Liver Transplantation for Patients with Cholestatic Liver Diseases

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Summary
Background: Cholestatic liver diseases (CD) account for 11% of all liver transplantations (LT) in the Eurotransplant region. Despite the excellent long-term outcome that is considerably superior to all other indications for LT, transplant surgeons and physicians face nowadays – in the era of MELD (Model of End-Stage Liver Disease)-based allocation, organ shortage, and extended allocation policies – more and more challenges in this patient cohort, especially since there is no curative medical treatment for these entities. Methods: Based on a literature review and personal experience in liver transplantation for CD, we show the status quo of indication, allocation, and outcome as well as potential strategies to overcome long waiting times and organ shortage. Results: Concerning graft and patient survival, CD remain the ‘best indications’ for LT. Since the implementation of MELD-based allocation results in patients with primary sclerosing cholangitis (PSC) could be preserved on good levels only by the implementation and revision of standard exceptions. Recurrence of PSC after LT remains a challenge for transplant surgeons and physicians. New data has kindled a debate on biliary reconstruction in LT for PSC. Promising data on living donor LT motivate to push the boundaries in this direction. Conclusion: CD are excellent indications for liver transplantation since excellent long-term outcomes are achievable when the transplant is performed at the right time. The decisions concerning evaluation, listing, and allocation should be made by an interdisciplinary team of gastroenterologists and transplant surgeons.

Introduction

According to the European Liver Transplant Registry (ELTR), cholestatic diseases account for 11% of all liver transplants in the Eurotransplant (ET) region. Biliary atresia is the main indication of cholestatic diseases in pediatric liver transplantation (LT), whereas in adult LT primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are the main indications [1]. In this review we focus on adult LT for cholestatic diseases, essentially PSC and PBC, and present the current clinical practice concerning listing, allocation, and surgical procedure. Data on etiology, epidemiology, as well as outcome and recurrence after LT are also provided. The main source of this review is the current clinical practice guideline of the European Association for the Study of the Liver (EASL) on the management of cholestatic liver disease (CD) accompanied by further literature research in PubMed.

Epidemiology, Etiology, and Disease Progression

Primary Sclerosing Cholangitis

PSC is a chronic cholestatic disease with a prevalence of 4–16/100,000 and an increasing incidence (with a recent increase of 35.1% over a period of 10 years alone) [2]. It affects men more commonly than women (approximately 62–70% males), generally in middle age [3], and is strongly associated with chronic inflammatory bowel diseases (IBD; mostly ulcerative colitis (UC) but also Crohn’s disease) [4–6]. The exact etiopathogenesis of PSC remains unknown; however, it is immune-mediated, occurring in genetically predisposed individuals [7]. In PSC, autoimmune- or immune-mediated injury affects the medium-sized intra- and extrahepatic bile ducts, causing concentric and obliterative fibrosis and multifocal bile duct stricturing. Immunoglobulin G4 (IgG4) levels are raised in 9–26% of patients with PSC, compared with only 1% in PBC [7]. It is important to test IgG4 levels in all patients with PSC since elevated levels (>1.4 g/l) may confer a poorer prognosis [8, 9].
The mean interval from the diagnosis of PSC to death in patients who do not undergo LT is 12–18 years [6]. In pertinent studies, the overall risk of a PSC patient to die from cancer ranges from 40 to 58% [10–12] and the cumulative risk for development of cholangiocellular carcinoma (CCC) in patients with PSC is described to be as high as 10% and more [11, 13]. Whenever PSC is diagnosed, a possible dominant bile duct stenosis or CCC should be actively ruled out [14]. Risk factors for CCC include advanced disease (elevated bilirubin, variceal bleeding), proctocolectomy, chronic UC with colorectal cancer or dysplasia, long history of IBD, and polymorphisms of the NKG2D gene [15–17]. Historically, the presence of such a tumor contraindicates LT because of the high rate of tumor recurrence. However, studies from the Mayo Clinic suggest that in highly selected cases, aggressive treatment with chemo- and radiotherapy may allow some patients to have a good outcome [18]. In Germany, a trial of adjuvant gemcitabine chemotherapy after LT in patients with hilar CCC is being conducted at present (DRKS00000805, product 001).

