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

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ABSTRACT

Cystic-fibrosis-related liver disease (CFLD) is a variable phenotype of CF. The severe CFLD variant with cirrhosis or portal hypertension has a poor prognosis and life expectancy.

CFTR modulator therapies are now available for people with CF and eligibility for such treatment is based on their CFTR genotype. We evaluated the genetic eligibility for elexacaftor, tezacaftor, ivacaftor (ETI), and ivacaftor (IVA) monotherapy in a previously reported CF cohort of 1591 people with CF of whom 171 with severe CFLD. Based on their CFTR mutations, 13% (N=184/1420) of subjects without CFLD and 11% (N=19/171) of those with severe CFLD are not eligible for either ETI or IVA therapy.

The non-eligible patients without CFLD or with severe CFLD can currently not take advantage of the potential benefits of these new treatments. Although this study cannot provide any data regarding the effect of ETI or IVA on the progression of severe CFLD, the consequences for ineligibility of patients with extreme liver phenotype may be even more significant because of their poorer disease risk profile.

1. Introduction

Highly effective CFTR modulators targeting specific genotypes of the Cystic Fibrosis (CF) Transmembrane Conductance Regulator (CFTR) protein are radically changing the natural history and management of CF. Their efficacy in improving respiratory outcomes has been demonstrated in randomized clinical trials, and also in the real world setting [1–6]. However, not all patient genotypes are eligible for CFTR modulators therapy.

CF-related liver disease is a common complication of CF and in its severe form occurs in 5-10% of the patients [7]. In the advanced stage, it is associated with pulmonary function decline, nutritional status deterioration and increased risk of death [8].

In this study, using data from a large, well characterised international cohort of patients with CF [9], we evaluated the genetic non-eligibility for potential CFTR modulator treatment with the triple combination of elexacaftor, tezacaftor, ivacaftor (ETI) or ivacaftor (IVA) monotherapy in patients with severe CFLD.

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2. Methods

This study is a follow-up analysis of genetic CFTR modulator eligibility based on the same patient cohort retrospectively studied for CF liver-related outcome and previously published [9]. In that study, 1591 patients had been enrolled in 11 CF centres and followed up for the occurrence of severe CFLD (portal hypertension with or without cirrhosis) from diagnosis of CF up to 31 December 2016. The characteristics of our cohort and the selection criteria were reported in details in our previous paper [9]

CFTR genotypes were determined by 1st level analysis for the screening of the most frequent pathogenetic variants/ rearrangements in the CFTR gene. If genotyping was inconclusive, because of the identification of only one or no pathogenetic variants, a 2nd level analysis was performed by sequencing all the coding sequence and part of the intronic regions of the gene. Genotypes were then classified according to whether patients would be eligible for treatment with CFTR modulators including ETI or Lumacaftor/IVA or Tezacaftor/ IVA for patients with at least one F508del mutation, and IVA monotherapy for patients with gating mutations [1]. More recently eligibility has been extended to a subgroup of non-F508del patients carrying other specific mutations, based on their in vitro response to CFTR modulators [10].

Occurrence of liver outcomes was compared between patients with a genotype compatible with CFTR modulator prescription and those with a genotype which was not. Incidence of severe liver disease, as defined by the occurrence of portal hypertension with or without cirrhosis, were computed as number of events per 1000 person-years with the corresponding 95% confidence intervals (CI) obtained from the Poisson distribution. To compare incidence between groups, we estimated the incidence rate ratio (IRR) using the group of patients eligible for the treatment as a reference.

The study was approved by the respective Ethics Committees of all 11 participating CF centres.

3. Results

The original study [9] had enrolled 1591 patients regularly followed in the participating centres up to a median age of 15 years (interquartile range: 12-19 years, min: range: 9-26 years); 1276 (80.2%) had at least one copy of the F508del mutation and thus would be eligible for treatment with CFTR modulators. This percentage rose to 87.2% (n=1388) when the new criteria based also on in vitro studies were applied.

