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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Retrospective Study

Cystic fibrosis patients on cystic fibrosis transmembrane conductance regulator modulators have a reduced incidence of cirrhosis

Mitchell L Ramsey, Michael R Wellner, Kyle Porter, Stephen E Kirkby, Susan S Li, Luis F Lara, Sean G Kelly, A James Hanje, Lindsay A Sobotka

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Abstract

BACKGROUND

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators significantly improve pulmonary function in patients with cystic fibrosis (CF) but the effect on hepatobiliary outcomes remains unknown. We hypothesized that CF patients on CFTR modulators would have a decreased incidence of cirrhosis compared to patients not on CFTR modulators or on ursodiol.

AIM

To investigate the effect of CFTR modulators on the development of cirrhosis in patients with CF.

METHODS

A retrospective analysis was performed using Truven MarketScan from January 2012 through December 2017 including all patients with a diagnosis of CF. Patients were excluded if they underwent a liver transplantation or if they had other etiologies of liver disease including viral hepatitis or alcohol use. Subjects were grouped by use of CFTR modulators, ursodiol, dual therapy, or no therapy. The primary outcome was development of cirrhosis. Kaplan-Meier curves estimated the incidence of cirrhosis and log-rank tests compared incidence curves between treatment groups.

RESULTS

A total of 7201 patients were included, of which 955 (12.6%) used a CFTR modulator, 529 (7.0%) used ursodiol, 105 (1.4%) used combination therapy, and 5612 (74.3%) used neither therapy. The incidence of cirrhosis was 0.1% at 1 year and 0.7% at 4 years in untreated patients, 5.9% and 10.1% in the Ursodiol group, and 1.0% and 1.0% in patients who received both therapies. No patient treated with CFTR modulators alone developed cirrhosis. Patients on CFTR modulators alone had lower cirrhosis incidence than untreated patients ($P = 0.05$), patients on Ursodiol ($P < 0.001$), and patients on dual therapy ($P = 0.003$). The highest incidence of cirrhosis was found among patients treated with Ursodiol alone, compared to untreated patients ($P < 0.001$) or patients on Ursodiol and CFTR modulators ($P = 0.01$).

CONCLUSION

CFTR modulators are associated with a reduction in the incidence of cirrhosis compared to other therapies in patients with CF.

Key Words: Cirrhosis; Ursodiol; Transmembrane; Cystic fibrosis; Market scan; Cystic fibrosis related liver disease

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Core Tip: The effect of cystic fibrosis transmembrane conductance regulator (CFTR) modulators on hepatobiliary outcomes in cystic fibrosis (CF) patients remains unknown. Utilizing a nationwide database, the incidence of cirrhosis in CF patients utilizing CFTR modulators, ursodiol, combination therapy or neither therapy was compared. A total of 7201 patients were studied including 12.6% on a CFTR modulator, 7.0% on ursodiol, 6.1% on combination therapy and 74.3% on neither therapy. Patients taking CFTR modulators had a lower incidence of cirrhosis than untreated patients ($P = 0.05$), or patients treated with Ursodiol ($P < 0.001$) or Ursodiol and CFTR modulators ($P = 0.003$). CFTR modulators may reduce the incidence of cirrhosis in patients with CF.

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INTRODUCTION

Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) leads to abnormal bicarbonate and chloride transport in the lungs, pancreas, liver, bile ducts and other organs and results in cystic fibrosis (CF). Cystic fibrosis affects approximately 1:2000 people of European descent[1-3]. Historically, disease complications and subsequent early mortality was linked to pulmonary complications including reduced pulmonary function, multidrug resistant infections, and pneumothorax[4]. Since the advent of targeted therapy with CFTR modulators, CF patients have significant improvement in lung function, decreased rates of pulmonary infection, improved patient reported quality of life, and life expectancy[5-8]. This will transition the focus of care to other leading causes of morbidity and mortality including hepatobiliary complications.

CF-related liver disease (CFRLD) that progresses to cirrhosis with concomitant portal hypertension is the third leading cause of death in patients with CF[7,8]. CFRLD ranges from abnormal liver function tests, hepatic steatosis, focal biliary cirrhosis, portal hypertension, and cirrhosis[7-11]. CFRLD affects between 2 to 37% of patients, and clinically significant liver disease is generally diagnosed in childhood

[7,8]. While the pathogenesis of cirrhosis in these patients is poorly understood, it is likely related to alkalization and dehydration of bile given ineffective CFTR channels on the apical surface of bile duct epithelium. This leads to plugging and inflammation of the bile ducts and development of hepatic fibrosis over time[12,13].

