Hepathobiliary therapy

Liver diseases

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Background

Cystic Fibrosis-associated Liver Disease (CFLD) is clinically one of the most signi?cant complications in CF and is believed to have an impact on morbidity and mortality (Betapudi B et al, 2021). As reported also in a previous review (Leeuwen L et al, 2014) liver disease is the third leading cause of death in CF; however, the impact of CFLD on morbidity and mortality remains controversial, at least in part because of the lack of a consistent de?nition of CFLD. The introduction of CFTR modulators could modify CFLD evolution (Baker RD and Baker SS, 2021), as well as new imaging procedures may impact CFLD diagnosis (Hojte C et al, 2020). New liver fibrosis indices, such as minimally invasive biomarkers APRI, FIB-4, and GPR, have been proposed for the detection and monitoring of CFLD (Sellers ZM, 2021).

A wide spectrum of classification of CFLD is reported from Bodewes F A J A et al, 2024.

Colombo 2002 CFLD is considered if at least 2 of the following conditions are present on at least 2 consecutive examinations spanning a 1-year period:

1. Clinical hepatomegaly (increase in liver span and consistency, with liver edge palpable more than 2?cm below the costal margin in the mid-clavicular line), confirmed by ultrasonography

2. Abnormal serum liver enzyme levels consisting of elevation above the upper normal limits of 2 of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT)

3. Ultrasound abnormalities other than hepatomegaly (ie, increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly)

Ultrasonographic pattern of steatosis and liver biopsy were not included in the definition

Debray 2011 Diagnosis of CFLD should be considered if 2 or more categories are present:

1. Physical examination: hepatomegaly: >2?cm below the costal margin on the mid-clavicular line, confirmed by ultrasonography, and/or splenomegaly, confirmed by ultrasound

2. Serum blood tests: increase of transaminases and GGT above upper limits of normal at least 3 consecutive determinations over 12 months after excluding other causes of liver disease

3. Radiologic testing: ultrasonographic evidence of liver involvement or portal hypertension or biliary abnormalities

4. Liver biopsy demonstrates abnormal hepatobiliary histology

Flass 2013 Classification of CFLD

1.CF related liver disease with cirrhosis/portal hypertension (based on clinical exam/imaging, histology, laparoscopy)

2. Liver involvement without cirrhosis/portal hypertension consisting of at least one of the following:

a. Persistent AST, ALT, GGT > 2 times upper limit of normal

b. Intermittent elevations of the above laboratory values

c. Steatosis (histologic determination)

d. Fibrosis (histologic determination)

e. Cholangiopathy (based on ultrasound, MRI, CT, ERCP)

f. Ultrasound abnormalities not consistent with cirrhosis

3.Preclinical: No evidence of liver disease on exam, imaging, or laboratory values

Koh 2017 Diagnosis of CFLD should be considered if 2 or more categories are present:

- 1.Liver biopsy demonstrating pathology or
- 2.Radiologic evidence demonstrating diffuse liver disease or cirrhosis
- 3.At least 2 persistently abnormal: ALT, AST, GGT, or ALP
- 4.Evidence of hepatomegaly, splenomegaly, or portal hypertension by imaging
- 5.Abnormal vibration controlled transient elastography (VCTE) on FibroScan® at any time
- 6.Persistently abnormal APRI, FIB-4, or AST-to-ALT ratio (AAR)

Persistently abnormal was defined as having abnormal values on multiple dates over at least 2 consecutive years

Predisposing factors as male gender, pancreatic insufficiency, meconium ileus (MI), severe but not specific CFTR mutations seem to be directly associated with the presence and severity of liver disease. Other non-CFTR genes may play a role in expression and severity of CFLD, e.g. individuals who carry the *SERPINA* 1 Z allele have a greater risk of developing advanced liver disease with portal hypertension (PHT) (Bartlett JR et al , 2009) (Boelle PY et al, 2019).

In the liver CFTR is expressed on cholangiocytes but not on hepatocytes. Bile is abnormally thick and deydrated and the lack of alcalinization due to reduced bicarbonate causes precipitation and ductular obstruction that may induce fibrosis in some porta tracts. Clinically this can result in a wide range of liver abnormalities such as elevated liver enzymes, neonatal cholestasis,hepatic steatosis, focal biliary cirrhosis, multilobar cirrhosis, cholangiopathy and gallbladder disease (Konrad J et al, 2020).