More patients from New Zealand (241/252, 95.6%) and Australian (383/415, 92.3%) centres would be eligible for treatment compared to patients followed-up in Swedish (160/181, 88.4%), Russian (126/153, 82.4%) and Italian (478, 590, 81.0%) centres.

Over the follow-up 171 patients developed severe liver disease (Table 1). Of them 23 (13.5%) were in the waiting list for liver transplantation and 14 (8.2%) were transplanted. Approximately 10% of cases with cirrhosis, portal hypertension, hypersplenism and esophageal varices occurred among patients not eligible for CFTR modulators, with 2 patients requiring liver transplantation.

Cumulative incidence of severe CFLD was 5.83 cases per 1000 person-years (95% CI: 3.51-9.11) among patients who were not eligible for CFTR modulators and 6.84 (95% CI: 5.80-8.02) among those who were eligible for treatment (IRR: 0.85, 95% CI: 0.50-1.38, P= 0.57).

The CFTR genotype and liver status of the 19 patients who developed severe liver disease and would not be eligible to receive ETI/IVA alone are described in **the online supplementary Table S1**. Overall, 20 variants were observed all of which, except 3, are known to be CF-causing [11]; 13 (65%) resulted in a truncated protein due to a stop codon, or ins/del mutations, and were present on both alleles in 7 out of 19 patients.

Table 1
Liver outcomes in patients with cystic fibrosis according to CFTR genotype groups, defined by eligibility for CFTR modulators.

Eligible for ETI/Ivacaftor alone			
	No	Yes	Total
No. of patients	203 (12.8)	1388 (87.2)	1591 (100)
Cirrhosis or PHT	19 (11.1)	152 (88.9)	171 (100)
Cirrhosis	16 (10.4)	138 (89.6)	154 (100)
PHT	13 (11.4)	101 (88.6)	114 (100)
Waiting list for Liver Tx	3 (13.0)	20 (87.0)	23 (100)
Liver Tx	2 (14.3)	12 (85.7)	14 (100)

Data are numbers (%)
ETI:Elexacaftor, Tezacaftor, Ivacaftor. PHT: Portal Hypertension.

4. Discussion

In this study, carried out in a period before availability of any CFTR modulators, we used data from a large retrospective international cohort focused on long term outcomes of liver disease, to demonstrate the size of the unmet need for potential prevention of severe CFLD using CFTR modulators.

Using the current extended eligibility criteria, we found a prevalence of patients not eligible to CFTR modulators in the whole cohort of 12.8%. This figure was similar to that reported by the US CF Foundation Patient Registry (~10% by end of 2021) [12], and slightly higher than a recent UK Registry prevalence report of 8.6% non-eligible patients, based on the presence of at least one copy of F508del mutation, with higher figures among minority ethnic groups [13].

Thus, if CFTR modulators are proven beneficial on the occurrence and progression of CFLD, the increasing international use of CFTR modulators may prevent the majority of cases of severe liver disease from developing. However, a significant proportion of patients will not have access to CFTR modulators due to their specific genotype and remain at risk of developing this serious complication.

The genotypes of the 171 patients with CFLD who progressed to severe liver disease were fully characterized and we found that 19 (11%), according to the current prescription indications, would not be eligible for CFTR modulator therapy. Of note, most carried severe mutations involving a premature stop codon resulting in a truncated protein, leading to complete loss of the CFTR function. Rare and unusual mutations, which have been suggested to represent possible features in otherwise undiagnosed end-stage liver disease in infancy, were seldom observed in our cohort [14].

Despite remarkable achievements in understanding disease mechanisms and developing treatments for CF over the last two decades, there are still significant unmet needs for patients, many involving the extrapulmonary complications of CF, including liver disease [15].

