Recurrence of cholestatic liver disease after living donor liver transplantation

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Abstract
End-stage liver disease, due to cholestatic liver diseases with an autoimmune background such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), is considered a good indication for liver transplantation. Excellent overall patient and graft outcomes, based mostly on the experience from deceased donor liver transplantation (DDLT), have been reported. Due to the limited number of organ donations from deceased donors in most Asian countries, living donor liver transplantation (LDLT) is the mainstream treatment for end-stage liver disease, including that resulting from PBC and PSC. Although the initial experiences with LDLT for PBC and PSC seem satisfactory or comparable to that with DDLT, some aspects, including the timing of transplantation, the risk of recurrent disease, and its long-term clinical implications, require further evaluation. Whether or not the long-term outcomes of LDLT from a biologically related donor are equivalent to that of DDLT requires further observations. The clinical course following LDLT may be affected by the genetic background shared between the recipient and the living related donor.

Key words: Liver transplantation; Primary biliary cirrhosis; Primary sclerosing cholangitis; Living donor; Recurrence

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INTRODUCTION
Primary biliary cirrhosis (PBC) is characterized by the destruction of interlobular and septal bile ducts, leading to cholestasis and fibrosis[1]. Primary sclerosing cholangitis (PSC) is also a chronic cholestatic liver disease, characterized by inflammatory and fibrotic bile duct lesions forming multiple strictures and dilatations of the intra- and extrahepatic bile ducts[2-4]. Disordered immune regulation is considered to have a role in both PBC and PSC, though the specific immunologic mechanisms are yet to be clarified despite recent advancements[5,6]. In both PBC and PSC, there is a gradual progression of cholestasis, which results in end-stage liver disease (ESLD). In PBC, the administration of ursodeoxycholic acid (UDCA) starting at an early stage of the disease improves the prognosis and is, therefore, recommended[5,6]. On the other hand, effective medical treatment for PSC remains a matter of debate. UDCA administration, with or without the use of immunosuppressive agents, seems to have
PBC

Whether the combined symptoms of intractable pruritus, lethargy, or osteoporosis encountered in PBC should be considered an indication for LDLT in patients without significant signs of portal hypertension or liver failure remains an open question. At our institution, the indication of LDLT for PBC is based on the potential for improvement or benefits in life expectancy. Unlike in DDLT, less importance may be placed on quality of life in LDLT. We have considered that quality of life issues in the recipient do not outweigh even the slightest possibility of donor mortality or morbidity that may result in disability. In addition to the above-mentioned MELD score, the results obtained from the Mayo model are taken into account. Although the model was developed prior to the MELD era, and is not considered a factor for organ allocation in DDLT, we find that the Mayo model is very useful in the LDLT setting. As reported by Kim and colleagues, there is a window of opportunity appropriate for LDLT, expressed as risk scores of 6 to 7.8. Risk scores higher than 10 are related to longer hospitalization after LDLT and mortality. When the risk of death by the natural disease course is predicted to outweigh the surgical risks of liver transplantation, LDLT may be planned and performed.

The 5-year survival rate after DDLT for PBC is approximately 80%. The anti-mitochondrial antibody (AMA) status does not change after liver transplantation and, therefore, is not diagnostic of recurrent disease after transplantation. PBC recurrence is currently defined according to the agreed criteria, including patient transplanted for PBC, persistence of AMA, and compatible liver biopsy. The largest single-center series with a mean follow-up period of 56 mo indicated a rate of such confirmed recurrence to be 17% at a mean follow-up period of 36 mo after transplantation. Interestingly, although histologically recognizable recurrence of the disease may be common, its effect on survival seems insignificant in LDLT. Liermann and colleagues demonstrated that patients with recurrent disease tended to be younger and receive organs from younger donors, and to have a longer warm ischemia time. But, such differences were considered to be clinically insignificant. The effect of a human leukocyte antigen (HLA) match between the donor and recipient remains unknown.

PBC is reported to recur after LDLT. Hashimoto and colleagues presented the first series of recurrent PBC after LDLT. All patients remained positive for AMA as in DDLT. The presence of mixed portal inflammatory infiltrates with granulomatous cholangitis was considered a definite histologic finding suggestive of recurrence. In 2 of 6 (33%) patients, such findings were established by protocol biopsy 1 to 2 years after LDLT. In the study, immunosuppression consisted of tacrolimus and steroids. Mycophenolate mofetil was not used. UDCA (600 mg/d) was administered to all patients.