Epidemiological studies reported that the clinical presentation of non-severe CFLD is relatively uncommon in young children; there is a peak early in adolescence up to 20% and a fall in prevalence of presentation over the age of 20 years. Neonatal cholestasis is an uncommon condition in CF, affecting only 5.7% of the screened newborn CF population. The greatest risk factor for developing cholestasis is the presence of MI. However, the presence of MI appears not to be associated with the development of CFLD. An effect of neonatal cholestasis on the development of CFLD cannot be excluded, as discussed in a previous study (Leeuwen L et al, 2014). Steatosis is the most common hepatic lesion in CF patients, with a prevalence of 23% to 67% and it appears to be unrelated to the direct CFTR secretory defect, but may be indirectly associated with malnutrition and deficiencies of essential fatty acids, carnitine and choline. Thus far, steatosis has been considered as a benign condition in CF. Focal biliary cirrhosis is the pathognomonic hepatic feature of CF. Focal biliary cirrhosis is often clinically silent and does not have clinical consequences, but it can eventually progress in approximately 5-10% of CF patients to clinically significant multilobular biliary cirrhosis, usually presenting in middle childhood and adolescence. Many of these patients later develop signs of portal hypertension with complications such as variceal bleeding. Previous guidelines on nutritional care in CF (Turck D et al, 2016) suggest to consider a regular supplementation with EFAs and fat-soluble vitamins, as previously an association between liver disease and hepatic steatosis (Lindblad A et al, 1999)(Van Biervliet S et al, 2010) has been suggested.

From a diagnostic perspective a prospective longitudinal study including 244 children from 3 to 12 years old with pancreatic insufficiency was performed to evaluate the ability of ultrasound to predict CF cirrhosis in children with a heterogeneous liver pattern vs children with normal US related to standard blood tests, spleen size, and non-invasive liver fibrosis indices. Main results suggest that US patterns correlate with clinically relevant liver disease (Ling SC et al, 2019).

Indeed, a prospective longitudinal cohort study for 4-5 years, including 36 children and 16 adults with CF at risk for developing CFLD, assessed the transient elastography (TE) as a non-invasive method to quantify liver stiffness by specific scores (Klotter V et al, 2017). Despite not conclusive, results should encourage a prospective, multi-center, long term follow up study to confirm the suggested cut-off for the rise in liver stiffness.

From a therapeutic perspective one therapeutic option currently used is ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid.

Recently (Bodewes F A J A et al, 2024) a committee's combined expert position statement on hepatobiliary involvement in CF, which has been endorsed by NASPGHAN and ESPGHAN, recommended using CFHBI (Cystic Fibrosis Hepato-Biliary Involvement) as an updated term to describe and classify all hepatobiliary manifestations in all pwCF alternative to currently use of CFLD. This classification is based on expert consensus and is not still validated for clinical practice and research purposes.

Elevation of liver enzymes (> 1.5× ULN†)		
E0	No elevation of liver enzymes	Either AST/ALT/GGT
E1	Transient elevation of liver enzymes	
E2	Persistent elevation of liver enzymes >6 months	
Imaging of the liver		Either ultrasound/MRI
I0	No imaging abnormalities	
I1	Heterogeneous increased signal	
I2	Nodular imaging abnormalities	
I3	Homogeneous increased signal	
In	No imaging available	
Histopathology of the liver		
H0	No histopathological abnormalities	
H1 a	Fibrosis F1–F2	METAVIR classification
b	Fibrosis F3–F4	
H2	Obliterative portal venopathy	
H3	Steatosis	
H4	Cholestatic histopathology	
Hn	No histology available	
Stiffness of the liver		Various modalities of elastography
S0	Normal liver stiffness	
S1	Increased liver stiffness	
Sn	Liver stiffness was not measured	
Portal hypertension‡		
PO	No portal hypertension	
P1	Cirrhotic portal hypertension	- Histology consistent with cirrhosis (F4) AND/OR - Severe increase of liver stiffness *Supportive cirrhosis: macronodular liver including an irregular edge, inhomogeneous parenchyma*
P2	Non-cirrhotic portal hypertension	- Histology not consistent with fibrosis or cirrhosis *Supportive of non-cirrhotic: normal or mildly elevated HVPG and/or no macronodular appearance*
Biliary manifestations		
B0	No biliary involvement	
B1	Cholelithiasis and hepatolithiasis	
B2	Biliary strictures	MRCP or ERCP
Malignancies of the liver and biliary tract		
M0	No malignancies	
M1	Hepatocellular carcinoma	
M2	Cholangiocarcinoma	

Issues

- To determine whether there is evidence of benefit in using UDCA in people with CF in terms of reducing the risk of developing chronic liver disease, improving indices of liver disease, improving outcomes in general in CF;
- to compare the efficacy of UDCA at low, medium and higher doses;
- to determine the effect of UDCA on serum biliary acids, on histological changes of liver disease, on essential fatty acids and retinol metabolism;
- to evaluate the effect of early treatment with UDCA in patients with predisposing factors;
- to evaluate the effect of new formulas of UDCA.

