Impact of CFTR modulatory therapies on liver function and fibrosis indices in cystic fibrosis patients: a retrospective analysis from two Romanian medical centers

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Abstract

Background. Patients with cystic fibrosis (CF) frequently require modulatory therapies such as Lumacaftor/Ivacaftor (LI) and Elexacaftor/Tezacaftor/Ivacaftor (ETI) to manage their condition. Given the potential hepatic complications associated with CF, it is critical to understand the impact of these therapies on liver function and fibrosis indices. This study aimed to evaluate the changes in liver function markers and fibrosis indices in CF patients undergoing LI and ETI therapies, with a specific focus on the influence of underlying hepatic disease.

Methods. In this retrospective analysis, liver function markers and fibrosis indices were assessed in CF patients receiving ETI (n=24), LI (n=4), or LI transitioned to ETI (LI/ETI, n=8). Key liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, platelet count, and fibrosis indices (APRI and FIB-4), were measured at baseline and at various time points up to 12 months.

Results. In patients receiving LI therapy, ALT and AST levels demonstrated a slight but non-significant decrease over six months, accompanied by significant fluctuations in total bilirubin levels. Among those receiving ETI therapy, ALT and AST levels initially increased but stabilized over time, while total bilirubin levels significantly increased from baseline to 12 months. No significant differences were observed in liver function markers between patients with and without hepatic disease under ETI therapy. Trends in fibrosis indices (APRI and FIB-4) were modest and largely non-significant across both therapies.

Conclusions. ETI therapy appears to be safe for CF patients, including those with pre-existing hepatic disease, with no significant deterioration in liver function over a 12-month period. However, the observed fluctuations in bilirubin levels underscore the necessity for ongoing monitoring. Further research is warranted to investigate the long-term hepatic effects of LI and ETI therapies.

Keywords: cystic fibrosis, Lumacaftor/Ivacaftor, Elexacaftor/Tezacaftor/Ivacaftor, liver function, fibrosis indices, hepatic disease, retrospective study

Introduction

Cystic fibrosis (CF) is a genetic disorder resulting from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which leads to the production of a defective CFTR protein [1]. The CFTR protein plays a crucial role in regulating the transport of chloride ions and water across cell membranes, particularly in the lungs, pancreas, liver, and digestive system [1]. Impairment of CFTR function causes the accumulation of thick, sticky mucus in various organs, leading to multisystem complications [2]. The prevalence of CF varies globally, with significant regional differences. In the European Union, the average prevalence is approximately 0.737 per 10,000 individuals, with notably higher rates in the Republic of Ireland at 2.98 per 10,000 [3]. The United States of America reports a similar prevalence of 0.797 per 10,000. However, global prevalence is lower in regions like Asia and Africa, primarily due to under diagnosis and the absence of comprehensive registries [4].

CF imposes a substantial burden on both patients and healthcare systems, with annual costs in Europe ranging from €14,174 to €53,256 per patient, largely driven by the continuous and intensive healthcare needs [5]. The disease also significantly impacts the quality of life for patients and their caregivers, with more severe cases leading to increased caregiver burden and reduced health-related quality of life [6].

Cystic fibrosis-related liver disease (CFLD) is a major concern in CF management, contributing significantly to morbidity and mortality. CFLD is the third leading cause of death in CF patients, following pulmonary complications and transplant-related issues [7]. It affects up to 37% of CF patients and can present in various forms, including steatosis, focal biliary cirrhosis, and multilobular cirrhosis [8,9].

The introduction of CFTR modulators, such as Lumacaftor/Ivacaftor (LI) and Elexacaftor/Tezacaftor/Ivacaftor (ETI), has revolutionized CF management by directly targeting the underlying protein dysfunction. These therapies have led to significant improvements in pulmonary outcomes and overall quality of life for many CF patients [10-12].

However, the impact of CFTR modulators on liver health remains less well understood. While some studies suggest that LI have potential hepatic benefits, including reductions in liver enzyme levels and fibrosis markers [12,13], there are also concerns about the potential for hepatotoxicity and liver enzyme abnormalities associated with these treatments [9,11]. Given the significant burden of liver disease in CF patients and the widespread use of CFTR modulators, it is essential to elucidate their effects on liver health [12].