In conclusion, the distribution of people not eligible for CFTR modulator therapy is not related to the absence or presence of severe liver disease. Even though CFTR modulators may help to prevent or slow CFLD progression, our data indicate that a substantial proportion of patients at risk of developing severe CFLD will not be eligible to receive them.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Carla Colombo: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Grant A Ramm:** Investigation, Writing – review & editing. **Anders Lindblad:** Investigation, Writing – review & editing. **Fabiola Corti:** Data curation, Investigation, Writing – review & editing. **Luigi Porcaro:** Investigation, Data curation, Visualization, Writing – review & editing. **Federico Alghisi:** Investigation, Writing – review & editing. **Irina Asherova:** Investigation, Writing – review & editing. **Helen Evans:** Investigation, Writing – review & editing. **Nataliya Kashirskaya:** Investigation, Writing – review & editing. **Elena Kondratyeva:** Investigation, Writing – review & editing. **Peter J Lewindon:** Investigation, Writing – review & editing. **Isabelle de Monestrol:** Investigation, Writing – review & editing. **Mark Oliver:** Investigation, Writing – review & editing. **Chee Y. Ooi:** Investigation, Writing – review & editing. **Rita Padoan:** Investigation, Writing – review & editing. **Sahana Shankar:** Investigation, Writing – review & editing. **Gianfranco Alicandro:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.01.012.

References

[1] Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple therapy for cystic fibrosis phe508del gating and residual function genotypes. N Engl J Med 2021;385:815–25. doi:10.1056/nejmoa2100665.
[2] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940–8. doi:10.1016/S0140-6736(19)32597-8.
[3] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single phe508del allele. N Engl J Med 2019;381:1809–19. doi:10.1056/nejmoa1908639.
[4] Mall MA, Mayer-Hamblett N, Rowe SM. Cystic fibrosis: emergence of highly effective targeted therapeutics and potential clinical implications. Am J Respir Crit Care Med 2020;201:1193–208. doi:10.1164/rccm.201910-1943SO.
[5] Regard L, Martin C, Burnet E, J DaS, Burgel P-R. CFTR modulators in people with cystic fibrosis. Real-World Evid France Cells 2022;11:1769. doi:10.3390/cells11111769.
[6] Graeber SY, Renz DM, Stahl M, Pallenberg ST, Sommerburg O, Naehrlich L, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two f508del alleles. Am J Respir Crit Care Med 2022. doi:10.1164/RCCM.202201-0219OC.
[7] Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology 1999;30:1151–8. doi:10.1002/hep.510300527.
[8] Ye W, Narkewicz MR, Leung DH, Karnsakul W, Murray KF, Alonso EM, et al. Variceal hemorrhage and adverse liver outcomes in patients with cystic fibrosis cirrhosis. J Pediatr Gastroenterol Nutr 2018;66:122–7. doi:10.1097/MPG.0000000000001728.
[9] Colombo C, Alicandro G, Oliver M, Lewindon PJ, Ramm GA, Ooi CY, et al. Ursodeoxycholic acid and liver disease associated with cystic fibrosis. A Multicenter Cohort Study J Cyst Fibros 2022;21:220–6. doi:10.1016/j.jcf.2021.03.014.
[10] Trikafta - Highlights of prescribing information. https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf (accessed June 20, 2022).
[11] Clinical and Functional Translation of CFTR. https://cftr2.org/(accessed June 20, 2022).
[12] Cystic Fibrosis Foundation. 2021 Cystic Fibrosis Foundation Patient Registry Highlights 2022. https://www.cff.org/medical-professionals/patient-registry (accessed October 13, 2022).
[13] Desai M, Hine C, Whitehouse JL, Brownlee K, Charman SC, Nagakumar P. Who are the 10%? - non eligibility of cystic fibrosis (CF) patients for highly effective modulator therapies. Respir Med 2022;199:106878. doi:10.1016/j.rmed.2022.106878.
[14] Khan HH, Mew NA, Kaufman SS, Yazigi NA, Fishbein TM, Khan KM. Unusual cystic fibrosis transmembrane conductance regulator mutations and liver disease: a case series and review of the literature. Transplant Proc 2019;51:790–3. doi:10.1016/j.transproceed.2018.11.007.
[15] West NE, Flume PA. Unmet needs in cystic fibrosis: the next steps in improving outcomes. Expert Rev Respir Med 2018;12:585–93. doi:10.1080/17476348.2018.1483723.