Given the proposed mechanism of CFRLD, ursodeoxycholic acid (ursodiol) was thought to be a promising intervention to prevent or slow progression of liver disease. However, there has been mixed results regarding its impact on CFRLD[14,15]. Otherwise, no medical intervention has been effective at reducing the incidence or progression of CFRLD. Given the ability for CFTR modulators to act directly upon the dysfunctional channels, these medications may be effective at improving hepatobiliary outcomes despite the risk of causing abnormal liver function tests in a recent systematic review[16].

This study aims to compare the incidence of cirrhosis during follow up among patients with CF who are treated with CFTR modulators and/or Ursodiol.

MATERIALS AND METHODS

Database

A retrospective analysis of the Truven Health MarketScan database was performed between the years 2012 and 2017. MarketScan is one of the largest, comprehensive, publicly available databases including information from over 100 private insurers representing over 150 million individual patients. Utilizing this database allows the researcher to track a patient through multiple years of inpatient and outpatient care[17]. Funding to utilize this database was obtained through The Ohio State University Center for Clinical and Translational Science (CCTS). The Ohio State University Institution Review Board deemed this study exempt from review.

Study sample

All patients with a diagnosis of CF identified *via* International Classification of Diseases (ICD) codes (ICD-9: 571.2, 571.5, 571.6, ICD-10: K70.3*, K71.7, K74.6*) codes were eligible to be included in this study. Patients were required to have either 2 outpatient appointments or 1 inpatient admission related to CF in order to increase the accuracy of the diagnosis. Patients were excluded if they had cirrhosis at the start of the analysis or within 12 months prior, hepatitis C virus, hepatitis B virus or alcohol use contributing to their liver disease. Patients were also excluded if they did not have at least 12 months of follow up after initiation of a CFTR modulator and/or ursodiol, periods of non-continuous drug claims enrollment, and no prescription coverage for any of the enrollment period. Diagnostic codes for each of these inclusion and exclusion criteria have been widely used in previous publications[18,19].

Outcome of interest

The primary outcome of interest was development of cirrhosis in CF patients taking a CFTR modulator, ursodiol, dual therapy or neither medication. Cirrhosis was defined as the presence of an ICD-9 or ICD-10 code for cirrhosis.

Definition of variables

The index date of evaluation was the medication start date or the start of the second medication if both a CFTR modulator and ursodiol were utilized. If patients were not taking either medication, their start date was considered to be the date they were enrolled in the database with a diagnosis of CF. The study inclusion date also corresponded with continuous MarketScan enrollment without any gaps over 90 days. Other variables evaluated included age, gender, insurance plan type, geographic region and the presence of comorbidities defined by the Carlson Comorbidity Index[20]. CFTR modulators included ivacaftor (Kalydeco), ivacaftor with lumacaftor (Orkambi), ivacaftor with tezacaftor (Symdeko), and ivacaftor, tezacaftor, and elxacaftor (Trikafta).

Statistical analysis

Kaplan-Meier curves were used to display and estimate cirrhosis incidence at select time points and log-rank tests were used to compare incidence curves between treatment groups. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographics

A total of 7201 patients met inclusion criteria of which 105 patients were taking both a CFTR modulator and ursodiol, 955 patients taking only a CFTR modulator, 529 patients taking only ursodiol and 5612 patients on neither medication (Table 1).

Table 1 Cystic fibrosis patient characteristics, time of enrollment and medication

Variable	CFTR modulator + ursodiol (n = 105)	CFTR modulator (n = 955)	Ursodiol (n = 529)	Neither therapy (n = 5612)
Age, mean (SD)	20.1 (12.0)	21.0 (13.0)	20.9 (13.2)	23.8 (17.3)
Age group				
0-5	7	97	63	952
44723	16	142	69	671
44912	30	206	97	709
18-25	27	219	160	1079
26-34	12	148	58	709
35+	13	143	82	1492
Sex				
Male	51	507	290	2613
Female	54	448	239	2999
Region				
Northeast	18	190	85	1138
North central	19	260	115	1341
South	42	374	204	1997
West	24	125	109	1039
Unknown	2	6	16	97
Charlson comorbidity index, mean (SD)	0 (0.0)	0.0 (0.1)	0.0 (0.2)	0.0 (0.3)
Chronic respiratory failure	0	1	0	53
Follow up available (years), median (IQR)	2.0 (1.6-3.1)	2.1 (1.5-3.3)	2.9 (2.0-4.6)	3.0 (2.0-5.0)
Percentage of time on CFTR, median (IQR)	95% (70-100%)	100% (75-100%)	0 (0-0)	0 (0-0)
Percentage of time on ursodiol, median (IQR)	70% (23-92%)	0 (0-0)	51% (19-81%)	0 (0-0)
Percentage of time on ursodiol and CFTR Modulator concurrently, median (IQR)	56% (13-85%)	0 (0-0)	0 (0-0)	0 (0-0)

CFTR modulators: Cystic fibrosis transmembrane regulator modulators; IQR: Interquartile range; SD: Standard deviation.