This study aims to evaluate the impact of CFTR modulators on liver function and fibrosis in CF patients, particularly focusing on whether these treatments induce or exacerbate liver damage. By analyzing liver function tests and fibrosis indices in patients treated with LI and ETI, we seek to provide critical insights into the hepatic safety profile of these therapies. Our findings will contribute to optimizing treatment strategies for CF patients, especially those with pre-existing liver involvement.

Methods

Study design and setting

This retrospective study was conducted using data from a prospective database. Between November 2023 and March 2024, a total of 71 pediatric patients diagnosed with CF were selected from two major pediatric centers in Bucharest, Romania: the "Alessandrescu-Rusescu" National Institute of Mother and Child Health, a Regional Center for Cystic Fibrosis, and the "Grigore Alexandrescu" Children's Emergency Clinical Hospital. Patients were included based on their attendance at regular clinical follow-ups during this period.

Inclusion and exclusion criteria

Inclusion criteria: From the initial cohort of 71 CF patients, we included those who had been undergoing treatment with CFTR modulators for at least six months. All participants had undergone genetic testing, confirming mutations consistent with established CFTR-related disease. The administration of LI was strictly limited to patients homozygous for the F508del-CFTR mutation (DF508/DF508), following international guidelines. Similarly, ETI was administered to patients who were either homozygous or heterozygous for the F508del-CFTR mutation (DF508/Others), in accordance with treatment protocols.

Exclusion criteria: Patients who did not received CFTR modulator therapy or had been on such therapy for less than six months were excluded from the study. After applying these criteria, 36 patients were included in the final analysis. The treatment regimens observed among these patients were as follows:

- 12 patients received LI for a duration of six months.
- 24 patients received ETI for 12 months.
- 8 patients transitioned from LI (after six months) to ETI for an additional 12 months, resulting in a cumulative treatment duration of 18 months.
- 4 patients remained on LI throughout the study period without transitioning to another CFTR modulator.

Data sources and measurement

Data were obtained from patient medical records, clinical examinations, laboratory tests, and genetic testing reports. Hepatic involvement was assessed through clinical evaluation, ultrasound imaging, and liver function tests. Genetic data on CFTR mutations were sourced from pre-existing genetic testing documented in the patients' medical files.

The data collected included the following variables:

• **Demographic data:** Age at the time of study (years) and sex. Age at CF diagnosis was recorded in months.

• **Clinical history:** Presence of meconium ileus, pancreatic insufficiency, and CF-related diabetes.

• **Anthropometric measurements:** Weight (kg) and height (cm).

• **Hepatic disease indicators:** Hepatic involvement was assessed through clinical examination and imaging studies. Indicators included hepatosplenomegaly, biliary lithiasis, hepatic ultrasound changes, cirrhosis, periportal fibrosis, and hepatomegaly. Hepatic and biliary involvement were categorized as follows:

o Advanced Cystic Fibrosis Liver Disease (aCFLD)

o Cystic Fibrosis Hepatobiliary Involvement (CFHBI)

o A broader category including all CF patients without liver involvement (PwCF) [7].

Clinical assessments also recorded the presence of hepatomegaly, splenomegaly, and ultrasound-confirmed liver disease.

• **Biochemical markers:** Key biochemical markers included aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (U/L), and total bilirubin (mg/dL). Liver function and fibrosis were evaluated using the AST to Platelet Ratio (PLT) Index (APRI) and Fibrosis-4 Index (FIB-4), calculated as follows:

✓ APRI index: [(AST / ULN AST) / PLT] × 100, where ULN is the upper limit of normal,

✓ FIB-4 index: (Age in years × AST) / (PLT × √ALT) [12].

• **Treatment:** Documentation of CFTR modulator treatments administered [14].

Genetic data: CFTR genotypes were classified as homozygous DF508/DF508, heterozygous DF508/Others, with further categorization based on disease severity.

Ethical considerations

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca (approval no. 71/19 April 2024).

Statistical analysis

Continuous variables were described using medians and interquartile ranges (IQRs) due to their non-normal distribution. Categorical variables were summarized as frequencies and percentages. Comparisons between categorical variables were conducted using the Chi-squared test, with Fisher's exact test employed when expected cell counts were low. Non-normally distributed continuous variables were analyzed using the Kruskal-Wallis test for comparisons across multiple groups, followed by non-parametric post-hoc pairwise comparisons. For repeated measures data, the Friedman test was used to assess within-subject differences across multiple time points, with the Conover post-hoc test applied to adjust for multiple testing when appropriate. All statistical tests were two-sided, with significance set at $P < 0.05$. Statistical analyses were conducted using R version 4.3.2 [15].