The number of patients in Hashimoto’s study is too small to draw a definitive conclusion. The high rate of recurrence (33% in 2 years) is in sharp contrast with that in an earlier DDLT series. As recently reviewed by Neuberger, early reports in DDLT in which the recurrence of PBC was evaluated in a smaller patient population and a shorter observation period indicated a tendency to underestimate the risk of disease recurrence, a finding that was later reversed by a larger series with a longer follow-up period. Compared to DDLT,
the history and volume of cases of LDLT for PBC is extremely limited. The rate of histologically confirmed recurrence at this very early stage is, therefore, somewhat disturbing.

Two single-center studies, both with 50 patients, were recently presented[21,25]. Hasegawa and colleagues[25] presented 3 and 5-year overall survival rates of 88% and 80%, respectively, with a median follow-up period of 35 mo. Before transplantation, AMA was positive in 42 patients (84%). AMA remained positive in 33 patients (66%) at 6 mo after transplantation. Multivariate analysis indicated that a lower updated Mayo risk score was a significant favorable factor for shorter hospitalization following LDLT, confirming the usefulness of the model in LDLT, as in DDLT[21]. In the study, periodic liver biopsies were not performed, and occasional biopsy in cases of abnormal liver function did not present with findings suggestive of recurrent PBC. Biopsy-proven acute cellular rejection was observed in 18 (36%) patients. Because histologic findings are indispensable for the diagnosis of recurrent PBC, the study provides little information on disease recurrence, though the excellent midterm patient survival warrants further application of LDLT for PBC.

On the other hand, Morioka and colleagues[25] presented 5-year overall survival rates of 67%. The recurrence of PBC was confirmed in 18% of patients within a median of 36 mo after LDLT (range 12-123 mo). The results of the study suggested that a lower number of HLA mismatches between donor and recipient, and a younger donor age resulted in better survival, though a lower number of HLA mismatches were also suggested to be a risk factor for PBC recurrence.

The study by Morioka and colleagues[25] included ABO incompatible cases, which were not included in the study by Hasegawa and colleagues[21], and recipients presented with higher MELD scores. The median MELD score in Hasegawa's study was 13, whereas that in Morioka's series was 23. Of the 50 patients, 14 (28%) died within 6 mo after LDLT in Morioka's series, whereas 3 (6%) died within 6 mo after LDLT in Hasegawa study[21]. It is not clear how the lower number of HLA mismatches affects short-term (6 mo) survival in the latter study. Recurrent PBC seems to be of less importance during this period as it was described to occur after 12 postoperative months. In fact, data more recently presented indicated that a simple comparison of HLA matching has little or no impact on survival[26]. Clearly, the impact of HLA mismatches on PBC recurrence in LDLT requires further study.

The most recent registry study from Japan, in which 221 PBC patients were analyzed, reports a 5-year survival rate of 79%. Histologic evaluation was available for 70 patients, among whom 7 presented with findings compatible with recurrent disease with a median follow-up period of 36 mo[27]. The information is limited, however, and it is, therefore, difficult to draw a universally acceptable conclusion on the overall long-term outcome of LDLT for PBC.

PSC

As for PBC, the indication for LDLT for PSC at our institution is based on the improved life expectancy. Although MELD score is considered more appropriate for DDLT, the new Mayo Model[20] may be helpful for deciding the optimal timing of LDLT and preparation once a living donor candidate becomes available. Development of the model was based upon a large cohort of patients followed for two decades. Histologic evaluation by liver biopsy is not required and the score is easily obtained from readily available clinical variables. Its validity among the Far East Asian population, however, requires further analysis. At our institution, we currently consider a MELD score > 15 and/or a Mayo risk score > 2.0 as good starting points to prepare for LDLT.