What is known

One CDSR (Palaniappan SK, 2020) evaluated all RCT focusing on therapeutic interventions for managing advanced liver disease (CFLD with cirrhosis or liver failure, PHT or variceal bleeding or both) in children and adults of all ages and either gender affected by CF. A comprehensive search of the literature did not identify any published eligible randomised controlled trial. Authors concluded that in order to develop the best source of evidence, there is a need to undertake randomised controlled trials of interventions for preventing and managing advanced liver disease in adults and children with CF.

One CDSR (Cheng K et al, 2017) has been planned with the aim to verify whether UDCA improves indices of liver function, reduces the risk of developing chronic liver disease and improves outcomes in general for CFLD. Three trials involving 118 participants were included in the analysis. The complex design used in two trials meant that data could only be analysed for subsets of participants. There was no significant difference in weight change, mean difference -0.90 kg (95% CI, -1.94 to 0.14) based on 30 participants from two trials. Long-term outcomes such as death or need for liver transplantation were not reported. To date the Authors concluded that there is insufficient evidence to justify the routine use of UDCA in CF.

Another CDSR review (Palaniappan SK et al, 2017) assessed various treatment options for the prevention and management of severe liver disease in children and adults with CFLD

1. comparing pharmacological interventions (e.g. non-selective beta-blockers) to placebo or no intervention;
2. comparing endoscopic interventions (e.g. band ligation, sclerotherapy) to active control;
3. comparing TIPSS to active control;
4. comparing surgical interventions (e.g. surgical PS shunt, liver transplantation) to active control.

A comprehensive search of the literature did not identify any published eligible randomised controlled trials.

Despite several controversials, there is growing evidence on the effect of UDCA regarding the reduction of liver stiffness in patients with well-defined, mild liver disease (van der Feen C et al, 2016), safety of long-term, high-dose UDCA treatment for CFLD (Colombo C et al, 2016), positive effect of its supplementation on fat digestion and absorption in pancreatic insufficient CF patients with mild liver involvement (Drzyma?a-Czy? S et al, 2016).

Regarding to other issues only data from observational studies have been reported. A previous observational study from 1983 to 2005 on 278 adults patients with CF and liver disease (Desmond CP et al, 2007) showed that UDCA is associated with improvement in hepatobiliary symptoms and liver function tests. A few observational studies speculate that UDCA is effective in improving cholestasis and hepatic dysfunction in nodular biliary cirrhosis and suggest that UDCA could affect the natural history of CFLD.

The biochemical response to UDCA is compatible with a dose from 10 to 20 mg/kg/day for at least 3 months. UDCA with or without taurine does not significantly affect the nutritional status while little effect of UDCA has been shown on liver enzymes. Inconclusive data are available for the effect of UDCA on histological changes.

A retrospective follow-up case-control study (performed from 1989 to 2005) for assessing the long-term effects of continuous UDCA therapy in CF patients with constantly elevated serum liver enzymes (98/382 patients) showed that UDCA therapy reduced the risk to develop severe liver disease, leading to a significant and persistent improvement in serum liver tests, without impairing long-term pulmonary outcome (Kappler M et al, 2012). Generally UDCA is employed by mouth twice or three times a day, initially for several months but possibly indefinitely and is well tolerated. Side effects are rare, but diarrhoea has been reported.

A retrospective multicenter cohort study (Colombo C et al, 2021) was conduced including 1591 CF patients (1192 patients from UDCA-prescribing centers and 399 from non-prescribing centers) born between 1990 and 2007 and followed from birth up to 31 December 2016 in order to evaluate the crude cumulative incidence (CCI) of portal hypertension (PH) at the age of 20 years in the two groups and estimated the subdistribution hazard ratio (HR) through a Fine and Gray model. Results showed that CF patients followed-up in UDCA prescribing centers did not show a lower incidence of PH as compared to those followed in centers not prescribing UDCA. These results do not clarify the question on the utility of UDCA in reducing the occurrence of severe liver disease in CF.

A non-RCT prospective study (Ye W, 2021) evaluated 141 children with CF at risk for development of advanced liver disease. ELASTIC (Longitudinal Assessment of Transient Elastography in CF) is a nested cohort of 141 patients, ages 7-21, enrolled in the Prediction by US of Risk of Hepatic Cirrhosis in CF (PUSH) Study. These results suggest that VCTE combined with routine screening biomarkers could be used to identify those individuals with CF most likely to have a nodular (NOD) US pattern, but its use in clinical practice requires further exploration through longitudinal assessment.

