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ORIGINAL ARTICLE

Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry

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Summary

Liver Transplant (LTx) has been rarely performed in cystic fibrosis (CF) patients and indications and outcomes are not well defined. A questionnaire was sent to all European CF and LTx centers to collect data on CF transplanted patients. We obtained information regarding 57 CF patients. LTx has been performed prevalently in males and in pediatric age. The main complication of cirrhosis was portal hypertension with hypersplenism. In the majority of cases the decision to transplant was based on the contemporary presence of various factors. Post-LTx survival was high and comparable with that expected for more common pediatric LTx indications. Poor respiratory function was the main risk factor for early death. In the short-term, respiratory function significantly improved after LTx. LTx is the appropriate treatment for patients with advanced CF-related liver disease and preserved pulmonary function (Forced Expiratory Volume at 1 s, FEV_1 >50%). This poll reveals that most European liver centers perform LTx prior to the development of end-stage liver disease or overt pulmonary or other clinical decompensation.

Introduction

Cystic fibrosis (CF) is a multisystemic genetic disease of secretory epithelia caused by mutations in the gene encoding for a cyclic-adenosyl mono phosphate-dependent chloride channel, the CFTR (cystic fibrosis transmembrane conductance regulator). Lack of CFTR or its functional deficiency affects the respiratory, gastrointestinal and male reproductive systems. Exocrine pancreatic insufficiency, chronic pulmonary infections with acute exacerbations leading eventually to respiratory insufficiency are the most frequent complications. In 90% of cases, respiratory failure leads to death.

Cystic fibrosis transmembrane conductance regulator is also located on the apical aspect of the biliary epithelium and regulates bile fluidity and alkalinity. Ultrastructural changes of the intrahepatic biliary epithelium are seen in CF patients; in most cases, however, with no clinical consequences. Liver disease is an early complication involving more than one-fourth of CF patients generally exhibiting a slowly progressive course [1]. In some cases, depending on still unclear concurrent factors [2], liver disease progresses to chronic obstructive cholangiopathy, focal biliary cirrhosis, and multilobular liver cirrhosis. As in other liver diseases involving primarily cholangiocytes, liver failure is a late event whereas portal hypertension and its complications are the main problems. According to the American CF patients registry, liver failure is presently the third leading cause of death in CF [3].

Except for ursodeoxycholic acid that may slow the progression of the disease in the precirrhotic cases [4] therapy remains only symptomatic, particularly for patients with established cirrhosis.

Liver transplantation (LTx) represents a possible option. In spite of reasonable concerns on the outcomes of the procedures in these frail patients and the effects of the immunosuppression on lung infections, successful LTx has been consistently reported [5–9]. Published series are small and report single center experiences thus several questions remain open regarding LTx for CF-related liver disease. Among them are the impact of poor respiratory function on post-transplantation survival and timing for LTx. This is a particularly difficult estimate, as the presence of end-stage liver disease (ESLD) as indicated by profound and progressive hepatocyte loss (presence of coagulopathy, hypoalbuminemia, hyperbilirubinemia and/or the major complications of liver cirrhosis as intractable ascites, hepatic encephalopathy, hepato-renal syndrome) are less frequent in CF liver disease and conventional liver function scores do not consider malnutrition and pulmonary function, which are the prominent factors in CF patients. The European Liver Transplant Registry (ELTR) reports only 79 CF patients in the period 1997–2002. In order to gain a better understanding of current practice in this field we conducted an inquiry among European CF and LTx centers, focusing on the indications and outcomes of LTx in CF.

Patients and methods

In January 2001, questionnaires were sent to all European CF (421) and LTx (113) centers. Addresses were provided by the European CF Society and by the ELTR. Various recalls were made to centers which did not reply, either by email or by contacting centers' representatives during European or International Meetings. The enrollment period was closed after 18 months to avoid potential bias related to differences in time.

The questions were partially different whether sent to CF or surgical centers. The following were inquired: number and characteristics (age, gender, genotype, pancreatic status, and diabetes) of CF patients who underwent LTx; liver and respiratory function and complications before LTx (esophageal varices, gastrointestinal bleeding, ascites, porto-systemic encephalopathy, hepato-renal syndrome); indications for LTx (liver failure, hypersplenism, gastrointestinal bleeding, malnutrition, worsening lung function, increasing number of respiratory infections, multiresistant bacteria in sputum, porto-systemic encephalopathy, and intractable ascites). Liver failure was defined by the presence of at least two of the following criteria: decreasing albumin level <30 g/l, prolonged coagulation prothrombin time >3 s over normal, increasing bilirubin level >50 μmol/l, development of ascites. Follow-up data concerned survival, complications (vascular and biliary complications, acute and chronic rejection, infections, lympho-proliferative disease, hypertension, renal insufficiency, osteoporosis, nasal polyposis, and diabetes) and pulmonary function. Informations concerning the transplant and early complications were obtained only from the surgical centers.

