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

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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Ramsey ML, Wellner MR, Porter K, Kirkby SE, Li SS, Lara LF, Kelly SG, Hanje AJ, Sobotka LA. Cystic fibrosis patients on cystic fibrosis transmembrane conductance regulator modulators have a reduced incidence of cirrhosis. World J Hepatol 2022; 14(2): 411-419
URL: https://www.wjgnet.com/1948-5182/full/v14/i2/411.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i2.411

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.
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[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 elexacaftor (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 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.

Institutional review board statement: The Ohio State University Institution Review Board deemed this study exempt from review given subjects were obtained from a de-identified nationwide database.

Conflict-of-interest statement: None of the authors have relevant financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: United States

ORCID number: Mitchell L Ramsey 0000-0002-6430-1924; Michael R Wellner 0000-0002-9165-9868; Kyle Porter 0000-0003-1363-9615; Stephen E Kirkby 0000-0002-0185-5356; Susan S Li 0000-0003-1241-5003; Luis F Lara 0000-0001-5123-5932;
REFERENCES

1. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, Ramsey BW, Rowe SM, Sass LA, Tullis E, Mckee CM, Moskowitz SM, Robertson S, Savage J, Simard C, Van Goor F, Waltz D, Xuan F, Young T; Taylor-Couras JR for the VX16-445-001 Study Group. VX-445–Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. NEJM 2018; 379: 1612-1620 [DOI: 10.1056/nejmoa1807120]

2. Scovet V, L’Hostis C, Féré C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. Genes (Basel) 2020; 11 [PMID: 32466381 DOI: 10.3390/genes11060589]

3. Flume PA, O’Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, Bujan J, Finder J, Lester M, Quittell L, Rosenblatt R, Vender RL, Hazle L, Sabadosa K, Marshall B; Cystic Fibrosis Foundation, Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2007; 176: 955-969 [PMID: 17761616 DOI: 10.1164/rccm.200705-664OC]

4. Flume PA, Mogayzel PJ Jr, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC; Clinical Practice Guidelines for Pulmonary Therapies Committee; Cystic Fibrosis Foundation Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med 2010; 182: 298-306 [PMID: 20657678 DOI: 10.1164/rccm.201002-0157OC]

5. Condren ME, Bradshaw MD. Ivacaftor: a novel gene-based therapeutic approach for cystic fibrosis. J Pediatr Pharmacol Ther 2013; 18: 8-13 [PMID: 23616732 DOI: 10.1086/655647]

6. Middleton PG, Mall MA, Drivneik P, Lands LC, McKone EF, Polinetti D, Ramsey BW, Taylor-Couras JL, Tullis E, Veerumeen F, Marigowda G, McKee CM, Moskowitz SM, Nair N, Savage J, Simard C, Tian S, Waltz D, Xuan F, Rowe SM, Jain R; VX17-445-102 Study Group. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med 2018; 381: 1809-1819 [PMID: 31697873 DOI: 10.1056/NEJMoa1908639]

7. Pettit RS, Fellner C. CFTR Modulators for the Treatment of Cystic Fibrosis. P T 2014; 39: 500-511 [PMID: 25083129]

8. Lopes-Pacheco M. CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine. Front Pharmacol 2019; 10: 1662 [PMID: 32153386 DOI: 10.3389/fphar.2019.01662]

9. Leung DH, Narkewicz MR. Cystic Fibrosis-related cirrhosis. J Cyst Fibros 2017; 16 Suppl 2: S50-S61 [PMID: 28986027 DOI: 10.1016/j.jcf.2017.07.002]

10. Colombo C, Battezzati PM, Crosisgani A, Morabito A, Costantini D, Padoan R, Giunta A. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. Hepatology 2002; 36: 1374-1382 [PMID: 12447862 DOI: 10.1001/hep.2002.37136]

11. Debraj D, Narkewicz MR, Bodewes FAJA, Colombo C, Housset C, de Jonge HR, Jonker JW, Kelly DA, Ling SC, Poynard T, Sogni P, Trauner M, Witters P, Baumann U, Wilschanski M, Verkade HJ; CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine. Front Pharmacol 2019; 10: 1662 [PMID: 32153386 DOI: 10.3389/fphar.2019.01662]

12. Cohn JA, Strong TV, Picciotto MR, Nairn AC, Collins FS, Fitz JG. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. Gastroenterology 1993; 105: 1857-1864 [PMID: 7504645 DOI: 10.1016/0016-5085(93)91085-x]