Follow up and length of time on therapy

Patients without therapy were followed up for a median of 3.0 years [Interquartile range (IQR): 2.0-5.0] compared to 2.9 years (IQR: 2.0-4.6) for patients on ursodiol only, 2.1 years (IQR: 1.5-3.3) for patients on CFTR modulators only and 2.0 years (IQR: 1.6-3.1) for patients on both a CFTR modulator and ursodiol (Table 1). Patients taking ursodiol only were on therapy a median percentage of 51% (IQR: 19-81%) of the studied time compared to a median percentage of 100% (IQR: 75-100%) in patients taking CFTR modulators only. Patients taking both a CFTR modulator and ursodiol were taking both medications concurrently a median percentage of 56% (IQR: 13-85%) of the studied time, though were taking the CFTR modulator a median of 95% (IQR: 70-100%) of the time and ursodiol a median of 70% (IQR: 23-92%) of the studied time (Table 1).

Incidence of cirrhosis

Of the 955 patients on CFTR modulators only, 954 patients remained eligible to be evaluated 1 year after initiating therapy. This decreased to 513 patients at 2 years, 288 patients at 3 years and 74 patients at 4 years after initiating therapy. The incidence of cirrhosis at four years was 0% (Figure 1, Table 2). By log rank testing, patients on CFTR modulators had a lower incidence of cirrhosis than patients on no treatment ($P = 0.05$), Ursodiol alone ($P < 0.001$), or Ursodiol and CFTR modulators ($P = 0.003$).

Of the 529 patients taking only ursodiol, 498 patients remained eligible to be evaluated at 1 year. This decreased to 320 patients at 2 years, 195 at 3 years and 139 patients at 4 years. The incidence of cirrhosis increased yearly and was 5.9% at 1 year, 7.5% at 2 years, 9.1% at 3 years and 10.1% at 4 years (Table 2, Figure 1).

Table 2 Kaplan-Meier estimates for incidence of cirrhosis at select timepoints

Time post-index	CFTR modulator + ursodiol	CFTR Modulator only	Ursodiol only	Neither therapy
3 mo	0.01	0	0.019	0.0002
6 mo	0.01	0	0.032	0.001
1 yr	0.01	0	0.059	0.001
2 yr	0.01	0	0.075	0.004
3 yr	0.01	0	0.091	0.005
4 yr	0.01	0	0.101	0.007

CFTR modulators: Cystic fibrosis transmembrane regulator modulators.

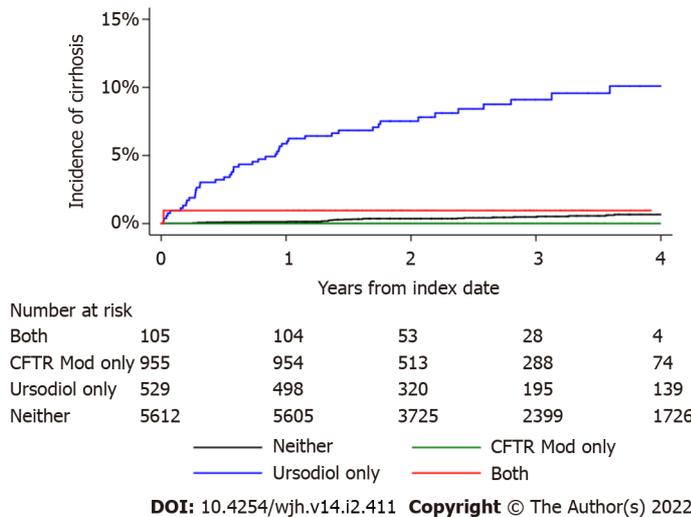


Figure 1 Kaplan-Meier curves for development of cirrhosis based on medication use.

