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Original Article

Evolution of hepatobiliary involvement in cystic fibrosis children on *CFTR* modulators

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ABSTRACT

Background: There are great changes in cystic fibrosis (CF) disease following introduction of modulator treatments. We aimed to focus on the evolution of hepatobiliary involvement following lumacaftor-ivacaftor (LI) and elexacaftor-tezacaftor-ivacaftor (ETI) initiation.
Methods: A retrospective monocentric observational study included 62 CF children treated with CFTR modulators. Data were collected at initiation and after one year of treatment. The primary objective was to describe the evolution of hepatobiliary involvement under CFTR modulator treatment.
Results: We identified hepatobiliary involvement before treatment in 37 patients (59.7 %). Fifteen had persistently (during >6 months) elevated liver enzymes (mostly ALT); 17 had abnormal ultrasound including 3 with nodular liver and 3 with pathological elastography; 5 had isolated splenomegaly. Biliary involvement was found in 19 patients. The evolution of hepatic parameters in the overall population was not significant ($p > 0.05$). However, we observed a trend towards improvement in laboratory values under treatment. There was only one inaugural diagnosis of nodular liver under LI and none under ETI. All patients had preserved liver function (PT>50 %).
Conclusions: We did not find a significant improvement or worsening of hepatobiliary involvement under CFTR modulators. We hypothesize that it could be stabilized with these treatments, but this will need confirmation through further studies with longer follow-up and larger cohorts. The other hypothesis proposed is that biological monitoring may not be an accurate assessment of the hepatobiliary response to modulators. This study supports the safety of CFTR modulator use.

1. Introduction

Advances in knowledge regarding the *Cystic Fibrosis conductance Transmembrane Regulator (CFTR)* gene have led to the development of protein therapies specifically targeting the defective CFTR protein, known as CFTR modulators. Various tolerance and efficacy studies have reported remarkable results in cystic fibrosis (CF) patients, with a significant improvement in forced expiratory volume in one second (FEV1), a decrease in exacerbation frequency, and sweat chloride levels [1–3]. With the increase in life expectancy among CF patients, liver involvement has become the third leading cause of mortality after respiratory-related deaths and those secondary to transplantation complications [4,5], although its proportion remains significantly lower. Hepatobiliary involvement in CF is frequently asymptomatic, and its phenotypic presentations are extremely variable. New studies evaluating the efficacy and safety of CFTR modulators on liver involvement,

Abbreviations: AST, Aspartate Transaminase; ALT, Alanine aminotransferase; ARFI, Acoustic Radiation Force Impulse; BMI, Body Mass Index; CF, Cystic Fibrosis; CFTR, Cystic Fibrosis conductance Transmembrane Regulator; ETI, Elexacaftor/Tezacaftor/Ivacaftor; FEV1, Forced Expiratory Volume in one second; GGT, Gamma-Glutamyl Transferase; LI, Lumacaftor/Ivacaftor.

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based on a universal classification, are important to harmonize clinical practices [6]. The objective of this study is therefore to describe the hepatobiliary phenotype of the CF paediatric population managed at the Toulouse Cystic Fibrosis Reference Center, and to evaluate its evolution under treatment with CFTR modulators, Lumacaftor/Ivacaftor (LI) and Elexacaftor/Tezacaftor/Ivacaftor (ETI).

2. Methods

2.1. Design and study population

This is a single-center retrospective observational non-interventional study with data collection covering the period from April 2017 to June 2023. Patients under 18 years with a confirmed CF diagnosis (sweat chloride > 60mmol/l and genetic confirmation) were included if treatment with CFTR modulator therapy was initiated at least one year before June 2023. At the time of inclusion, LI was approved in France for F508del homozygous patients who were older than 2 years, and ETI for patients with at least one F508del mutation who were older than 12 years. Among 118 pediatric patients followed at the Toulouse CF reference center, 62 (52 %) fulfilled the inclusion criteria and none objected. Fifty-six patients were not included because they were not eligible for CFTR modulators (either their mutation was not eligible for treatment or they did not meet the age criteria for the molecule's marketing authorization). This study was declared to the French authorities and approved by the Ethics Committee of the French-speaking Society of Paediatric Gastroenterology, Hepatology and Nutrition (reference number: 2023–55). Patients and their parents were informed with an information leaflet, and their non-opposition was obtained.