13. Feranchak AP. Hepatobiliary complications of cystic fibrosis. Curr Gastroenterol Rep 2004; 6: 231-239 [PMID: 15128491 DOI: 10.1007/s11894-004-0013-6]

14. Desmond CP, Wilson J, Bailey M, Clark D, Roberts SK. The benign course of liver disease in adults with cystic fibrosis and the effect of ursodeoxycholic acid. Liver Int 2007; 27: 1402-1408 [PMID: 18036103 DOI: 10.1111/j.1478-3231.2007.01570.x]

15. Cheng K, Ashby D, Smyth RL. Ursodeoxycholic acid for cystic fibrosis-related liver disease. Cochrane Database Syst Rev 2017; 9: CD000222 [PMID: 28891588 DOI: 10.1002/14651858.CD000222.pub6]

16. Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. Sci Rep 2019; 9: 7234 [PMID: 31076617 DOI: 10.1038/s41598-019-43652-2]

17. BM Watson Health. IBM MarketScan Research Databases for Health Services Research. Updated April 2019. Accessed August 1, 2020 [DOI: 10.1007/978-3-030-51455-6_20]

18. Sobotka LA, Spitzer C, Hinton A, Michaels A, Hanje AJ, Muntau K, Coneth LF. Management of hepatic hydroporax and effect on length of stay, mortality, cost, and 30-day hospital readmission. J Gastroenterol Hepatol 2020; 35: 641-647 [PMID: 31441096 DOI: 10.1111/jgh.14842]

19. Sobotka LA, Hinton A, Coneth LF. African Americans are less likely to receive curative treatment for hepatocellular carcinoma. World J Hepatol 2018; 10: 849-855 [PMID: 30533185 DOI: 10.4254/wjh.v10.i11.849]

20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383 [PMID: 3558716 DOI: 10.1016/0021-9681(87)90171-8]

21. Gawler GF, Shwachman H. Cystic fibrosis in adults: an autopsy study. Pathol Annua 1979; 14 Pr 2: 357-382 [PMID: 547223]

22. Victor KD, Randen I, Thompson K, Forre O, Natvig JB, Fu SM, Capra JD. Rheumatoid factors isolated from patients with
autoimmune disorders are derived from germline genes distinct from those encoding the Wa, Po, and Bla cross-reactive idiotypes. *J Clin Invest* 1991; **87**: 1603-1613 [PMID: 2022732 DOI: 10.1172/JCI115174]

23 **Leeuwen L**, Fitzgerald DA, Gaskin KJ. Liver disease in cystic fibrosis. *Paediatr Respir Rev* 2014; **15**: 69-74 [PMID: 23769887 DOI: 10.1016/j.prrv.2013.05.001]

24 **O’Brien S**, Fitzgerald MX, Hegarty JE. A controlled trial of ursodeoxycholic acid treatment in cystic fibrosis-related liver disease. *European Journal of Gastroenterology and Hepatology* 1992; **4**: 857-863. [DOI: 10.1002/hep.510230627]

25 **Merli M**, Bertasi S, Servi R, Diamanti S, Martino F, De Santis A, Goffredo F, Quattrucci S, Antonelli M, Angelico M. Effect of a medium dose of ursodeoxycholic acid with or without taurine supplementation on the nutritional status of patients with cystic fibrosis: a randomized, placebo-controlled, crossover trial. *J Pediatr Gastroenterol Nutr* 1994; **19**: 198-203 [PMID: 7815243 DOI: 10.1097/00005176-199408000-00010]

26 **Kutney K**, Donnola SB, Flask CA, Gubitosi-Klug R, O’Riordan M, McBennett K, Sferra TJ, Kaminiski B. Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients. *World J Hepatol* 2019; **11**: 761-772 [PMID: 31966908 DOI: 10.4254/wjh.v11.i12.761]

27 **Bessonova L**, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, Konstan MW, Sawicki GS, Sewall A, Nyangoma S, Elbert A, Marshall BC, Bilton D. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018; **73**: 731-740 [PMID: 29748252 DOI: 10.1136/thoraxjnl-2017-210394]

28 **Cystic Fibrosis Agents**. Liver Tox: Clinical and Research Information on Drug-Induced Liver Injury. Updated December 5, 2018. Accessed November 18, 2020 [DOI: 10.1201/b15279-24]

29 **Genta RM**, Sonnenberg A. Big data in gastroenterology research. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 386-390 [PMID: 24594912 DOI: 10.1038/nrgastro.2014.18]