Results

A total of 36 pediatric patients with cystic fibrosis were included in the study. The median age of the cohort was 11 years (IQR: 9-14 years), with ages spanning from 2 to 17 years. The demographic and clinical characteristics of the patients, stratified by the type of CFTR modulator therapy received, are summarized in table I.

Significant differences were observed between the treatment groups in several parameters, including age, weight, height, AST levels, platelet counts, FIB-4 index, and CFTR genotype distribution ($P < 0.05$ for all comparisons). However, no significant differences were found between the groups in ALT levels, total bilirubin levels, APRI index, or the prevalence of hepatic and biliary disease.

Evolution under LI therapy

The progression of key clinical and biochemical variables was analyzed in patients receiving LI therapy, with measurements taken at treatment initiation, three months, and six months post-initiation (Table II).

ALT and AST levels

Both ALT and AST levels exhibited a slight downward trend over the six-month period. Median ALT levels decreased from 25 U/L at treatment initiation to 24 U/L at three months, and 23 U/L at six months. Similarly, median AST levels declined from 27 U/L at baseline to 26 U/L at three months, and 25 U/L at six months. However, these changes did not reach statistical significance.

Bilirubin levels

Total bilirubin levels showed significant variation over time ($P < 0.05$). A significant decrease was observed between baseline (median: 0.3 mg/dL) and three months (median: 0.2 mg/dL). By six months, the median value returned to baseline levels (0.3 mg/dL). Direct bilirubin levels remained constant throughout the observation period, with a median value of 0.1 mg/dL.

Platelet counts

Median platelet counts increased from $380 \times 10^3/\mu L$ at baseline to $434 \times 10^3/\mu L$ at three months, before returning to near-baseline levels at six months ($381 \times 10^3/\mu L$). This fluctuation, however, was not statistically significant.

FIB-4 index

The FIB-4 index, an indicator of liver fibrosis, demonstrated a decreasing trend from 0.15 at baseline to 0.11 at three months. At six months, the median value slightly increased to 0.12. Despite these fluctuations, the changes were not statistically significant.

APRI index

The APRI index, another marker of liver fibrosis, showed a consistent downward trend, decreasing from 0.23 at baseline to 0.20 at three months and 0.15 at six months. Although the decrease approached statistical significance, it did not reach the threshold.

Evolution under ETI therapy

The analysis included 24 pediatric patients who received ETI therapy exclusively for 12 months, as well as 8 patients who transitioned from LI therapy after 6 months to ETI therapy for an additional 12 months. The evolution of key clinical and biochemical markers was monitored at the initiation of ETI therapy and at regular intervals from 1 to 12 months thereafter (Table III).

Table I. Baseline characteristics of CF patients stratified by type of CFTR modulator therapy.

Characteristics/Therapy	ETI (n=24)	LI (n=4)	LI/ETI (n=8)	P - value
Age (Years), median (IQR)	12.5 (10 - 14.5)	4.5 (3.5 - 5.25)	11 (9 - 13)	0.002
Female, n (%)	9 (37.5)	3 (75)	5 (62.5)	0.265
Weight (Kg), median (IQR)	42.5 (31.72 - 51.62)	13.5 (12.47 - 18)	34 (30.75 - 43)	0.009
Height (cm), median (IQR)	153 (137.5 - 158.25)	94.5 (93.75 - 102.5)	142 (135.5 - 158.25)	0.005
Hepatic and biliar lesions, n (%)				0.584
aCFLD	2 (8.33)	0 (0)	0 (0)	
CFHBI	9 (37.5)	0 (0)	3 (37.5)	
PwCF	13 (54.17)	4 (100)	5 (62.5)	
ALT (U/L), median (IQR)	30 (22 - 38.25)	33.5 (29.25 - 35.25)	24.5 (23.75 - 33)	0.815
AST (U/L), median (IQR)	28.5 (24.75 - 40.25)	53.5 (39.5 - 67)	25 (22.75 - 28.5)	0.008
Direct bilirubin (mg/dL), median (IQR)	0.1 (0.08 - 0.12)	0.1 (0.1 - 0.12)	0.1 (0.1 - 0.1)	0.65
Total bilirubin (mg/dL), median (IQR)	0.4 (0.3 - 0.41)	0.35 (0.2 - 0.65)	0.3 (0.27 - 0.43)	0.538
Platelets (*10^3), median (IQR)	358.5 (252.75 - 450)	487 (462.5 - 517)	333.5 (266.5 - 391.75)	0.025
APRI, median (IQR)	0.23 (0.19 - 0.36)	0.21 (0.16 - 0.27)	0.22 (0.16 - 0.24)	0.723
FIB-4, median (IQR)	0.18 (0.13 - 0.4)	0.08 (0.05 - 0.11)	0.17 (0.14 - 0.2)	0.002
Genotype, n (%)				0.013
DF508/DF508	11 (45.83)	4 (100)	8 (100)	
DF508/Others	13 (54.17)	0 (0)	0 (0)	

