Review

Liver involvement in cystic fibrosis

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Cystic fibrosis (CF), an autosomal recessive inherited disease that disrupts ion transport in epithelial-lined organs, is the most common potentially lethal genetic disorder of the Caucasian population, affecting between 1 in 2000 and 1 in 4500 newborns in different ethnic groups (1). The CF secretory defect determines inability to maintain the luminal hydration of ducts, leading to physicochemical abnormalities of secretions and duct obstruction. Sweat glands, pancreas, lungs and, in males, the Wolffian ducts are the most commonly affected organs.

Since the involvement of liver in CF is much less frequent than pulmonary and pancreatic disease, which affect around 80–90% of patients, it has received little attention for many years. Only recently, with improved life expectancy, which now exceeds 30 years in the majority of patients (2), has there been increasing observation of liver-related events, and liver disease is now one of the major causes of death in CF (3).

Focal biliary cirrhosis is considered the pathognomonic hepatic lesion and represents the end-result of bile duct plugging with inspissated secretions. The impact of CF-associated liver disease on quality of life and survival is related to progression of the fibrogenic process and development of multilobular cirrhosis. The purpose of this paper is to review and update the most relevant aspects of CF-associated liver disease.

Basic Defect and Genetics of CF

The discovery of the gene responsible for CF on the long arm of chromosome 7 in 1989 (4) has led to a very rapid collection of information regarding the structure and function of the CF gene product, that is, the Cystic Fibrosis Transmembrane Regulator (CFTR). It has been clearly established that CFTR functions as a cAMP-dependent chloride channel in the apical membrane of secretory epithelial cells of most tissues, where it promotes transmembrane efflux of chloride ions (5). However, defective or missing chloride conductance cannot by itself explain all the manifestations of CF, suggesting that absence or dysfunction of CFTR causes secondary abnormalities that may contribute to organ-specific damage (6). Evidence has been provided that CFTR also regulates other ion channels and operates in parallel with different anion exchangers, i.e., Cl−/HCO3− and Na+/H+, in epithelia where these exchangers play an important physiologic role (7). Decreased chloride transport in CF would also alter mucin secretion by affecting exocytosis and the activities of enzymes involved in glycoprotein secretion (8).

Over 750 different disease-causing mutations have been identified to date, with marked variability in their ethnic distribution (9). Such mutations have been grouped into five classes according to the way they influence CFTR-mediated anion secretion (10). Class I, II and III mutations, which are considered to be severe mutations, result in complete loss of chloride channel function through different molecular mechanisms (11). On the other hand, class IV and V mutations, defined as mild mutations, are associated with altered conductance properties or reduced synthesis of normal CFTR. It has become clear that patients with pancreatic insufficiency, who generally have more severe disease (3), carry two severe mutations. In contrast, patients with preserved pancreatic function, who have milder disease and better prognosis (3), carry at least one mild mutation, thus suggesting a dominant effect of the allele linked with preserved pancreatic function (12).

Two percent of adult CF patients present with atypical or monosymptomatic disease, frequently due to rare alleles and characterized by chronic bronchitis, sinusitis with nasal polyposis, pancreatitis and male infertility due to obstructive azoospermia (13).

It should be noted that a relation between genotype and phenotype has been established only for pancre-
atic status, suggesting that genetic factors other than CFTR, namely histocompatibility antigens, differences in medical treatment, and environmental and infectious events may modify the clinical expression of other manifestations of CF, including lung and liver disease (14).

**Pathogenesis of Liver Disease in CF**

CF-associated liver disease is considered the first inherited liver disease due to impaired secretory function of the biliary epithelium. In fact, at the hepatobiliary level, CFTR is expressed exclusively at the apical domain of epithelial cells lining the intra- and extrahepatic bile ducts and gallbladder (15). CFTR is not expressed on hepatocytes and other liver cells, and its main role is to participate in the first step of ductal secretion (16). The cAMP-stimulated Cl⁻ secretion through a low conductance Cl⁻ channel imposes a negative luminal potential and an osmotic gradient that drives into the lumen Na⁺, through the paracellular pathway, and water via water-selective channels (17). The change in apical Cl⁻ gradient facilitates HCO₃⁻ extrusion via Cl⁻/HCO₃⁻ exchange, providing the biliary alkalinization required for the digestive function and for the solubility of organic components of bile. Therefore, although studies directly assessing the effects of mutated CFTR in cholangiocytes are not yet available, it appears reasonable that in CF patients the absence or dysfunction of CFTR leads to reduced fluidity and alkalinity of bile.