**Primary Biliary Cirrhosis**

The exact etiopathogenesis of PBC remains unknown, but it is believed that genetic susceptibility and environmental factors (including infectious triggers) are involved [19]. PBC exhibits a number of autoimmune features, including the presence of autoreactive T cell and B cell responses against mitochondrial self-antigens, in particular the E2-domain of pyruvate dehydrogenase complex (PDC-E2) [20, 21]. Recently, the FoxO3a/Bim signaling pathway, a Bcl-2 interacting mediator of apoptosis, was reported to be enhanced in PBC patients compared to that in patients suffering from other liver disorders [22]. In PBC, a strong female predominance (F:M ratio 10:1) and an association with other autoimmune diseases in the same individual and their close family is described. A concurrent autoimmune disorder occurs in between 32 and 53% of patients, most notably autoimmune thyroid disease, systemic lupus erythematosus, or systemic sclerosis [23, 24]. In PBC, the autoimmune injury affects the small, interlobular bile ducts, causing the typical appearance of non-suppurative, destructive cholangitis.

PBC usually remains asymptomatic for a long time, with fatigue and pruritus being the most common initial symptoms. The progression of the disease is manifested by skin changes like dermatographism, hyperpigmentation, xanthomas, and jaundice. Some patients have sore muscles and arthritis. Because of the unspecific symptoms most of the patients are diagnosed at a more advanced stage of the disease. Three major clinical courses of the disease are described: Firstly comes slowly progressing PBC, which is the most typical form. Here, progressive ductopenia is accompanied by advancing fibrosis, leading eventually to liver cirrhosis over a period of 10–20 years. Secondly, a course affecting approximately 10–20% of PBC patients shows fluctuating or persistent features of autoimmune hepatitis, leading to a more severe clinical course. The third and most severe form affects 5–10% of the patients and is characterized by premature ductopenia, rapid onset of icteric cholestasis, and thus a faster progression to cirrhosis usually in less than 5 years [25].

**Non-Surgical Treatment of Cholestatic Liver Diseases**

There is no curative medical treatment of PSC or PBC. In PBC, the use of ursodeoxycholic acid (UDCA) was shown to improve liver function tests, to delay fibrosis progression, and to decrease the histopathological stage of the disease [26]. The use of UDCA in PSC is still under debate as it has been studied in varying doses with only modest results. In lower doses (13–15 mg/kg body weight (BW)) it reduced cholestatic liver enzymes but did not influence death, the need for LT, or progression in liver histology [27]. In intermediate dosage (17–23 mg/kg BW) a trend towards reducing LT or death was found without reaching statistical significance [28]. A trial with high doses (28–30 mg/kg BW) had to be terminated early because of increased numbers of adverse clinical endpoints (including death and LT) in the UDCA group [29].

**Listing/Indication for Liver Transplantation**

In general, LT in CD patients is indicated when liver failure occurs with complications similar to those for end-stage liver disease caused by other etiologies. An unacceptable quality of life because of severe, treatment-resistant pruritus or severe hepatic encephalopathy may also merit consideration for transplantation [20]. Fatigue in PBC and other CD is often severe and disabling; however, cross-sectional studies have shown no evidence of improved fatigue after LT [30–32].

LT is the only curative treatment option for PSC patients. The optimal timing of LT is a matter of debate; for each patient, the timing should be based on the individual prognosis. Many studies have been performed with the intention of determining valid markers of prognosis. At the very latest, a PSC patient should be put on the LT waiting list when he or she is found to have severe, progressive liver disease with persistent elevation of serum bilirubin concentration or recurrent cholangitis, with or without the development of dominant stenoses, despite optimal endoscopic treatment and despite having lost weight to lower the body mass index (BMI) by at least 10% over a period of 1 year [14].

PBC is considered ‘one of the best’ indications for LT since excellent outcomes are achievable. Obviously, LT should only be considered when the probability of survival after LT is higher than without. One popular tool in determining the prognosis of PBC patients is the Mayo Risk Score [33]. According to the EASL guidelines, PBC patients should be referred for an initial evaluation for LT when serum bilirubin approaches 6 mg/dl, a Mayo Risk Score ≥ 7.8 is present, and/or a MELD (Model of End-Stage Liver Disease) score higher than 12 is calculated [5].