Of the 105 patients taking both a CFTR modulator and ursodiol, 104 patients remained eligible to be evaluated at 1 year. This decreased to 53 patients at 2 years, 28 patients at 3 years and 4 patients at 4 years. The incidence of cirrhosis increased to 1.0% by 3 mo after initiation of therapy and remained at 1.0% for 4 years (Table 2, Figure 1).

Of the 5612 patients taking neither therapy, 5605 patients remained eligible to be evaluated at 1 year. This decreased to 3725 patients at 2 years, 2399 patients at 3 years and 1726 patients at 4 years. The incidence of cirrhosis increased to 0.1% at 1 year, 0.4% at 2 years, 0.5% at 3 years and 0.7% at 4 years (Table 2, Figure 1).

DISCUSSION

Given the success of CFTR modulators in improving pulmonary function and life expectancy in patients with CF, the focus of care will shift to other leading causes of mortality in these patients, such as CFRLD. The mechanism of cirrhosis and portal hypertension in patients with CF is incompletely understood; therefore, interventions have been ineffective in improving hepatobiliary outcomes. In this retrospective study, we determined that patients with CF using CFTR modulators have a significantly decreased yearly incidence of cirrhosis compared to patients on just ursodiol, dual therapy with a CFTR modulator and ursodiol, or neither therapy.

CFTR modulators are likely effective at reducing the incidence of cirrhosis or delaying the progression of CFRLD due to the ability to directly act upon CFTR channels in the bile ducts[12,21]. While the mechanism of CFRLD is not fully understood, the pathogenesis is currently attributed to lack of chloride secretions from the cholangiocytes leading to intrahepatic cholestasis, biliary cirrhosis, and portal hypertension[9,13]. The CFTR channel is considered to act as a master regulator of the cholangiocyte and plays a crucial role in the regulation of ductular secretions contributing to the dilution and subsequent flow of bile from the liver into the intestines[12,13,22]. Unlike ursodiol, CFTR

modulators act directly upon these dysfunctional channels to improve flow of bile. Ursodiol is postulated to improve flow of bile in patients with CF by improving the bicarbonate content and by decreasing the resultant inflammation from biliary stasis[23]. Few trials have been completed evaluating the ability of this intervention to reduce the risk of cirrhosis[15]. One study cited improved bile secretion when measured by isotopes[24] and delayed development of portal hypertension when monitored for 6 mo[15,25]. However, ursodiol has not proven to be effective in long term reduction in CFRLD mortality, thus new agents are needed to improve outcomes among patients with CFRLD[7,8].

Our study suggests that CFTR modulators may be effective at reducing the incidence and delaying progression of cirrhosis in patients with CF when compared to ursodiol or dual therapy. Reduction in hepatobiliary complications with the use of CFTR modulators is supported by other smaller studies. Steatosis is considered an early marker of CFRLD though its clinical implications in patients with CF remains unknown[26]. CFTR modulators have been shown to reduce the hepatic fat fraction by half[26]. An observational study of patient registries in the United States and United Kingdom, demonstrated that patients on ivacaftor have significantly less hepatobiliary complications including abnormal liver function tests, cirrhosis, and cirrhosis-related complications[27]. Our study adds to this growing body of evidence that CFTR modulators may improve outcomes among patients with CFRLD.

It should be noted that CFTR modulators carry a risk of causing abnormal liver function tests in all CF patients regardless of underlying CFRLD[16,28]. Elevation in serum aminotransferases were noted in up to 25% of patients while on therapy, although only 5% of patients develop clinically significant elevation greater than 5 times the upper limit of normal. Elevations to this extent typically resulted in a temporary cessation of therapy; however, there is no clear guidance regarding the safety of restarting therapy[28]. Furthermore, there is mixed data in predicting patients that are at highest risk of developing liver function tests abnormalities with on CFTR modulators[16]. Further studies will be necessary to determine whether these transient elevations in transaminases at initiation of therapy predict the development of CFRLD, and whether CFTR modulators have a net benefit in this population.

This study does have limitations. Data was collected from a nationwide database and therefore the information could not be verified in each patient's medical chart. Laboratory testing is not available in this dataset, which limits our ability to assess specific CFTR mutations and serial assessment of liver enzymes. While the ICD-9 and ICD-10 based diagnostic algorithm used here has been used in previous studies on patients with cirrhosis related to alcohol or viral hepatitis, the accuracy has not been determined in patients with CF. However, the prevalence of cirrhosis in our study was similar to the prevalence of cirrhosis in patients with CF, suggesting that the diagnostic coding strategy is valid[10]. In addition, cirrhosis may take many years to develop, and we were only able to include 4 years of follow up due to limited follow up time available in the MarketScan database. Some patients may have developed cirrhosis after the study period. Furthermore, a significant number of patients were lost to follow up during this analysis and were unable to be evaluated for total studied time. Therefore, we are only able to determine correlation not causation given the retrospective utilization of a database[29].