aCFLD, advanced CF liver disease; CFHBI, CF hepatic biliary involvement; PwCF, Children with CF; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; FIB-4, Fibrosis-4 Index; APRI, AST to Platelet Ratio Index; IQR, interquartile range; p-values for the overall comparison.

Table II. Longitudinal changes in clinical and biochemical markers in CF patients treated with LI over a six-months period.

Characteristic/Time	0 months	3 months	6 months	P-value
ALT (U/L), median (IQR)	25 (23.5 - 35)	24 (19 - 32)	23 (17.5 - 28)	0.929
AST (U/L), median (IQR)	27 (23.5 - 37)	26 (23.5 - 41)	25 (21.5 - 28.5)	0.404
Direct bilirubin (mg/dL), median (IQR)	0.1 (0.1 - 0.1)	0.1 (0.1 - 0.1)	0.1 (0.1 - 0.1)	0.135
Total bilirubin (mg/dL), median (IQR)	0.3 (0.3 - 0.5)	0.2 (0.2 - 0.3)	0.3 (0.2 - 0.37)	0.013
Platelets (*10^3), median (IQR)	380 (286.5 - 453.5)	434 (342.5 - 503)	381 (363.5 - 407.5)	0.529
FIB-4, median (IQR)	0.15 (0.11 - 0.18)	0.11 (0.1 - 0.16)	0.12 (0.09 - 0.17)	0.078
APRI, median (IQR)	0.23 (0.16 - 0.26)	0.2 (0.14 - 0.22)	0.15 (0.12 - 0.22)	0.078

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; FIB-4, Fibrosis-4 Index; APRI, AST to Platelet Ratio Index; IQR, interquartile range.

Table III. Longitudinal changes in clinical and biochemical markers in CF patients treated with ETI over a 12-months period.

Characteristic/Time	0 months	1 month	3 months	6 months	9 months	12 months	P-value
ALT (U/L), median (IQR)	31.5 (24.75 - 38.25)	36.5 (34.75 - 40.75)	32 (29 - 38.5)	30 (27 - 38.25)	31.5 (27.75 - 37.25)	29.5 (25.5 - 49.75)	0.694
AST (U/L), median (IQR)	27 (24.75 - 29.5)	26 (21.75 - 31.75)	27.5 (22.75 - 34.25)	28.5 (24.5 - 36)	29 (24.75 - 36.75)	30 (24.75 - 34)	0.298
Direct bilirubin (mg/dL), median (IQR)	0.1 (0.1 - 0.1)	0.15 (0.12 - 0.18)	0.15 (0.12 - 0.18)	0.15 (0.12 - 0.18)	0.2 (0.15 - 0.25)	0.2 (0.2 - 0.2)	0.416
Total bilirubin (mg/dL), median (IQR)	0.3 (0.3 - 0.41)	0.35 (0.3 - 0.7)	0.45 (0.4 - 0.77)	0.55 (0.32 - 0.91)	0.5 (0.4 - 0.65)	0.6 (0.32 - 0.82)	0.002
Platelets *10^3, median (IQR)	373.5 (273 - 415)	309.5 (214.5 - 365.25)	334.5 (275.5 - 363.5)	294 (275 - 334)	325.5 (264 - 383.25)	315 (252 - 372.75)	0.319
FIB-4, median (IQR)	0.15 (0.14 - 0.19)	0.17 (0.13 - 0.23)	0.16 (0.14 - 0.23)	0.18 (0.14 - 0.24)	0.15 (0.14 - 0.3)	0.17 (0.14 - 0.26)	0.071
APRI, median (IQR)	0.22 (0.19 - 0.24)	0.24 (0.2 - 0.29)	0.23 (0.18 - 0.32)	0.26 (0.2 - 0.31)	0.23 (0.19 - 0.39)	0.29 (0.2 - 0.33)	0.201

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; FIB-4, Fibrosis-4 Index; APRI, AST to Platelet Ratio Index; IQR, interquartile range.