**Allocation**

**Primary Sclerosing Cholangitis**

Organ distribution for PSC patients is not regulated solely according to the MELD score because the latter does not adequately...
reflect the true urgency of LT in these patients. Since the implementation of MELD-based allocation in Germany, it has been suspected that PSC patients may be disadvantaged as liver function in these patients usually stays comparatively stable over a longer time period until they decompensate or develop CCC and then will not profit from LT anymore. MELD-based allocation is founded on impaired kidney function, abnormal coagulation, and increased levels of serum bilirubin. Although possibly requiring urgent LT, only high serum bilirubin levels are usually observed in PSC patients. Thus, conditions for earning extra MELD points as a standard exception were defined: two or more episodes of microbiologically proven bacteremia within the last 6 months or septic complications of cholangitis [34]. However, only a few PSC patients fulfill these criteria while they still carry the risk of developing CCC and are often suffering from pruritus and fatigue. This led to an adaption of allocation policies: From March 2012 onward, PSC patients fulfilling the criteria for LT have been taken onto the LT waiting list with a MELD score of 22 points. They are then automatically assigned a higher urgency level every 3 months, corresponding to an assumed mortality of 10%, regardless of their laboratory findings [35].

In a recent study by the Hanover group it was shown that the adaption of allocation policies for PSC patients during the MELD era was able to prevent the increase in 1-year mortality after LT that is currently present for almost all other indications after the implementation of MELD-based allocation in Germany [36–38]. Nevertheless the authors state that no analysis of patients who were removed from the waitlist due to severe complications (e.g. development of CCC or death) during waiting time was performed. They conclude that the criteria which must be fulfilled to gain exception points do not represent the whole spectrum of potential complications with prognostic relevance and that by the adaption of the allocation policies only a deterioration of results could be prevented and no improvement gained [36].

**Primary Biliary Cirrhosis**

Allocation in patients with PBC in the ET region is MELD-based, with the exception of those patients developing hepatocellular carcinoma (HCC). HCC occurs in patients with CD who developed cirrhosis with variable incidence (PBC 4–12.3% at 10 years [39–41]; PSC 2%/year [42]) and represents an indication for LT. The prioritization of these patients for LT is the same as for other liver diseases associated with HCC [35].

**Technical Aspects of Liver Transplantation in Patients with Cholestatic Liver Disease**

The surgical procedure in PBC recipients is not different from that of all other LTs. In PSC patients, although there are reports of duct-to-duct reconstructions with comparable outcomes concerning biliary strictures and leakages [43], it is usually recommended to perform a Roux-en-Y hepaticojejunostomy for reconstruction [5, 43]. In a most recent meta-analysis of ten studies comprising 910 patients, the authors reported comparable results concerning anastomotic bile leak rates, biliary strictures, graft survival, PSC recurrence, and number of patients diagnosed with cholangiocarcinoma following transplantation. The Roux-en-Y hepaticojejunostomy reconstruction was associated with a higher risk of cholangitis. The incidence of de novo cholangiocarcinoma was similar in both groups. The authors conclude that duct-to-duct reconstruction should be considered when feasible in patients with PSC [44]. Thus, the debate about biliary reconstruction in PSC patients is still ongoing, and randomized controlled trials are warranted.

In our clinic we regularly perform a Roux-en-Y hepaticojejunostomy and insert a ‘Roeder tube’ for splinting the anastomosis and for control of initial liver function (bile production). On the fifth postoperative day, a cholangiographic control of the anastomosis is performed. The Roeder tube is closed and left in situ for another 4–6 weeks before removal after another cholangiographic control.

**Living Donor Liver Transplantation in Patients with Cholestatic Liver Disease**

As already mentioned, the current situation in Germany [36–38] forces the transplant community to discuss solutions for organ shortage and possible disadvantages for specific indications in the MELD-based allocation system. Although there could be enough deceased donors to avoid a threat to the life of potential living donors, the German society seems to favor the transplant community to step in that direction.

About 10 years ago it was already stated that both PBC patients who have to wait a long time with a severely impaired quality of life and young PSC patients facing the risk of developing bile duct cancer could be transplanted in an elective situation using a living donor liver graft and may also overcome a surgical complication [45].