2.2. Data collection

Clinical and biological data were collected from medical records stored in electronic database. The data collected were used to define the presence or absence of hepatobiliary involvement (ultrasound results, elastography, liver enzymes values), as well as demographic data (sex, date of birth, genotype, age at initiation of treatment, weight, height) and data to assess CF (sweat chloride, FEV1, fecal elastase, fecal calprotectine, association with diabetes). These data were collected before treatment initiation (M0) and twelve months after (M12). Patients were divided into two subgroups: 1) "LI alone", 2) "ETI group". The ETI group included patients who received only ETI and also patients who received LI then ETI, with at least 1 year of ETI. These differences in the initiation of treatment were due to conditions of access and eligibility to CFTR modulators treatment in France. The occurrence of side effects was monitored through systematic patient/parent interviews and laboratory tests during multi-disciplinary outpatient visits.

2.3. Classification of cystic fibrosis hepatobiliary involvement (CFHBI)

We used the classification recently proposed by Bodewes et al. [7]. Liver enzymes were considered "persistently" elevated if it lasted more than six months. For the criterion of "Imaging of the liver", we used the results of liver ultrasound, a non-irradiating examination that could be performed in almost all of our patients. For the criterion of "Stiffness of the liver", we used 6.8 kPa as the pathological threshold, measured by Acoustic Radiation Force Impulse (ARFI) elastography during an ultrasound scan performed by pediatric radiologists [8]. For the criterion of "Portal hypertension", we included patients with splenomegaly (clinical or imaging) associated with signs of hypersplenism (thrombocytopenia) or complications of portal hypertension (for example, esophageal varices). For the criterion of "Biliary manifestations", we included patients diagnosed with gallstones (cholelithiasis or hepatolithiasis) or biliary strictures. We did not develop the "Histology" criterion as none of our patients underwent liver biopsy due to its invasive nature and often limited contribution in focal or multifocal lesions. Similarly, none of our patients had hepatocellular carcinoma or cholangiocarcinoma.

2.4. Statistical analysis

For the descriptive part, all available variables of interest were described at M0 and M12. Numerical variables were described using mean and standard deviation, median and quartiles (Q1, Q3). Categorical variables were described using frequencies and percentages. For the comparative analysis, we only analysed data available both at M0 and M12. For numerical variables, paired *t*-test or Wilcoxon signed-rank test was used, depending on the distribution of differences, whether normal or not, respectively. For categorical variables, the McNemar's Chi-squared test was used. These tests are adapted to paired data.

3. Results

The 62 patients eligible for treatment at the time of inclusion were enrolled in our study. Population characteristics are mentioned in Table 1. All patients carried at least one F508del mutation. FEV1

Table 1
Demographic description of study population ($n = 62$) and of subgroup "Hepatobiliary involvement" ($n = 37$) and "No hepatobiliary involvement" ($n = 25$) before treatment.