Table IV. Comparison of 12-months changes in clinical and biochemical parameters between CF patients with and without hepatic disease receiving ETI therapy.

Hepatic disease	Yes (n=14)	No (n=18)	P-value
ALT (U/L), median (IQR)	-1 (-17 - 7)	4 (-1.5 - 13.5)	0.17
AST (U/L), median (IQR)	2 (-6 - 6)	1 (-4 - 5)	0.811
Direct bilirubin (mg/dL), median (IQR)	0 (0 - 0)	0 (0 - 0.05)	0.324
Total bilirubin (mg/dL), median (IQR)	0.14 (0.05 - 0.28)	0.19 (0.1 - 0.29)	0.936
Platelets (*10^3), median (IQR)	-35 (-82 - 43)	-46 (-132 - 2.5)	0.482
APRI, median (IQR)	0.04 (-0.03 - 0.09)	0.02 (-0.01 - 0.11)	0.907
FIB-4, median (IQR)	0.06 (0.02 - 0.08)	0.01 (-0.04 - 0.03)	0.174

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; FIB-4, Fibrosis-4 Index; APRI, AST to Platelet Ratio Index; IQR, interquartile range.

ALT and AST levels

The median ALT levels increased from 31.5 U/L at the initiation of ETI therapy to 36.5 U/L at one month, before stabilizing near baseline levels (ranging from 29.5 U/L to 32 U/L) over the remaining observation period. In comparison, AST levels showed an initial decrease at one month, followed by a slight upward trend throughout the 12-month period. However, these changes did not reach statistical significance.

Bilirubin levels

Total bilirubin levels exhibited significant overall variation ($P < 0.05$). Median total bilirubin increased from 0.3 mg/dL at baseline to 0.55 mg/dL at six months, maintaining this level through to 12 months. Pairwise comparisons revealed significant differences between baseline and the 3- to 12-month time points. Direct bilirubin levels also showed a slight increase from 0.1 mg/dL at baseline to 0.2 mg/dL at 12 months, although this change was not statistically significant.

Platelet counts

Median platelet counts decreased from 373.5 × $10^3/\mu L$ at baseline to values ranging from 294 × $10^3/\mu L$ to 334.5 × $10^3/\mu L$ during the 12-month observation period. No consistent trend was observed, and the changes were not statistically significant.

FIB-4 index

The FIB-4 index displayed fluctuations throughout the study period, with values ranging between 0.15 and 0.18. No statistically significant difference was observed between baseline and the 12-month mark ($P = 0.071$).

APRI index

The APRI index also fluctuated, with median values ranging from 0.22 to 0.29, showing a slight overall increase. However, this trend did not reach statistical significance.

Association between hepatic disease and changes in observed parameters in patients receiving ETI therapy

To evaluate the impact of hepatic disease on the changes in clinical and biochemical parameters among patients receiving ETI therapy, we calculated the difference between values recorded at 12 months and those at treatment initiation. These changes were then compared between patients with hepatic disease and those without (Table IV).

No significant differences were found between the two groups. For both patients with and without hepatic disease, there were increases in AST, total bilirubin, APRI index, and FIB-4 index. Platelet counts decreased in both groups. Direct bilirubin levels remained stable, while ALT values showed inconsistent changes.

Discussion

In this study, we investigated the impact of LI and ETI therapies on liver function markers and fibrosis indices in CF patients. Under LI therapy, we observed a slight, though statistically non-significant, decrease in ALT and AST levels over six months. Total bilirubin exhibited significant fluctuations, particularly between treatment initiation and three months, before stabilizing back to baseline levels. Fibrosis indices, including FIB-4 and APRI, showed a downward trend, but these changes did not achieve statistical significance.

In contrast, patients on ETI therapy initially experienced an increase in ALT and AST levels, with a significant rise in total bilirubin from three to twelve months. Platelet counts remained stable, and FIB-4 index values demonstrated only minor fluctuations. Notably, the presence of hepatic disease did not significantly influence the changes in these parameters over the 12-month period of ETI therapy, indicating that the observed trends were consistent regardless of hepatic status.