In Asia, where due to cultural, religious, and traditional reasons deceased donor LT is hardly available, living donor liver transplantation (LDLT) is a highly effective strategy to overcome organ shortage [46]. In Japan, where most of the current experience with LDLT was gained [47], 1-year and 5-year survival rates for adults are 90% and 83%, respectively [48]. In the United States, the Adult-to-Adult Living Donor Liver Transplantation Study (A2ALL), a prospective cohort of nine centers, documented an overall 1-year and 3-year patient survival of 94 and 78%, respectively [49]. Results of LDLTs in Europe have an overall 5-year graft survival rate of 69%, while survival is better for children than for adults (78 vs. 63%) [1]. These promising results and most recent studies from Asia pushing the frontiers in LDLT [50] may encourage the transplant community in Germany to follow the path of increasing LDLT numbers in patients with CD, especially since the transplants could then be available for CD recipients before they suffer an advanced stage and consecutively an impaired outcome. In general, due to the impending high risk for a functional small-for-size syndrome in the highly urgent situation, neither fulminant liver failure nor acute-on-chronic deterioration was considered a good indication for LDLT [51].
In contrast, the procedure of LDLT carried (and carries) a 0.5% risk of death and is followed by severe donor complications of about 20% [45]. Thus, it should be limited to very well experienced transplant centers that also perform a high number of advanced liver surgery.

**Outcome after Transplantation**

After receiving a liver transplant, CD patients tend to do very well: 5- and 10-year survival rates of 87.4 and 83.2% in PSC [52] or even 67.5% at 20 years (PBC, PSC, and autoimmune hepatitis) [53] have been reported. Data from the ELTR report 5-year survival rates of 83 and 82% for PSC and PBC, respectively [1].

**Recurrence after Transplantation**

PBC and PSC recur in many recipients, and recurrence may be more aggressive than the original disease [20]. The prevalence rate of recurrent PBC (rPBC) ranges from 0 to 35%. The reported incidence rate is 21–37% at 10 years after LT and 43% at 15 years after LT [54]. Concerning PSC, disease recurrence (rPSC) occurs in the donor liver in approximately 20–25% after 5 years [55, 56]. In a UK outcome report, rPSC was more common in male patients with an intact colon [57]. Further risk factors for rPSC are early acute cellular rejection and coexistent IBD with an intact colon at the time of transplantation [7]. Absence of inflammation in the intestine either due to colectomy before or during LT or non-existence of concurrent IBD has been shown to have a protective effect against rPSC [58]. This is in keeping with the so-called ‘leaky gut theory’ [7]. However, not only concomitant IBD was identified as a risk factor for rPSC. Acute cellular rejection, especially steroid-resistant [59–61], chronic rejection [62], and the use of extended criteria donor grafts [58] were also described to increase the risk of rPSC.

The mean time interval between LT and onset of rPSC was described to be as early as 6 months after LT although also longer intervals (5 years) are seen [54]. In other studies, rPSC after LT has been said to arise in 20% or more of all cases; however, it is important to have in mind that rPSC is hard to distinguish from secondary changes in the bile ducts, and the data on this question are inconsistent [57, 63]. Because of the typical epidemiological features of PBC (an ‘old ladies’ tale’) and PSC (usually younger patients) graft loss due to recurrent disease is not a major issue in PBC (1.3%), but in PSC (8.4%) [64]. Several studies showed that tacrolimus-based immunosuppression (IS) is associated with an increased risk of rPBC as well as a reduced time to recurrence when compared with ciclosporin-based IS [65, 66]. However, a meta-analysis from 2006 showed no significant influence of the immunosuppressive regimen on PBC recurrence [67]. On this basis, and since the influence of PBC recurrence on graft and patient survival is almost inexistent, tacrolimus-based regimens remain the standard at most transplant centers.

**Colectomy Post Liver Transplantation in Patients with Primary Sclerosing Cholangitis**

The course of IBD is variable after LT although reports describe that about 30% of the patients may worsen and need an increase in their medical therapy or even a colectomy [68]. Indications for colectomy after LT are chronically active severe UC, benign strictures, colonic dysplasia, or colorectal cancer [69]. There are no data supporting prophylactic colectomy during or after LT; however, colectomy should be considered in severe relapsing UC in PSC patients before they develop liver cirrhosis and dysfunction [70]. In general, colectomy after LT is less frequent in PSC patients with concomitant UC. As described by the Cleveland group, when observing 167 patients, the necessity of colectomy after LT was only 34.9% compared to 76.5% in the non-LT group [71].

**Disclosure Statement**

All authors state that no conflict of interest exists.
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