	Study population ($n = 62$)	Hepatobiliary involvement ($n = 37$)	No hepatobiliary involvement ($n = 25$)
Sex, n (%)			
Male	33 (53.2 %)	20 (54.1 %)	13 (52.0 %)
Female	29 (46.8 %)	17 (45.9 %)	12 (48.0 %)
Genotype, n (%)			
Homozygous for F508del	37 (59.7 %)	21 (56.8 %)	16 (64.0 %)
Heterozygous for F508del	25 (40.3 %)	16 (43.2 %)	9 (36.0 %)
Mutation class, n (%)			
1	7 (11.9 %)	6 (17.1 %)	1 (4.0 %)
2	47 (79.7 %)	27 (77.1 %)	20 (80.0 %)
3	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
4	3 (5.1 %)	1 (2.9 %)	2 (8.0 %)
5	2 (3.4 %)	1 (2.9 %)	1 (4.0 %)
Indeterminate	3 (5.1 %)	2 (5.8 %)	1 (4.0 %)
Age at T0 (y)			
Mean (SD)	10.4 (3.8)	10.6 (3.9)	10.2 (3.8)
Min, Max	2.3, 17.8	2.3, 17.8	3.3, 17.1
ppFEV1 (%)			
N	54	32	22
Median (Q1, Q3)	92.0 (81.0, 101.8)	87.5 (79.0, 96.8)	98.0 (86.0, 112.5)
Min, Max	60.0, 135.0	60.0, 129.0	61.0, 135.0
Pancreatic insufficiency, n (%)			
No	3 (4.8 %)	2 (5.4 %)	1 (4.0 %)
Yes	59 (95.2 %)	35 (94.6 %)	24 (96.0 %)
Glucose metabolism abnormalities, n (%)			
No	34 (54.8 %)	20 (54.1 %)	14 (56.0 %)
Yes	28 (45.2 %)	17 (45.9 %)	11 (44.0 %)
Weight (Z-score) at T0			
Mean (SD)	−0.1 (0.9)	−0.2 (0.9)	−0.1 (0.9)
Min, Max	−2.0, 1.8	−2.0, 1.6	−1.6, 1.8
BMI (Z-score) at T0			
Mean (SD)	−0.3 (1.0)	−0.4 (0.9)	−0.4 (1.0)
Min, Max	−2.4, 2.1	−2.4, 1.2	−2.3, 2.1
Treatment, n (%)			
ETI alone	25 (40.3 %)	16 (43.2 %)	9 (36.0 %)
LI alone	16 (25.8 %)	8 (21.6 %)	8 (32.0 %)
LI then ETI	21 (33.9 %)	13 (35.2 %)	8 (32.0 %)

measurement was only available for 54 patients because pulmonary function tests were not feasible in 8 patients due to their young age. FEV1 was slightly lower in the group of patients with hepatobiliary involvement (Table 1, $p = 0.05$).

The hepatobiliary phenotype of our population prior to the initiation of any treatment is reported in Table 2 and the evolution of hepatic parameters after one year of treatment in Table 3. Patients in the LI group and the ETI group were not comparable due to genotype and age differences related to treatment eligibility criteria. Among these 62 patients, 20 (32.3 %) were on UDCA at T0.

Among the 4 patients with a nodular liver under ETI, 3 of them already presented this condition before the initiation of treatment, and the 4th patient developed it during LI treatment. Therefore, no cases of nodular liver were diagnosed under ETI. The "ETI" column includes patients who received only ETI and also patients who received both treatments sequentially, because there was no significant difference between these two subgroups regarding the progression of liver parameters. Platelet count remained normal for all of our patients, and none of them presented hepatic insufficiency or gastrointestinal bleeding. Of note, none of our patients had hepatocellular carcinoma or cholangiocarcinoma.

3.1. Evolution of other gastrointestinal parameters

The study demonstrated a significant improvement in fecal elastase with LI ($p = 0.006$), with elastase values below 15 µg/g of stool for all patients at M0, increasing to 228 µg/g for one patient at M12 (Table 3 and Fig. 1A). However, the elastase values of the other patients remained in the pancreatic insufficiency range, mean 30.8 ± 58.1 µg/g. There was no significant change in fecal elastase with ETI, from 51.3 ± 176.2 to 62.1 ± 191.4 µg/g ($p = 0.1$) at M0 and M12 respectively.

The fecal calprotectin significantly decreased on ETI from 316.9 ± 394.8 to 100.2 ± 93.4 µg/g at M0 and M12 respectively ($p = 0.001$), while the decrease was not significant on LI (199.4 ± 178.4 to 163.4 ± 179.3 µg/g, $p = 0.4$) (Fig. 1B).

Regarding auxologic parameters, we noted a significant improvement of BMI with LI with a mean difference of 0.23 [95 % CI: 0.03, 0.43] ($p = 0.026$). With ETI, we did not observe a significant improvement in weight or BMI in the overall population.