Our study observed a slight, though statistically non-significant, decrease in ALT and AST levels over six months of LI therapy. This finding is partially consistent with a recent study that reported significant reductions in ALT, AST, and gamma-glutamyl transferase (GGT) after 12 months of LI treatment in adolescents with CF. The discrepancy in our results, which show a less pronounced effect, may be attributed to the shorter duration of therapy or differences in patient demographics [16].

In contrast with our study, literature reports a trial involving 54 young patients treated with LI, who were followed for 24 weeks post-initiation. During this period, 11 patients exhibited AST or ALT levels exceeding three times the ULN at some point. Specifically, 5 patients had elevations greater than five times ULN, 3 patients had levels exceeding eight times ULN, and none showed elevated bilirubin levels. It is important to note that patients with multiple instances of enzyme elevation were only counted once per enzyme. Treatment was discontinued in two patients due to elevated transaminase levels. For a third patient, treatment was temporarily halted after transaminase elevation, resumed following recovery, but was ultimately permanently discontinued after further transaminase elevation [17].

Our observation of a decreasing trend in FIB-4 and APRI indices, with the LI therapy, although not statistically significant, is consistent with the findings of other recent studies [6,7]. In their study, they reported significant decreases in APRI index and GGT-to-Platelet Ratio (GPR) in patients with CFLD treated with LI [7]. The lack of statistical significance in our study could be attributed to differences in sample size or duration of therapy.

Our findings partially align with a recent study that reported significant decreases in GGT, APRI index, and GPR in patients with CFLD treated with LI. However, this study did not observe similar improvements with ETI, which is consistent with our results for ETI therapy [12].

In our study was an initial increase in ALT and AST levels after ETI therapy in children with CF. This finding aligns with a study done on adult patients who received ETI therapy for 12 months and which reported a significant increase in ALT levels after one year of ETI treatment [18]. Our results are consistent with several other studies that have also documented increases in liver enzymes, particularly ALT, in patients undergoing ETI treatment [19-21]. These observations suggest that increases in liver enzymes may be a common early response to ETI therapy, highlighting the importance of close monitoring during the initial stages of treatment.

- **Limitations**

Several limitations of this study should be acknowledged. As a retrospective analysis, it is subject to inherent biases, including selection bias and potential inaccuracies in medical record data. The relatively small sample size, particularly within subgroups, may limit the generalizability of the findings and reduce statistical power. Moreover, the observational nature of the study precludes causal inferences and introduces potential confounding biases.

- **Strengths**

Despite these limitations, this study has several strengths. It represents the first investigation in Romania assessing the impact of CFTR modulators on hepatic function in children with CF. Furthermore, it is the first study to evaluate the sequential administration of LI followed by ETI and its effects on liver function. The inclusion of multiple time points allows for a comprehensive analysis of temporal trends in liver function markers and fibrosis indices, offering a nuanced understanding of the therapies' impacts over time. The use of real-world clinical data enhances the applicability of the findings to everyday clinical practice. Additionally, comparing patients with and without hepatic disease under ETI therapy provides

valuable insights into the safety and efficacy of the therapy across different patient subgroups.

- **Clinical implications**

The results of this study have significant clinical implications for managing CF patients on LI and ETI therapies. The stability of liver function markers over time, coupled with the lack of significant differences between patients with and without hepatic disease, suggests that ETI therapy can be administered safely across a broad spectrum of patients, including those with pre-existing liver conditions. However, the observed fluctuations in bilirubin levels underscore the importance of regular liver function monitoring, particularly during the initial months of treatment, to promptly identify and address any potential adverse effects.

Conclusion

This study offers important insights into the effects of LI and ETI therapies on liver function and related parameters in CF patients. Both therapies demonstrated some impact on liver enzymes and fibrosis indices; however, these changes were generally modest and did not achieve statistical significance. A notable exception was the significant fluctuation observed in total bilirubin levels during the early months of treatment with both therapies.

Crucially, the presence of hepatic disease did not significantly influence the response to ETI therapy, suggesting that ETI is a broadly applicable treatment option regardless of hepatic status. These findings support the continued use of ETI in CF patients, including those with pre-existing liver conditions, while highlighting the need for ongoing monitoring of liver function, particularly in the initial phases of treatment.

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