PSC is considered to be a good indication for DDLT with an excellent 5-year graft survival rate of approximately 80%. A higher rate of re-transplantation compared to that for other indications (9.6% vs 4.9% within 2 years), however, has been recognized. But, its relation with recurrent disease is unclear. Recurrence of PSC after DDLT has been reported at rates between 1% to 33%, depending on the diagnostic criteria and follow-up duration[40]. Graziani and colleagues[29] proposed combined cholangiographic and hepatic histologic criteria with strict exclusion criteria (cases with ABO incompatibility between donor and recipient, nonanastomotic strictures before posttransplantation day 90, anastomotic strictures alone, hepatic artery complications, or ductopenic rejection were excluded) and reported that PSC recurs after DDLT in 20% with typical radiologic manifestations found within a year, and histologic presentation within 3 years after DDLT. In their study, 5-year patient and graft survival rates were comparable between patients with recurrent PSC and patients with PSC without signs of recurrence.

A case suspected of recurrent PSC following LDLT was first reported by Kita et al[40]. There have been sporadic case reports from Asian regions[40-44], as well as from the West[35-39], of LDLT for PSC from living related donors since then, but none reported recurrence; follow-up periods were less than 2 years in most case reports. Aside from the above case reports, cases of LDLT for PSC are found in moderate to large registries worldwide[40-44]. Moon et al[42] reported 2 cases of LDLT for PSC among their large series of 580 LDLTs. Soejima et al[43] also reported 2 cases of LDLT for PSC in their series of 52 LDLTs. Both, however, lacked a specific description of the long-term outcome. The largest registry analysis by Maheshwari et al[44] reported the outcome of 3309 PSC patients who underwent liver transplantation, among whom 69 underwent LDLT. Only 10 of those presented with a follow-up period longer than a year, however, and details regarding the outcome were not provided.

Thus, there is a significant lack of information specifically on the long-term outcome of LDLT for PSC, especially regarding recurrence. One explanation may be the rare incidence of PSC in the Far East
Table 1 Recurrence of PSC following LDLT

| Series | No. | Rate of blood related donors | No. rec. of PSC | Median period to dx. of rec. |
|--------|-----|------------------------------|-----------------|-----------------------------|
| Tokyo  | 9   | 89% (5 out of 9)              | 4 (44%)         | 40 mo (range 14-66 mo)      |
| Kyoto  | 22  | 82% (23 out of 28)            | 13 (59%)        | 31 mo (range 22-71 mo)      |

No.: Number of patients; rec.: Recurrence; dx.: Diagnosis.

Recently, two additional studies on LDLT for PSC were published from high volume centers in the region. The Tokyo group described the outcome of 9 adult LDLT cases, of which 8 were living-related. The median follow-up period was 3.5 years after LDLT. No ABO blood type-incompatible cases were performed. The outcome in terms of patient survival was satisfactory with a 5-year rate of 90%. When recurrence of PSC was evaluated according to Graziadei's criteria, however, recurrent PSC was diagnosed in four patients. Rates of freedom from recurrent PSC at 1, 3, and 5 years were 100%, 73%, and 49%, respectively. The mean time to recurrence was 3.3 years. When limited to biologically related donor-recipient cases, recurrent PSC was diagnosed in 50% of cases. Interestingly, none of the patients presented with the HLA haplotypes associated with a higher susceptibility for developing PSC in the Caucasian population.

The Kyoto group reported 28 patients with PSC who underwent LDLT. Among the 22 patients who survived for more than a year, 13 (59%) presented with PSC recurrence with a mean follow-up period of 31 mo, 5 of whom died or required re-transplantation for graft failure. The HLA haplotypes that may affect recurrence of the hepatic condition remain unclear, although HLA-DR15 is positively associated with ulcerative colitis. The group concluded that unlike PBC, the recurrence of PSC adversely affects the outcome in LDLT. Although there is a difference in the short-term mortality between the two reports, the high rate of recurrence reported in both studies requires further attention. Key features of the two series are summarized in Table 1. The clinical manifestations of recurrence described in both series seem more aggressive than those in patients that underwent LDLT for PBC. The risk factors and susceptible genetic characteristics in LDLT remain unclear. Further prospective study with a protocol cholangiogram and genetic considerations with an HLA haplotype analysis is necessary.

CONCLUSION

LDLT provides a satisfactory short-to-midterm outcome for PBC and PSC. Both PBC and PSC, however, can recur after LDLT. The incidence of recurrence appears to be higher in LDLT compared to DDLT. The long-term impact of recurrence on survival, however, remains unknown at this point. PSC may present with a poorer long-term outcome, but further studies are necessary.

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