During the study period, no serious adverse event was reported. Among patients treated with LI, abdominal pain was reported in 16 % of them, inaugural elevation of liver enzymes in 8 % of cases, and no treatment-related side effects in 81 % of cases. Among patients treated with ETI, abdominal pain occurred in 16 % of cases, 13 % experienced psychomotor agitation with irritability, 5 % reported asthenia, an inaugural elevation of liver enzymes in 3 % of cases, and 69 % did not experience any side effects.

Table 2
Hepatobiliary manifestations before treatment ($n = 62$).

Elevation of liver enzymes, n (%)	
No elevation of liver enzymes	34 (54.8 %)
Transient elevation of liver enzymes	13 (21.0 %)
Persistent elevation of liver enzymes	15 (24.2 %)
Ultrasound, n (%)	
N	60
Nodular imaging abnormalities	3 (5.0 %)
Heterogeneous increased signal	6 (10.0 %)
Homogeneous increased signal	5 (8.3 %)
Normal	46 (76.7 %)
Elastography (kPa), n (%)	
N	50
>6.85	3 (6.0 %)
<6.85	47 (94.0 %)
Portal hypertension, n (%)	
No	57 (91.9 %)
Yes	5 (8.1 %)
Biliary manifestations, n (%)	
No	54 (87.1 %)
Cholelithiasis and hepatolithiasis	7 (11.3 %)
Biliary strictures	1 (1.6 %)

Table 3
Evolution of hepatic parameters after one year of treatment.

	T0, $n = 62$	**T12** LI, $n = 37$	**P***	**T12** ETI, $n = 46$	**P***
Elastography (kPa)					
N	50	30		38	
Median (Q1, Q3)	4.2 (3.5, 4.7)	4.4 (4.0, 5.0)	0.06	4.2 (3.5, 5.0)	0.2
Min, Max	1.9, 8.0	2.8, 7.9		2.2, 5.8	
GGT, n (%)					
N	61	37		45	
<1.5 ULN	55 (90.2 %)	37 (100.0 %)	0.08	43 (95.6 %)	0.3
>1.5 ULN	6 (9.8 %)	0 (0.0 %)		2 (4.4 %)	
AST, n (%)					
N	61	37		45	
<1.5 ULN	54 (88.5 %)	34 (91.9 %)	>0.9	43 (95.6 %)	0.4
>1.5 ULN	7 (11.5 %)	3 (8.1 %)		2 (4.4 %)	
ALT, n (%)					
N	61	37		45	
<1.5 ULN	43 (70.5 %)	30 (81.1 %)	>0.9	37 (82.2 %)	0.07
>1.5 ULN	18 (29.5 %)	7 (18.9 %)		8 (17.8 %)	
Ultrasound					
N	60	36		43	
Nodular imaging abnormalities	3 (5.0 %)	3 (8.3 %)		4 (9.3 %)	
Heterogeneous increased signal	6 (10.0 %)	2 (5.6 %)		5 (11.6 %)	
Homogeneous increased signal	5 (8.3 %)	3 (8.3 %)		4 (9.3 %)	
Normal	46 (76.7 %)	29 (77.8 %)		32 (69.8 %)	
Sweat chloride (mmol/L)					
N	58	36		44	
Median (Q1, Q3)	97 (87, 107)	72 (61, 85)	<0.0001	40 (26, 53)	<0.0001
Min, Max	48, 137	34, 109		26, 93	

* Wilcoxon signed rank test with continuity correction; McNemar's Chi-squared test with continuity correction.

3.2. Evolution in the "Hepatobiliary involvement before treatment" subgroup

The analyses carried out in this subgroup did not show any worsening of hepatic parameters compared to the overall population. Indeed, before the initiation of treatments, the elastography was slightly higher than in the overall population (median 4.5 kPa), the same after one year of LI, and lower after one year of ETI (median 4.1 kPa). The evolution of liver enzymes and ultrasound findings were comparable to what had been found in the overall population, with no significant improvement or worsening of parameters.