Recent data strongly suggest that the absence of CFTR regulatory function on anion exchanger activity in CF may play a major role in the pathophysiology of liver disease (18). In fact, in normal cholangiocytes, the introduction of luminal Cl⁻-free solution imposes a gradient for Cl⁻ exit from cells, that runs the Cl⁻/HCO₃⁻ exchanger backward, resulting in alkalization of the cell due to HCO₃⁻ uptake. This response did not occur in cholangiocytes derived from CF patients, despite the presence of the appropriate anion exchanger, and it was restored by transfection of cells with wild-type CFTR (18).

Abnormalities in mucin secretion may also increase bile viscosity in CF patients. Secretion of chondroitin sulfate was shown to be markedly increased in CF biliary epithelium in vitro compared to non-CF cells (19), thus suggesting that its accumulation may contribute to bile duct plugging by cosinophilic material, which is one of the early histologic changes found in infants and children with CF (20).

Abnormal bile composition and reduced bile flow would ultimately lead to intrahepatic bile duct obstruction and focal biliary cirrhosis. By means of hepatobil-

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lary scintigraphy, abnormalities in biliary drainage are often documented in CF patients, including dilation of intra- and extrahepatic bile ducts associated with delayed biliary excretion and intestinal appearance of the tracer (21,22). In addition, prominent ultrastructural abnormalities of cholangiocytes, with irregular shapes, necrosis and increased collagen deposition have been consistently documented in CF patients (23). These lesions may represent the anatomical expression of long-standing impairment in ductular bile flow, which may increase susceptibility of the biliary epithelium to damage by cytotoxic compounds excreted into the bile and to aggression by infectious agents. In addition, retention of detergent endogenous bile acids may be responsible for cell membrane injury also at the hepatocellular level (24). Oxidative injury to the liver cell membrane may occur through increased free radicals production favored by decreased lipid-soluble antioxidant activity (25). Injured cholangiocytes may release cytokines and growth factors that would induce collagen synthesis by stellate cells (26).

Defective CFTR expression in bile duct cells represents the main pathogenic mechanism leading to liver disease in CF patients. However, it is still unclear why the distribution of hepatic lesions is focal, at least at the early stages of the disease, and why the majority of patients with CF do not develop liver disease. It should be noted that, in addition to CFTR, a number of Cl⁻ conductive pathways, including a Ca²⁺ activated Cl⁻ channel and a G-protein-regulated voltage dependent Cl⁻ channel, are located at the apical cell membrane of the cholangiocytes (27) and may partly compensate the CF secretory defect in the liver.

None of the so-far identified CFTR mutations has been specifically associated with the development of liver disease (28–33), although affected patients are generally found to carry the severe type of mutation (30,33). The presence of a severe mutation seems to represent a necessary condition but not a sufficient one for the development of liver disease in CF. A role of additional, still unknown, pathogenic mechanisms has therefore been postulated.

**Clinical Relevance of Liver Disease in CF**

The prevalence and incidence of liver disease in CF patients are not clearly defined, mainly because there are no sensitive and specific diagnostic markers for focal biliary cirrhosis, which is generally asymptomatic and is often associated with normal liver biochemistry. In addition, to determine the impact of liver disease in CF, mostly cross-sectional or retrospective studies are available (32–39) which have substantial shortcomings depending on the criteria used for patient selection and
diagnosis of liver disease (40). Prevalence figures obtained by retrospective analyses of clinical records range between 4.2% (38) and 7% (39). These studies have also reported a preponderance of male patients among those with liver disease and an incidence peak in adolescence, with a subsequent decrease during the third decade of life (38,39). On the other hand, data derived from autopsy studies indicated a progressive increase in prevalence with age, from 10% in infants to 72% in adults (20,41).