Received data were cross-checked in order to identify patients reported twice because they had been followed by two different referral centers. This was done comparing initials (if available), birth and LTx date, and country. Identity was ascertained in eight cases whose data were considered only once. Centers were subsequently contacted for queries on the provided data.

Statistical analyses were performed using the Kaplan–Meier estimator for describing the occurrence of re-transplant or death and the Fisher exact test or the Student's *t*-test for paired data where appropriate.

Results

Information was obtained from 15 LTx centers (13.2% of those contacted) and 62 CF centers (14.7%). Of these five

LTx centers and 45 CF centers reported that they had not transplanted any cases, while 10 LTx (8.8%) and 17 CF (4%) centers provided data on 60 patients. These patients were identified as transplanted in the period October 1990– June 2001 and their follow up was updated at December 2001. Data of 57 cases were analyzed, while three patients were excluded due to poor quality of information.

There was a great prevalence of males (74%). Age at transplantation ranged 2–27 years (median 12.2 years). There is no significant change in the mean age of liver transplant from 1990 to 2001 (Table 1). Patients' genotype was known in 37 cases, the DF508 mutation being present on 78% of the chromosomes. Pancreatic status was reported in 40 cases and pancreatic insufficiency was present in 98%. CF-related diabetes was present in 12/57 (21%) of the patients.

Severity of liver disease

Before transplant 89% of the patients presented esophageal varices, with at least one episode of gastro-intestinal bleeding in 42%. Ascites and porto-systemic encephalopathy were present in 44% and 13% of cases, respectively. Only one patient had a hepato-renal syndrome.

The Child-Turcotte-Pugh Score [10] could be calculated in 21/57 cases showing mild–moderate functional stage of cirrhosis at transplant (class A6–B9) in 86% of the cases and severe liver impairment in the remaining 14%.

Indications for LTx

In most cases, the decision to transplant was based on the concomitant presence of several factors. Main indications as recorded by the centers were liver failure (69%), hypersplenism (57%), malnutrition (45%), esophageal bleeding (27%), worsening lung function (16%), appearance of multiresistant bacteria in sputum (4%) and porto-systemic encephalopathy (2%). Although ascites was reported in 32% of the patients, only in 14% it represented an indication for transplant. The single first indication for transplant was liver failure (64%), followed by hypersplenism (16%) gastro-intestinal bleeding (12%) and malnutrition (8%).

Table 1. Years of age at liver transplant by period of transplant.

Transplant period	No. patients	Median (range)
1990–1996	25	12.2 (2.1*–23.5)
1997–2001	32	12.5 (6.5–27.1)

*One patient transplanted at 2.1 years of age (all others above 7 years of age).

Respiratory function

Pulmonary function tests were available for 37 patients. At the time of transplant, respiratory function was normal (Forced Expiratory Volume at 1 s, FEV_1 >80% of the predicted values for age and sex) in 22% of the patients while lung disease was moderately severe (FEV_1 between 40% and 80%) in 67% of cases. In 11% respiratory function was severely compromised (FEV_1 <40%).

Operative procedure

Whole liver, reduced liver, split liver and living related transplant were performed in 79%, 10.5%, 7%, and 3.5% of cases, respectively. In two cases, a triple combined transplant (heart–lung and liver) was performed.

Outcome

The median follow up was 3.7 years (range 0–11). Four patients had to be re-transplanted and two died subsequently. The estimate of the event-free survival (EFS) probability was computed taking into account the time from transplant to re-transplant or death, whichever occurred first, for a total of 11 events. The survival curve included all nine deaths as events. Curves are reported in Fig. 1 (one re-transplant that occurred after 9 years from first transplant does not appear on the graph). The causes of death are reported in Table 2.

Complications after transplantation are reported in Table 3. The most prevalent were diabetes, acute rejections, and infections.

