Recurrence of Primary Biliary Cholangitis After Liver Transplantation: A Japanese Perspective

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Primary biliary cholangitis (PBC) is a chronic cholestatic disease characterized by granulomatous destruction of intrahepatic bile ducts. The precise pathogenic mechanisms of developing PBC are still poorly understood, and the development of disease is believed to result from a combination of multiple genetic factors interacting with environmental triggers.[1]

Although relatively rare, up to 10% of patients listed for liver transplant (LT) in North America and Europe have a diagnosis of PBC. The outcome after LT for patients with PBC is generally good, with 1-year and 5-year patient survival rates reported between 93%-94% and 82%-90%, respectively.[2,3] However, recurrent PBC (*r*PBC) is common, and the risk of recurrence increases with time following LT (Table 1). In the majority of studies, *r*PBC has been linked to the more potent immunosuppression regimens, especially with the initial use of tacrolimus following LT. This observation may appear counterintuitive as increased risk with immunosuppression is usually associated with infectious rather than autoimmune disease processes. However, it is notable that specific immunosuppressive treatments are not routinely used for patients with PBC due to lack of efficacy and undue side effects. Following LT, initial tacrolimus therapy is associated with both earlier and more severe recurrence, whereas cyclosporine has been shown to be protective against *r*PBC in Europe and North America (Table 1). The reasons for this observation are not clear and could include issues concerning alloreactivity, hastening any infectious process linked with PBC, immune reconstitution with immunosuppression withdrawal, and even off-target effects of different regimens. In this regard, it is notable that cyclosporine is known to have broad antiviral effects and has been shown to block the replication of a betaretrovirus that has been linked with PBC.[4]

In this issue of *Hepatology Communications,* Kogiso et al.[5] present a large, retrospective, multicenter study of patients with PBC who survived for more than 1-year after receiving a living donor liver transplantation. Approximately 15% of patients developed *r*PBC (median, approximately 5 years), and this was associated with a younger age at time of LT, preserved liver function status manifested with lower Child-Pugh and Model for End-Stage Liver Disease scores, high serum immunoglobulin (Ig)M level, sex mismatch, human leukocyte antigen B60 and D-related 8, and initial treatment with cyclosporine. These findings are consistent with other Japanese studies reporting an association of *r*PBC with high IgM, sex mismatch, and initial immunosuppression with cyclosporine.[6]

As discussed, the increased risk of *r*PBC with initial use of cyclosporine in Japan is contrary to observations from the majority of the LT series from North America and Europe reporting a protective effect of this calcineurin inhibitor (Table 1). Of note, the

Abbreviations: Ig, immunoglobulin; LT, liver transplant; PBC, primary biliary cholangitis; rPBC, recurrent PBC; UDCA, ursodeoxycholic acid.

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Aldo J. Montano-Loza, M.D., Ph.D.
Division of Gastroenterology and Liver Unit
Zeidler Ledcor Centre, Room 1-20B
University of Alberta
8540 112 Street NW
Edmonton, Alberta, Canada T6G 2X8
E-mail: aldo.montano-loza@ualberta.ca
Tel.: +1-780-248-1892

TABLE 1. RECENT STUDIES REPORTING TRANSPLANTATION, RECURRENCE RATE, AND RISK FACTORS FOR RECURRENCE OF PBC

Author, Year, Country	n	Cadaveric LT/LDLT	Rate of *r*PBC	Risk Factors for *r*PBC
Sanchez et al., 2003 United States	169	All cadaveric LT	11% at 6 years	- Use of tacrolimus
Levitsky, 2003 United States	46	All cadaveric LT	15% at 6.5 years	- None
Neuberger, 2004 United Kingdom	485	All cadaveric LT	23% at 6.6 years	- Use of tacrolimus
Jacob et al., 2006 Germany	100	All cadaveric	14% at 10 years	- Younger age at LT - Use of tacrolimus
Charatcharoenwitthaya et al., 2007 United States	154	All cadaveric LT	34% at 11 years	- Shorter duration of maintenance corticosteroids - Male recipients - Older recipient age at transplant - Use of tacrolimus
Morioka et al., 2007 Japan	50	All LDLT	18% at 3 years	- Lower number of HLA-A, B, DR mismatches - Lower trough level of tacrolimus within 1 year
Montano-Loza et al., 2010 Canada	108	97% cadaveric LT	29% at 10 years	- Use of tacrolimus
Manousou et al., 2010 United Kingdom	103	All cadaveric LT	35% at 9 years	- Azathioprine had protective effects *r*PBC - Graft failure in 6% of *r*PBC
Egawa et al., 2016 Japan	444	All LDLT	21% at 10 years	- Younger age at LT - IgM >554 mg/dL - Sex mismatch - Use of cyclosporine - HLA-DR locus mismatching
Kogiso et al., 2017 Japan	388	All LDLT	15% at 5 years	- Younger recipient age - HLA B60 positivity - Lower MELD score at LT - Initial treatment with cyclosporine - Donor sex mismatch - Shorter operative time