A significant improvement in weight (SD) and BMI (SD) was observed for both treatments. For weight, the mean difference was 0.34 [95 % CI: 0.06, 0.62] ($p = 0.02$) with LI, and the median at M0 was −0.4 and 0.2 at M12 for ETI ($p = 0.03$). For BMI, the mean difference was 0.32 [95 % CI: 0.03, 0.62] ($p = 0.03$) for LI and the median at M0 was −0.3 and −0.2 at M12 of ETI ($p = 0.04$).

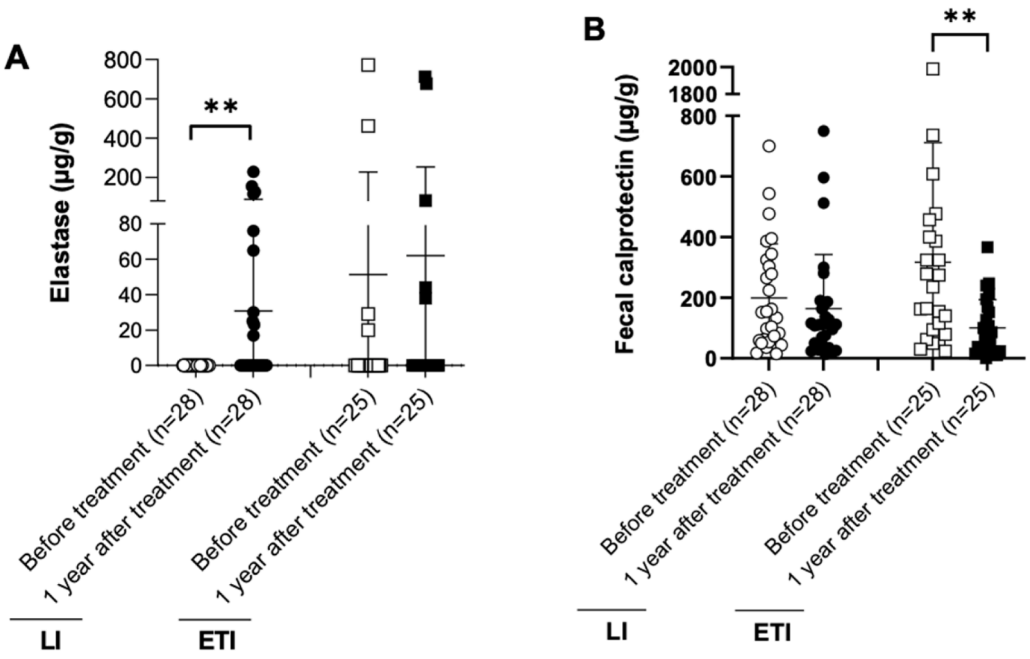

Fig. 1. Evolution of fecal elastase (A) and fecal calprotectin (B) with Lumacaftor-Ivacaftor (LI) and Elexacaftor/Tezacaftor/Ivacaftor (ETI). A. There was a significant improvement of fecal elastase on LI ($p = 0.006$) but not on ETI. The paired values showed that this improvement concerned quite all of the children on LI but they were mild and variable on ETI. B. There was a significant improvement of fecal calprotectin after 12-month treatment with ETI ($p = 0.001$) but not on LI.

In this subgroup, abdominal pain was reported in 10 % of patients with LI and 18 % with ETI, inaugural elevation of liver enzymes for 5 % with LI and 3 % with ETI, irritability in 15 % with ETI and asthenia in 5 % with ETI.

4. Discussion

In this study, the prevalence of hepatobiliary involvement before treatment was higher (59.7 % (37 children)) than in the literature (40 %) [9]. The significant proportion found in our study can be explained by the use of the recently proposed classification [7], which allows for the description of all hepatobiliary manifestations found in CF.

Regarding the demographic description before treatment, there was a difference in FEV1 between the subgroup with hepatobiliary involvement and the subgroup without hepatobiliary involvement. This difference was slightly significant, and the impact of liver involvement on respiratory function is still debated [5,10]. Moreover, it could change in the next years with the new definition.