Data from the American Cystic Fibrosis Foundation patient registry (3), which rely on voluntary reporting, indicate that only 1% of the 19,064 CF patients seen in 113 CF care centers during 1996 were affected by liver cirrhosis and portal hypertension, which, however, accounted for 4.2% of total complications (3). Liver disease was the third cause of death after cardiorespiratory problems and transplantation complications, accounting for 2.3% of overall CF mortality (Table 1). This is in striking contrast with the low prevalence figure reported, which likely represents an underestimation (42). Furthermore, studies in which liver disease was actively searched for in large series of CF patients, using biochemical and ultrasonographic assessment, have reported prevalence figures ranging from 18 to 37% (32–37).

Only a few studies have prospectively evaluated the incidence and outcome of liver involvement in CF patients. Lindblad et al. have recently reported preliminary data on a population of 123 CF patients whose hepatic status was followed up for a mean period of 9.1 years (range 2–17 years) (43). Biochemical liver disease or multilobular biliary cirrhosis developed in 43 cases at a mean age of 14 years, and in none of the patients did this occur in adulthood. In addition, liver disease was not more frequent at the end of the study period, despite the fact that the median age of the patients under surveillance was higher.

Overall, these findings are in agreement with data we have recently obtained from a cohort of 183 patients followed at the Milan CF Center for a mean period of about 10 years (44): liver disease developed by the age of 11 years and no incidence peak was observed in any age group. There is therefore substantial evidence to suggest that liver disease is a relatively early complication of CF, which may be susceptible to prevention strategies.

Liver biopsy was performed in 41 patients prospectively followed up by Lindblad, 15 of whom had had a previous biopsy, and in whom histologic changes showed a slow rate of progression (43). In addition, as in our cohort (44), liver disease did not seem to influence the severity of other clinical manifestations of CF, including nutritional status and severity of pulmonary involvement (43). No specific risk factor for the development of liver disease could be identified. In particular, there was no evidence of an association, linking inspissated intestinal content with inspissated biliary secretions, between liver disease and neonatal meconium ileus, which had been reported by a necropsy study (45) and by a previous survey from our group (32). These conflicting results suggest that the pathogenesis of liver disease in CF may be heterogeneous and not simply related to the consequences of inspissated biliary secretions plugging bile ductules.

In summary, available information indicates that liver disease associated with CF usually develops before or at puberty, displays a slowly progressive course and frequently is asymptomatic. Only in a minority of patients may the liver disease represent the main clinical problem and its progress be unusually rapid.

**Clinical Features**

The most common presentation of liver disease in CF is the occasional finding of hepatomegaly on routine physical examination, which may be associated with abnormalities of liver biochemistry. This presentation can also be related to hepatic steatosis, which should be adequately recognized and followed up, since steatosis may represent the first step in the development of more severe hepatic lesions (46).

Jaundice is generally limited to patients presenting with neonatal cholestasis or in those with end-stage multilobular biliary cirrhosis. As in other liver diseases characterized by initial involvement of bile ducts, liver failure is a late event, whereas the most severe complication is portal hypertension; variceal bleeding may also occur in patients showing only mild biochemical abnormalities (47). In a recent retrospective study spanning a 26-year period and performed in a group of 44 children with CF and associated cirrhosis, 86% of them developed esophageal varices, 50% of whom ultimately bled early in
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TABLE 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Approximate frequency (%)</th>
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<tbody>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic elevation of serum liver enzymes</td>
<td>10–35</td>
</tr>
<tr>
<td>Neonatal cholestasis</td>
<td>rare</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>20–60</td>
</tr>
<tr>
<td>Focal biliary cirrhosis</td>
<td>11–70</td>
</tr>
<tr>
<td>Multilobular biliary cirrhosis</td>
<td>5–15</td>
</tr>
<tr>
<td><strong>Gallbladder</strong></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis and cholecystitis</td>
<td>1–10</td>
</tr>
<tr>
<td>Microgallbladder</td>
<td>30</td>
</tr>
<tr>
<td><strong>Biliary tree</strong></td>
<td></td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>rare</td>
</tr>
<tr>
<td>Common bile duct stenosis</td>
<td>&lt;2</td>
</tr>
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</table>