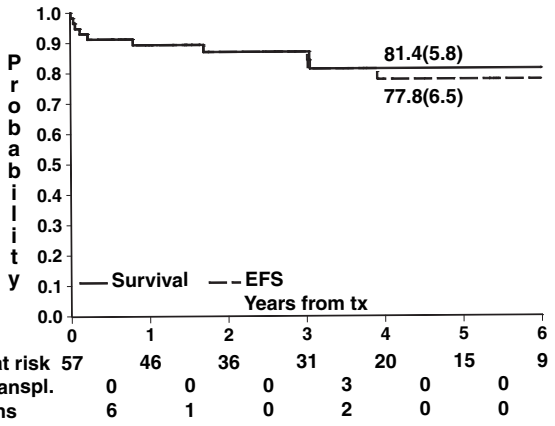

Figure 1 Kaplan–Meier curves of event-free survival and survival for 57 cystic fibrosis patients after liver transplant. The 5-year estimates (SE) are reported. The number of patients at risk and the number of events (re-transplants and deaths) are listed below the time axis.

Table 2. Causes of death in patients who underwent liver transplant.

Cause of death	No. patients
Chronic rejection	2
Impaired lung function	3
Liver failure	1
Sepsis	2
Multiorgan failure	2
Intracerebral hemorrhage	2
Thrombosis of hepatic artery	1
Disseminated aspergillosis	1

Table 3. Complications after transplantation.

Condition	*n* (%)
Diabetes	40 (55)
Acute rejection	37 (19)
Infections (other than lung)	38 (18)
Renal insufficiency	38 (16)
Nasal polyposis	34 (14)
Hypertension	36 (14)
Biliary complications	37 (14)
Vascular complications	39 (10)
Chronic rejection	38 (5)
Lympho-proliferative disease	37 (3)
Osteoporosis	32 (3)
Others	34 (32)

The number of patients with data available (*n*) and the percentage of cases with complication (%) are reported.

Table 4. Mortality by FEV1 at 6 months before transplant.

	Status at last follow up		
FEV1	Alive	Dead	Total
<40%	1	3	4
40–80%	22	3	25
≥80%	7	1	8
Total	30	7	37

Mortality was significantly higher in patients with lower pulmonary function at 6 months before transplant, i.e. FEV_1 <40% (Fisher exact test *P*-value = 0.02). Two other patients who died in the FEV_1 category 40–80% had FEV_1 = 42% and 46% (see Table 4).

No significant difference in mortality was detected in patients with Child-Turcotte-Pugh Score ranked A6–B9 when compared with those who ranked C10-C11 (Fisher exact test *P*-value = 0.271) (Table 5).

In 29 patients, surviving the intervention longer than 6 months, a significant functional improvement could be documented at 6 months (average increase in FEV_1 was 5.9%, Student's *t*-test for paired data, *P*-value = 0.03).

Table 5. Mortality by Child-Turcotte-Pugh (C-T-P) score.

	Status at last follow up		
C-T-P Score	Alive	Dead	Total
A6–B9	17	1	18
C10–C11	2	1	3
Total	19	2	21

Discussion

Our survey describes for the first time the current practice for LTx in patients with advanced CF-related liver disease in Europe and also provides information on its outcome in a large number of CF patients. The study indicates that LTx is clearly an option in CF. It is prevalently performed in male patients who develop cirrhosis at a young age; outcome is good and respiratory function may improve. CFTR mutations have been classified into various groups and categorized as severe (class I–III) or mild (classes IV and V) according to the residual function of the protein, which relates to the presence of pancreatic sufficiency. The DF508 mutation, a severe class II mutation, was present on 78% of the chromosomes of LTx patients and 98% of those with pancreatic insufficiency indicating that severe mutations are highly represented among patients with liver cirrhosis.

Thus, the demographic and genetic characteristic of these patients are in line with those previously reported by prospective studies aimed at defining the natural history of CF-associated liver disease [1,11]. Our data therefore confirm that liver disease is a part of the severe phenotype and represents an early complication of CF (occurring mostly during the first decade of life). According to the ELTR there is no significant change in the mean age of liver transplant in CF patients from 1990 to 2002.

Only small series about single center experiences of CF patients undergoing LTx have been reported and several questions remain open. In the ELTR, CF has not been specifically indicated as a cause for intervention until January 1997. From 1997 to 2002, 79 patients are identified as having CF. Thus, on average liver transplant is performed in 13 European CF patients yearly.

We tried to collect data about CF patients undergoing LTx and contacted CF and LTx centers, irrespective of the age of the patients in care. The response rate of 8.8% from transplant centers is not low because, according to ELTR data, just 19 of 113 centers (17%) which were contacted were performing liver transplant in CF patients at the time of the study. Thus, the response rate is 10 of 19 centers (52%) which is more representative, particularly as these centers contribute 15% of the total European

liver transplant activity. All 57 patients of the study except two are registered in ELTR and 38 of the 79 (48%) patients registered as F12 (CF) in the ELTR in the period 1997–2002 were included in this poll.