A phase II trial (NCT00004441), comparing optimized doses of TUDCA (tauroursodeoxycholic acid) with Ursodiol for effects on biliary bile acid composition and metabolism, serum biochemistries, fat absorption, and fat-soluble vitamin, has been completed. Results are not available.

One prospective multicenter case-controlled cohort study (Siegel MJ, 2023) enrolled children with pancreatic insufficient CF aged 3-12 years without known cirrhosis that underwent screening US. This study examined whether heterogeneous (HTG) pattern on liver ultrasound (US) identifies children at risk for advanced cystic fibrosis liver disease (aCFLD). Participants with HTG were matched by age, Pseudomonas infection status and center 1:2 with participants with normal (NL) US pattern. Clinical status and laboratory data were obtained annually and US bi-annually for 6 years. Primary endpoint was development of nodular (NOD) US pattern consistent with aCFLD. 722 participants underwent screening US, with 65 HTG and 592 NL. Final cohort included 55 HTG and 116 NL with ? 1 follow-up US. ALT, AST, GGTP, FIB-4, GPR and APRI were higher, and platelets were lower in HTG compared to NL. HTG had a 9.5-fold increased incidence (95% confidence interval [CI]:3.4, 26.7, p<0.0001, 32.7% vs 3.4%) of NOD versus NL. HTG had a sensitivity of 82% and specificity of 75% for subsequent NOD. Negative predictive value of a NL US for subsequent NOD was 96%. Multivariate logistic prediction model that included baseline US, age, and log(GPR) improved the C-index to 0.90 compared to only baseline US (C-index 0.78). Based on survival analysis, 50% of HTG develop NOD after 8 years. Research US finding of HTG identifies children with CF with a 30-50% risk for aCFLD. A score based on US pattern, age and GPR may refine the identification of individuals at high risk for aCFLD.

Recently more studies have been terminated in order to evaluate whether CFTR corrector/potentiator combinations lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor may also impact the progression of liver fibrosis. A retrospective, single-center analysis of children and adolescents with CF treated with lumacaftor/ivacaftor and/or elexacaftor/tezacaftor/ivacaftor therapy, focusing on alterations in liver function tests and fibrosis indices using increased liver elastography showed that those with CF-associated liver involvement experienced significant decreases in gamma-glutamyl transferase, aspartate aminotransferase-to-platelet index, and gamma-glutamyl transferase-to-platelet ratio while on lumacaftor/ivacaftor. These differences were not observed in patients treated with elexacaftor/tezacaftor/ivacaftor, nor were they observed in patients without underlying CF-associated liver disease. These results provide the first evidence that lumacaftor/ivacaftor may improve liver fibrosis in children and adolescents with CF and suggest it may be beneficial in the treatment of CF-associated liver disease (Levitte S et al, 2023).

Standard of care have been recently suggetsed on this topic. In particular, severe CF liver disease has been associated with greater pulmonary and extra-pulmonary disease burden, and worsening survival. The earliest signs of emerging or established CFLD may be in the form of hepatomegaly and/or splenomegaly (on palpation or imaging) and consistently raised liver transaminases in blood. Routine assessment for liver disease is recommended in people with CF, including annual blood tests and regular ultrasonography. Early referral to a gastroenterologist or hepatologist with CF expertise is needed to investigate for portal hypertension and its complications,

exclude non-CF-related liver diseases, and consider further management (Burgel PR et al, 2024).

Up to 25% of people with CF and modulator therapy have raised levels of liver transaminases genrallytransient and not clinically relevant. Dose adjustment is recommended in those with persistent transaminitis (Southern KW et al, 2023)

Unresolved questions

Much remains unknown about any factors associated with the development of CFLD, the reasons for the variability in disease progression of CFLD and the best clinical approach towards diagnosing and managing CFLD. Therefore, further studies using a uniform de?nition of CFLD are necessary to accurately investigate these issues. There are a number of debates surrounding the treatment of people with CF who have liver involvement. These problems mean that clinicians are faced with the dilemma of when UDCA should be commenced: early to prevent liver involvement; or later as a therapeutic option. There is a need to investigate on longitudinal outcomes, as many of the trials were short-term.

The clinical role for non-invasive markers (e.g. serum biomarkers, elastography) in early diagnosis and follow-up of CFLD is emerging but not fully established.

Future trials should define the target population clearly, with separate trials for those without clinically detectable liver disease, but at risk to liver disease and those with liver disease.

In the era of HEMT it is not clear whether ETI use may modifiy the risk of disease progression (Gardiner A et al, 2022) in CFLD.

Keywords

Cholestasis; Cirrhosis; Liver Diseases;