Diagnosis and Clinical Follow-Up

Evidence of liver disease in CF patients is often subclinical, since symptoms and signs tend to appear only when pathological changes are pronounced. Early diagnosis should be pursued since only the early lesions are likely to be reversible. A sensitive and specific test for the evaluation of biliary cell function is not available; diagnosis of CF-associated liver disease is still based on clinical examination and on a combination of biochemical tests and imaging techniques. Serum liver enzymes have low sensitivity, since abnormalities may be mild or intermittent and do not correlate with the severity of hepatic lesions. Serum concentrations of those enzymes related to cholestasis, i.e., \( \gamma \)-glutamyl transpeptidase (\( \gamma \)-GT), alkaline phosphatase and 5’-nucleotidase are more likely to be increased rather than serum transaminase levels.

The diagnostic value of fasting and post-prandial serum bile acid concentrations may be limited by the presence of bile acid malabsorption in those patients with pancreatic insufficiency (55). In addition, such determinations do not reflect the severity of histologic lesions (56).

New and potentially useful tests have been proposed, including serum glutathione S-transferase B1 (57) and serum markers of fibrogenesis, i.e., collagen VI (58) and prolyl hydroxylase (59). However, their diagnostic value needs to be confirmed.

Liver biopsy is still employed infrequently in the diagnostic work-up of CF patients for the well-recognized risk of sampling error due to the heterogeneous distribution of hepatic lesions. It may be useful for determining the type of the predominant lesion (steatosis or focal biliary cirrhosis), the extent of portal fibrosis, and may also provide information on progression of liver disease and on the effects of treatment (42). Recently a “clinical liver score”, which includes hepatomegaly, splenomegaly and increased serum concentrations of ALT and \( \gamma \)-GT, was shown to be associated with significant injury at histology (60). However, it is still questionable whether liver histology may reflect the clinical course of a disease which is characterized by focal distribution of the typical lesions.

There are only limited data on the diagnostic value of dynamic tests of liver function, such as the aminopyrine breath test, galactose elimination capacity or caffeine tolerance test. Although their sensitivity in the early stage of the disease is probably limited, again, by the focal distribution of hepatic lesions (36), these tests may provide valuable information on disease progression when serially performed (61).

With regard to imaging techniques, it seems reasonable to perform an ultrasound scan and hepatobiliary scintigraphy in all CF patients in whom liver disease is suspected. A simple echographic scoring system based on coarseness of liver parenchyma, nodularity of the...
liver edge and increased periportal echogenicity has been reported to correlate with a number of clinical and biochemical and ultrasonographic parameters, and has been proposed for the hepatic follow-up of these patients (62). Hepatobiliary scintigraphy with iminodiacetic acid derivatives can document the presence of biliary drainage impairment and is sensitive enough to document time-related progression of liver disease. It can be usefully employed to monitor the response to treatment (21,22).

Endoscopic retrograde cholangiography (ERCP) is an invasive procedure with considerable potential for complications and is not suitable for screening and diagnostic purposes. It remains the investigation of choice for sclerosing cholangitis, distal stenosis of the common bile duct and for choledocholithiasis, for which it also provides a therapeutic option.

Recently, magnetic resonance imaging (MRI) has been successfully employed to image the biliary tree in other forms of biliary diseases, where sensitivity has been reported to be comparable to ERCP (63). Although the sensitivity of MRI may not be adequate for evaluation of peripheral intrahepatic ducts, preliminary evaluation in CF has shown excellent imaging of the extrahepatic and intrahepatic biliary tree (64).