Lastly, since ursodiol is only used in patients with CF who have liver disease, this group is likely enriched for baseline abnormal liver function. Thus, there is a selection bias for this group which likely influenced the increased risk of developing cirrhosis observed in our study. In addition, patients with pre-existing liver disease may have not been started on a CFTR modulators due to the risk of abnormal liver function tests and hepatic decompensation which may have further contributed to this selection bias. However, it is important to note that when CFTR modulators were added to ursodiol, the incidence of cirrhosis was lower. Despite this selection bias, the study still has merit by measuring the open label use of CFTR modulators among patients with CF who may be at risk for hepatic complications.

Despite these limitations, this study has significant strength. This is one of the first longitudinal analyses evaluating a nationwide population of pediatric and adult patients to determine the incidence of cirrhosis among patients with CF. We also provide a direct comparison to ursodiol which is commonly used in patients with CFRLD. The MarketScan dataset is also used to assess compliance based on refill rate, so we are able to include only patients who were consistently taking these medications throughout the study period. We also excluded other causes of liver disease, such as viral hepatitis or alcohol use, which allowed us to include subjects with CF as the main driver of hepatobiliary outcomes.

CONCLUSION

In this large database analysis, we demonstrate that CFTR modulator use is associated with a decreased incidence of cirrhosis compared to no therapy and compared to ursodiol. While concerns exist regarding hepatic side effects of CFTR modulators, we observed improved long term hepatic outcomes compared to other therapies. This study supports the utilization of CFTR modulators in patients with CF to not only improve pulmonary outcomes but also hepatobiliary outcomes.

ARTICLE HIGHLIGHTS

Research background

Due to improvements in pulmonary care in cystic fibrosis (CF), CF-related liver disease (CFRLD) is emerging as a leading cause of morbidity and mortality. Cystic fibrosis transmembrane conductance regulator (CFTR) modulators correct the CFTR dysfunction and dramatically improve pulmonary outcomes, but the effects of CFTR modulators on CFRLD have not been evaluated.

Research motivation

Currently, there is insufficient data examining the impact of CFTR modulators on the incidence of cirrhosis among patients with CF.

Research objectives

To investigate the effect of CFTR modulators on the development of cirrhosis in patients with CF.

Research methods

A retrospective analysis was performed using Truven MarketScan from January 2012 through December 2017 including all patients with a diagnosis of CF. Subjects were grouped by use of CFTR modulators, ursodiol, dual therapy, or no therapy. The primary outcome was development of cirrhosis.

Research results

A total of 7201 patients were included, of which 955 (12.6%) used a CFTR modulator, 529 (7.0%) used ursodeoxycholic acid, 105 (1.4%) used combination therapy, and 5612 (74.3%) used neither therapy. The incidence of cirrhosis was 0.1% at 1 year and 0.7% at 4 years in untreated patients, 5.9% and 10.1% in the Ursodiol group, and 1.0% and 1.0% in patients who received both therapies. No patient treated with CFTR modulators alone developed cirrhosis. Patients on CFTR modulators alone had lower cirrhosis incidence than untreated patients ($P = 0.05$), patients on Ursodiol ($P < 0.001$), and patients on dual therapy ($P = 0.003$). The highest incidence of cirrhosis was found among patients treated with Ursodiol alone, compared to untreated patients ($P < 0.001$) or patients on Ursodiol and CFTR modulators ($P = 0.01$).

Research conclusions

Patients treated with CFTR modulators have a lower incidence of cirrhosis compared to no treatment, ursodiol, or combination therapy.

Research perspectives

The risk of developing cirrhosis is lower among patients treated with CFTR modulators than those not treated with CFTR modulators. Whether this represents a selection bias or represents a treatment effect of CFTR modulators should be studied in a prospective, randomized study.

FOOTNOTES

Author contributions: Ramsey ML and Sobotka LA designed the research project, drafted the manuscript, and provided final approval of the manuscript; Porter K performed the statistical analysis and provided final approval of the manuscript; Wellner MR, Kirkby S, Li SS, Lara LF, Kelly SG, and Hanje AJ made critical revisions related to important intellectual content of the manuscript and provided final approval of the manuscript.

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