European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:
Characterization of CFTR mutations in people with cystic fibrosis and severe liver disease who are not eligible for CFTR modulators.

Lay Title:
CFTR modulators: a new therapeutic approach but not for all CF patients

Authors:
Carla Colombo[1,2], Grant A Ramm[3], Anders Lindblad[4], Fabiola Corti[1], Luigi Porcaro[1], Federico Alghisi[5], Irina Asherova[6], Helen Evans[7], Nataliya Kashirskaya[8], Elena Kondratyeva[8], Peter J Lewindon[9], Isabelle de Monestrol[10], Mark Oliver[11], Chee Y. Ooi[12], Rita Padoan[13], Sahana Shankar[11] and Gianfranco Alicandro [1,2]

Affiliations:
[1] IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[2] Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy
[3] QIMR Berghofer Medical Research Institute, Brisbane, Australia
[4] Queen Silvia Children's Hospital, Gothenburg, Sweden
[5] Ospedale Pediatrico Bambino Gesù, Rome, Italy
[6] City Children's Hospital N1, Yaroslavl, Russia
[7] Starship Children's Health, Auckland, New Zealand
[8] Federal State Budgetary Scientific Institution «Research Centre for Medical Genetics», Moscow, Russia
[9] Queensland Children's Hospital, Brisbane, Australia
[10] Karolinska University Hospital, Stockholm, Sweden
[11] Royal Children's Hospital, Melbourne, Australia
[12] Sydney Children's Hospital & School of Women's and Children's Health, Medicine, University of New South Wales, Sydney, Australia
[13] ASST Spedali Civili Brescia, Brescia, Italy

Corresponding author:
Carla Colombo
Professor of Pediatrics
University of Milan
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Cystic Fibrosis Research News

Cystic Fibrosis Centre
Via Della Commenda 9, 20122, Milan, Italy
e-mail: carla.colombo@unimi.it
Tel. +39 0255032456, Fax. +39 0255032814

What was your research question?

CFTR modulators (CFTR-Ms) have had a dramatic impact on lung disease in people with CF and eligibility for such treatment is based on the type of CFTR mutations they carry. However, the effects of CFTR-Ms on CF-liver disease (CFLD) are limited. CFTR-Ms may reduce or even prevent its development and progression, but this will take time to demonstrate.

Why is this important?

CF-related liver disease is a common complication of CF which may progress to portal hypertension with or without cirrhosis in 5-10% of cases. In the advanced stage, it is associated with pulmonary function decline and nutritional status deterioration. Meanwhile there remains an unmet therapeutic need for people with CF carrying mutations not eligible for CFTR-Ms treatment, particularly for those with advanced liver disease, which is often associated with poorer prognosis and reduced survival.

What did you do?

Our aim was therefore to quantify this unmet need in a large group of 1591 people with CF previously enrolled in a retrospective international study from 11 centers (in Europe, Russia, Australia, and New Zealand) to characterize development and progression of CFLD (Colombo C et al., J Cyst Fibros 2022;21:220-6). These patients had been followed from birth up to a median age of 15 years and severe CFLD had developed in 171 of these people with CF. A further analysis of genetic eligibility for elexacaftor, tezacaftor, ivacaftor (ETI), and ivacaftor (IVA) monotherapy was performed in people with CF who had developed severe CFLD with portal hypertension and in those who did not (1420 patients).

What did you find?

Based on CFTR mutations, 13% (N=184/1420) of people with CF without CFLD and 11% (N=19/171) of those with severe CFLD were not eligible for either ETI or IVA therapy. Among the 19 non-eligible people with CF having severe CFLD, we identified 20 genetic variants (17 CF-causing, 2 of uncertain significance, 1 non-disease-causing); 13/20 (65%) resulted in an incomplete protein due to the type of genetic mutation (stop codon or insertion/deletion).

Cystic Fibrosis Research News

All the 19 ineligible people with CF carried at least one mutation leading to complete loss of the CFTR function and 7/19 were carriers of two mutations of this type.

What does this mean and reasons for caution?

Our data indicate that a significant proportion of people with CF could not have access to currently available CFTR-Ms due to their specific CFTR mutations and thus would remain at risk of developing severe CFLD. Even if CFTR-Ms will prove effective in mitigating its development, there remains an unmet therapy need for ineligible patients.

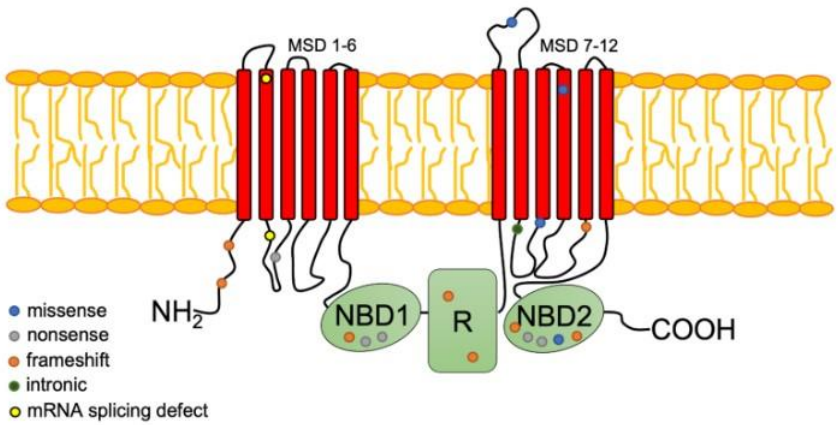
What's next?

Despite remarkable achievements in understanding disease mechanisms and developing treatments for CF over the last two decades, there are still significant unmet needs for people with CF, many involving non-pulmonary complications, including CFLD. There is a clear need for novel, more effective CFTR-Ms and/or of alternative mutation-agnostic therapeutic strategies to cover these unmet needs.

In a large retrospective international cohort study, 171 patients developed severe liver disease

19 of them were ineligible for CFTR modulators

All ineligible patients carried at least one mutation leading to complete loss ofCFTR function



MSD: Membrane Spanning Domain.

NBD: Nucleotide Binding Domain.

R: Regulatory Domain.

Original manuscript in PubMed

https://pubmed.ncbi.nlm.nih.gov/36739240/