Management of Patients with Liver Disease
Due to the decreasing mortality from extrahepatic causes, management of liver disease in CF patients is becoming a relevant clinical issue. Several therapeutic approaches acting at different steps of the pathogenic process have been suggested (65) and are summarized in Table 3. Correction of the secretion defect and somatic gene therapy aiming at replacing the defective gene to the biliary epithelium may be curative but, unlike the airways epithelium, cholangiocytes are relatively inaccessible by targeted drug and gene delivery, and the clinical application of this approach remains to be established. Successful insertion of wild-type CFTR into normal and CF intrahepatic biliary epithelial cell lines has been achieved in culture (16); in addition, retrograde infusion of recombinant adenoviruses expressing the human CFTR gene into the rat biliary tract resulted in successful gene expression in bile duct cells (66).

**Bile acid therapy**
Oral bile acid therapy, aimed at improving biliary secretion in terms of bile viscosity and bile acid composition (67), is currently the most useful therapeutic approach in CF-associated liver disease and is virtually devoid of serious side effects. Ursodeoxycholic acid (UDCA) has been employed in the treatment of patients with chronic cholestatic liver diseases, such as primary biliary cirrhosis (68). UDCA seems to act by displacing detergent, toxic bile acids from the enterohepatic circulation, thus preventing perpetuation of liver damage caused by their retention during cholestasis (24,69).

In vitro studies have shown that high concentrations of UDCA, similar to those reached in biliary ducts, exert a membrane-stabilizing effect on biomembranes exposed to hydrophobic, toxic bile acids (70). In addition, the taurine-conjugate of UDCA may enhance the secretory capacity of hepatocytes by promoting hepatocellular exocytic secretory events (71) and in cholangiocytes, UDCA appears to stimulate Ca2+-dependent Cl− efflux (72). There is also preliminary evidence suggesting immunoregulatory properties of bile acids (73).

Improvements of liver biochemistry (74–76), hepatic excretory function and biliary drainage (21,22,75), liver histology (77) and nutritional status (75) have been documented during UDCA administration to CF patients with liver disease. The improvement in essential fatty acid status recently documented in a placebo-controlled crossover study (78) may have important extrahepatic implications. In fact, essential fatty acid deficiency occurring in a substantial proportion of patients with CF is not corrected by essential fatty acid supplementation (79) and may have a negative impact on the progression of pulmonary disease by altering eicosanoid production and immune function.

There is limited information on the long-term effects of UDCA treatment on clinically relevant events. Of the four placebo-controlled trials available so far (80–

### Table 3
Theoretical prospect for treatment of liver disease in cystic fibrosis based on pathogenesis

<table>
<thead>
<tr>
<th>Objective</th>
<th>Approach</th>
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<tr>
<td>Replace the defective gene</td>
<td>adenovirus or liposomal-mediated gene transfer</td>
</tr>
<tr>
<td>Stimulate accessory Cl− and HCO3−</td>
<td>agonists of Ca2+-activated Cl− channels (purinergic nucleotides, UDCA?)</td>
</tr>
<tr>
<td>Reduce the inflammatory reaction</td>
<td>anti-inflammatory agents, FANS</td>
</tr>
<tr>
<td>Reduce fibrogenesis</td>
<td>colchicin, antioxidants, steroids, IFNγ, growth factor modulators</td>
</tr>
<tr>
<td>Reduce hepatocellular damage</td>
<td>antioxidants, UDCA, glutathione, avoid malnutrition, antiviral prophylaxis</td>
</tr>
<tr>
<td>Stimulate bile flow at the level of the hepatocyte</td>
<td>UDCA, glutathione, strategies to increase MDR-mediated ATP-release</td>
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</table>
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83), none has assessed treatment efficacy in terms of survival, mainly because of the short duration of the studies (the maximum duration was 12 months) and of the small sample size. Although the results reported from these trials provide important preliminary information, they have been considered insufficient to justify the routine use of UDCA in CF patients with liver disease (84). However, in consideration of the striking improvement of biochemical and scintigraphic expression of cholestasis occurring in these patients, the execution of long-term, placebo-controlled trials is no longer feasible and ethically justifiable.

