elexacaftor-tezacaftor-ivacaftor.

Methods: 65 CF Lung transplant candidates from 47 French centres, >12 y.o., having at least one Δ508del mutation, who have initiated **elexacaftor-tezacaftor-ivacaftor** were prospectively followed up from initiation to July 2021 (median **363 days**).

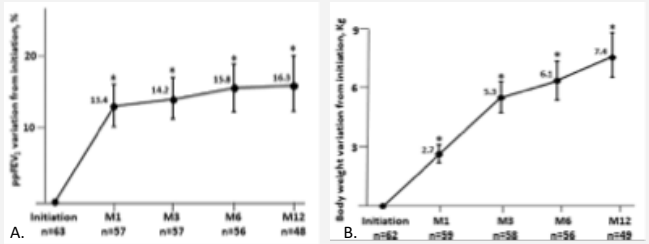
Results:

- **61 patients no longer met transplantation criteria**, 2 transplanted after 5 and 11 days from initiation, 2 listed for transplantation
- Only **mild** and transient **side effects**
- **ppFEV1 mean increase of 13.4%** at 1 month, then stable throughout the follow up
- **Body weight** mean i**ncrease of 7.4 kg**, mean BMI from 18.7 to 21.4 kg/m2 after one year
- **IV antibiotics required** in 93.7% before VS **36.5%** after initiation
- **Long term Oxygen** therapy **required** in 73% before vs **30%** after one year of treatment
- **Non-invasive ventilation required** in 52.4% before vs **20%** after one year of treatment

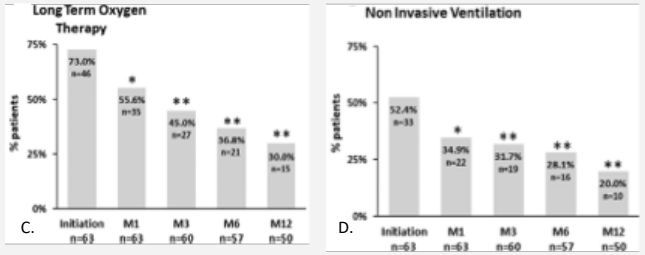
CENTRAL FIGURE



Status towards lung transplantation at initiation of elexacaftor-tezacaftor-ivacaftor, 1-3-6 and 12 months



Evolution of ppFEV1 (A) and Body weight (B) at initiation, 1-3-6 and 12 months



Proportion of patients treated with long term oxygen therapy (C) or noninvasive ventilation (D) at initiation, 1-3-6 and 12 months

REVIEWER'S COMMENTS

✓ Patients experienced rapid and substantial clinical improvement, sustained over 12 months

✓ First evidence of prolonged disease modification in patients with very advanced pulmonary disease

LIMITATIONS of THE STUDY

✗ **No control group:** some effects may be not entirely related to treatment initiation (ex. reduction in IV antibiotic related with preventative measures taken during Sars-Cov2 pandemic?)

✗ **Follow up length**: data on patients with Gly551Asp mutation on ivacaftor suggests that lung function decline remains unchanged over 5 years, despite initial improvement

? **QUESTION RAISED**

Current criteria for lung transplant listing may need to be revisited?