We found that the main complication of cirrhosis in these CF patients was portal hypertension with hypersplenism; while the clinical complications of ESLD were present only in a minority of patients. The indication to LTx thus, in most cases, considered a variety of factors including liver failure, hypersplenism, malnutrition, gastro-esophageal bleeding, and worsening pulmonary function. It might be argued that LTx could have been delayed in some of the cases presented here. Patients with hypersplenism and normal or nearly normal hepatic function might be stable for years, esophageal bleeding and malnutrition may be controlled in many patients. The difficult problem of optimal timing for LTx in CF patients has been the object of considerable debate in literature. Some authors [6,12] suggest that LTx should be considered only in patients with profound and progressive hepatocyte loss as indicated by coagulopathy, hyperbilirubinemia, and hepatic encephalopathy. Others [13] believe that transplantation should be considered earlier, before signs of hepatocellular failure are prominent because the risk of premature death from respiratory complications is increased in patients with hepatic cirrhosis [14]. In the patients who could be enrolled in this poll, LTx was more often performed prior to the development of ESLD or overt pulmonary or other clinical decompensation. This could also be an explanation for the good outcome observed. We cannot establish whether this is the correct option. The progressive nature of lung disease makes the choice difficult in CF despite the fact that combined liver and bipulmonary transplantation has been successfully reported [15,16]. We do not intend to establish or to suggest indication for LTx in CF based on our retrospective survey. An answer to this would need a prospective follow up of CF patients with severe liver involvement and a comparison of their outcomes whether transplanted or not. It is necessary to develop and improve a scoring system establishing the probability of survival of CF patients with liver disease [5,16], which was far behind the aims of our poll. We did not ask to the centers neither information regarding mortality of CF patients awaiting for liver transplant nor about CF patients to whom LTx was not offered because of severity of lung disease. Thus, we cannot exclude that the cases reported here represent a very select subgroup of 'better' cases and that many others were not offered transplantation because of the severity of their lung disease.

Diabetes was a relatively frequent complication of LTx in CF patients. This is not unexpected as CF related diabetes occurs in 10–20% of young CF patients [17]. Increased rate of diabetes has been recently reported in CF patients with ESLD undergoing LTx or conservative treatment [18] and also in CF recipients of lung Tx [19]. Other complications did not differ from what expected after LTx for other conditions. Osteoporosis occurs in even young CF patients and may be worsened by liver disease [18,20].

Infectious complications were not higher than expected for other indications despite CF patients airways are usually heavily colonized by pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*. One patient, however, died from invasive *Aspergillus* disease and, in the last years, airway colonization by *Bulkhorderia cepacia* has been associated with early death after lung transplant [21]. Thus, the risk of infections should not be underestimated [22].

The 3-year survival probability of liver transplanted CF patients in the ELTR (79%) is comparable with that reported in this series (81.4%). An analysis of the data of the ELTR does not show any period effect in survival after liver transplant in CF patients, nor this can be shown in our patients.

The EFS probability calculated in our study was similar to that found in other conditions and higher in CF patients with better lung function. Thus, while CF does not seem to contraindicate LTx, lung disease is a major prognostic factor. Lung function progressively declines in CF patients and is relevant for optimal timing of LTx. This may lead to anticipate the timing for LTx, otherwise it might be necessary to perform a multiorgan Tx. A satisfactory survival has also been achieved after combined lung–liver or heart–lung–liver Tx [15,16], but restricted access to donor organ results in a greater waiting time for a triple procedure than for a single liver, increasing the risk to lose the patient.

Data have been published suggesting that LTx may improve lung function [5–9] in patients with CF. This, indeed, is confirmed by our study, but the reason is unclear. Improving nutritional conditions, removal of ascites, improving diaphragmatic function, possible effect of immunosuppression have been advocated [5,23].

We conclude that LTx is clearly an option in patients with advanced CF-related liver disease. Until more sensitive and specific markers of CF liver disease severity and progression will become available [24] LTx should probably be performed before severe worsening of respiratory function (FEV_1 <50%). On the other hand, LTx may improve lung function in some patients. Clearly, more data are still needed on the long-term follow up of CF patients undergoing liver LTx, as ultimately the cause of death would highly depend on the progression of lung disease. Prospective studies are needed which would be of great help in rigorously definition timing for LTx.

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