Interestingly, clinical and biochemical response to long-term UDCA administration tended to be confined to those patients who showed impairment of biliary drainage, while other patients presenting similar biochemical abnormalities but no scintigraphic alterations did not seem to benefit from treatment (85). As discussed before, it is likely that different pathogenetic mechanisms are involved in CF patients with liver disease and that UDCA may be ineffective in some.

We believe that all patients with a diagnosis of liver disease should be treated, and that treatment should be started as soon as possible since only early lesions are likely to be reversible. The optimal daily dose of UDCA has been established as 20 mg/kg body weight in dose-response studies (69,86). This dose is higher than that conventionally used in other cholestatic liver diseases to achieve comparable biliary enrichment, probably due to poor intestinal absorption in CF patients (87). Due to the characteristics of intestinal absorption of UDCA (88), the drug should be administered in multiple divided doses. To prevent taurine depletion and its consequences on fat malabsorption (89), taurine supplementation at the dose of 30–40 mg/kg/day is advisable in CF patients with pancreatic insufficiency and poor nutritional status during chronic administration of unconjugated UDCA (83).

Management of complications of liver cirrhosis

Since the most severe complication of CF-associated liver disease is portal hypertension, it is important to monitor the development of esophageal varices. Severe portal hypertension and variceal bleeding may require sclerotherapy and vasopressin administration during the acute episode (90). Surgical portosystemic shunt (91) and transjugular portosystemic shunt (TIPSS) (92) may also be indicated for the management of portal hypertension in these patients, while partial splenectomy with conservation of the upper pole of the spleen has been successfully performed in patients with massive splenic enlargement (93).

Prophylactic treatment aimed at avoiding bleeding is indicated in various forms of liver cirrhosis (90). However, the efficacy of β-receptor blockade has not been evaluated in CF because of the adverse effects of β-blockers on airway reactivity. As for any other form of liver disease, there is no evidence to support the use of esophageal varice prophylactic injection sclerotherapy for CF patients with liver disease (42). Treatment of variceal bleeding by repeated injection sclerotherapy in CF patients is not always effective in relieving clinical problems associated with portal hypertension (94). In the series reported by Debray, injection sclerotherapy of esophageal varices did not prevent recurrence of bleeding in five out of seven treated children (48). In contrast, elective surgical porto-systemic shunt was successfully performed in patients with preserved liver function and without severe pulmonary disease, allowing prolonged post-operative survival up to 15 years. In this series, recurrent bleeding episodes and high risk of variceal bleeding were considered the indications for such a surgical approach (48). Finally, TIPSS can be employed as a short-term method for portal decompression in patients waiting for liver transplantation (92).

Liver transplantation

Liver transplantation should be offered to patients with life-threatening sequelae of portal hypertension or, more rarely, to those patients with severe functional impairment and growth failure. The 1-year survival is approximately 80% and a beneficial effect on lung function has been reported in most cases (31,95). Special attention to pulmonary conditions should be provided, with intensive care beginning in the pre-transplant period. Regarding the postoperative management, CF patients often need higher doses of cyclosporin, due to both intestinal malabsorption and altered drug metabolism, and a careful monitoring of serum cyclosporin levels should be accomplished (96). Although experience with combined liver-heart-lung transplantation is at present limited, problems with rejection may be less severe following the triple transplant than after liver graft only (95).

Conclusions

The growing knowledge of the pathophysiology of CF has led to novel therapeutic approaches which are expected to further improve life expectancy. The impact of liver disease on quality of life and survival of CF patients is going to increase in future years. Pharmacologic correction of the defective ion transport and transfer of the normal CFTR gene into the epithelial cells of CF patients in different organs are under study, but to date they are not useful for liver disease.
UDCA is relatively safe and inexpensive compared to other medications used in CF, and widespread use of this bile acid in the treatment of CF-associated liver disease may be anticipated, even if its effect in delaying the occurrence of major clinical outcomes is yet to be demonstrated. It is likely that the effectiveness of bile acid therapy is improved in patients with early-stage liver disease, before symptoms have become evident. Early diagnosis and identification of CF patients who are more likely to develop liver disease should be actively pursued in the attempt to evaluate if there is a role for UDCA, not only in the treatment of but also in the prevention of liver disease.

References