The most common manifestation of hepatobiliary involvement in this cohort was the elevation of liver enzymes. Although common, it was rarely found at high levels. These increased values persisted more than six months for a quarter of these patients. However, it could be underestimated due to the short duration of our study. Indeed, a study conducted over more than twenty years found even more frequent abnormalities in liver function tests (at least one abnormal value for AST (63 %) and ALT (93 %) occurred by 21 years of age) [11].

Abnormal hepatic ultrasound was found in 28.3 % of patients, among whom 4 (6.5 %) had a nodular liver, which was reported to be an early positive predictive marker of portal hypertension with or without cirrhosis [12]. These patients were aged 9 to 12 years at the time of nodular liver diagnosis.

In the literature, the prevalence varies widely depending on the diagnostic criteria used. Using the definition proposed by Debray et al. in 2011 [13], the study by Boëlle et al. [10] conducted on 3328 children and young adults found abnormal laboratory findings in 50 % of patients, clinical abnormalities associated with abnormal ultrasound in 26 % of patients, and abnormal laboratory findings associated with abnormal ultrasound in 24 % of patients. Using the same criteria [13], this study would identify hepatobiliary involvement in 20 patients (32.2 %), with the association of a clinical abnormality with an ultrasound abnormality in 6 of them (9.7 %), the association of a laboratory abnormality with an ultrasound abnormality in 8 of them (12.9 %), and 5 of them (8.1 %) met all three criteria.

The new classification [7] appears to allow for the identification of more cases of liver involvement. This could be explained by the fact that this new classification considers more criteria, such as elastography.

These results on the evolution of liver enzymes under treatment are discordant with what can be found in the literature. Indeed, a study conducted in F508del homozygous teenagers in 2021 demonstrated a significant decrease in transaminase and GGT levels with LI and found no cases of hepatotoxicity secondary to the treatment [14]. Conversely, another study including 230 children and adolescents did not find a significant improvement in markers of liver fibrosis but found an increase in ALT levels with ETI [15]. These discordant results may indicate that monitoring liver enzymes is not the best criterion for assessing the progression of liver damage and that it may be preferable to follow other markers (such as elastography or liver and portal hypertension signs on ultrasound). It underlines the need for additional studies with larger cohorts and longer follow-up periods.

Regarding the potential hepatotoxicity of these modulator treatments, in this study, an inaugural increase of liver enzymes occurred in 8 % of patients with LI and in 3 % of patients with ETI. To determine whether these abnormalities could be attributed to the treatment or were rather directly related to a hepatobiliary manifestation of CF, the pharmacovigilance department was contacted. The physician in charge of the patient reported every side effect to the pharmacovigilance regional center sending a specific sample form available in France to a dedicated email address. Their conclusions were that the worsening of the laboratory findings could be attributed to the treatment in 5 of our patients (8 %), with causality scores ranging from probable to very probable. The average onset time of the increase of liver enzymes secondary to treatment was 5 months, and treatment had to be discontinued for 2 of them, later resumed and well tolerated. There are proportionally no more adverse effects in the hepatobiliary involvement group than in the overall population; this lack of significance may be related to an insufficient number of patients.

This study has certain limitations. Indeed, the size of our cohort and its monocentric nature limited its statistical power, and its duration may be responsible for the lack of significance in some results. To better evaluate the effects of CFTR modulators on the liver, it is necessary to expand the population and to conduct long-term prospective follow-up study. The use of multiple factors to define the notion of liver involvement can introduce biases, and it would be interesting to conduct further studies specifically focusing on elastography or liver ultrasound, for example. Despite these limitations, this study provides data on the real-world effects of LI and ETI on the liver in children with cystic fibrosis and supports the notion that there is no worsening of liver disease under CFTR protein modulator treatments.

In conclusion, the comparison of elastography, values of liver enzymes and hepatic ultrasound before the initiation of CFTR protein modulator treatment and after one year of treatment did not reveal a significant improvement in liver involvement. However, we can highlight the absence of worsening hepatobiliary involvement under treatment in our patients, encouraging their use even in patients with previous liver involvement, under regular and attentive monitoring of hepatic parameters.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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