Abbreviations: DR, antigen D-related; HLA, human leukocyte antigen; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease.

authors had previously reported that the switch from tacrolimus to cyclosporine decreased the risk of *r*PBC in a different study, suggesting that timing of cyclosporine use is an important factor.[6] While the opposing findings concerning cyclosporine use and *r*PBC in Japan are likely related to differences in management and immunosuppression practices worldwide, there remains a possibility that ethnicity, genetic predisposition, and environmental factors also play a role in the development of *r*PBC. For example, a recent study from the United Kingdom showed an association of *r*PBC with the recipient's interleukin-12A polymorphisms that have been linked with a predisposition to PBC in genome-wide association studies of subjects of European descent.[1] Specifically, the use of tacrolimus in patients with the genotype AG or GG of the rs62270414 single-nucleotide polymorphism had an increased risk of *r*PBC, and the use of cyclosporine in patients with the AA genotype had a lower risk for *r*PBC.[7] In contrast, genome-wide association studies from Japan have suggested that the interleukin-12 axis plays far less of a role in the genetic predisposition to PBC in this ethnic group.[8] These data suggest the possibility that the influence of distinct immunosuppressive agents on *r*PBC might vary as a result of the immunogenetic differences that impact the initial development of PBC in Japan.[1,4]

The association of increased risk of *rP*BC with a younger age at the time of LT and less advanced liver disease appears counterintuitive as well. However, it is conceivable that the sicker patients may not have had a chance of developing *r*PBC if they succumbed in the first year following LT, particularly as *r*PBC was associated with a shorter duration of surgery, perhaps implying that longer surgeries are associated with increased mortality within the first year. Indeed, the 1-year survival rate of 80% reported in this article[5] is approximately 10% lower than that reported in other studies. Notably, a younger age has been associated with *r*PBC in other reports and an increased risk of progressing to LT due to a lack of response to ursodeoxycholic acid (UDCA) (Table 1). It is not clear

why younger patients would have genetic or environmental risk factors that lead to an accelerated disease process either before or after LT.

In this study, the authors found that higher IgM levels prior to LT were associated with a higher risk of *r*PBC,[5] indicating ongoing immune dysregulation at the time of LT. These data suggest that disease recurrence may well be a continuum of a systemic disease before LT, leading to recurrence after transplantation. Similar observations have been reported in patients with autoimmune hepatitis; those with elevated IgG levels and aminotransferases at the time of transplantation have been shown to be predisposed to recurrent disease after LT.[2,9] It is not clear why this should be the case, but parallels exist with infectious disease processes in LT recipients. For example, patients with biochemical features of hepatitis and increased viral loads prior to LT are at risk of earlier and more severe disease recurrence. It is interesting to speculate that there might be a role of infectious agents in triggering recurrent (or *de novo*) autoimmune liver disease in addition to the contribution of genetic predisposition in the donor and recipient.

Possibly the most relevant issue for patients is to establish the clinical significance of *r*PBC. In most studies, overall long-term graft and patient survival have not been adversely affected even though the frequency of graft failure due to *r*PBC has been established in some studies (Table 1). However, most studies have only reported a follow-up between 5 and 10 years. In addition, studies with protocol biopsies are uncommon, and therefore the real frequency of *r*PBC remains unknown. Larger population studies with longer follow-up and protocol biopsies may be required to demonstrate the trend of reduced long-term graft and patient survival. Another issue that needs to be addressed is the question of progression of fibrosis with minimal changes in liver biochemistry tests in patients who do not undergo protocol biopsies.

Finally, strategies to reduce the risk of *r*PBC following LT have recently been reported. An uncontrolled multicenter study including French and Swiss centers was able to show that administration of UDCA soon after LT for PBC was associated with a lower risk of *r*PBC.[10] While the efficacy of UDCA in preventing *r*PBC should be evaluated in clinical control trials, this postoperative treatment seems a sensible addition in the management of PBC following LT because it is well tolerated and of proven benefit in patients prior to LT. However, the institution of cyclosporine as a preventative measure against *r*PBC appears less straight forward. The accumulated data suggest that tacrolimus provides better graft and overall survival than cyclosporine, and further studies will be necessary to determine whether cyclosporine therapy results in improved patient and graft survival in patients with PBC following LT.

Aldo J. Montano-Loza
Andrew L. Mason
Division of Gastroenterology and Liver Unit
University of Alberta Hospital
Edmonton, Canada

REFERENCES

1) Hirschfield GM, Chapman RW, Karlsen TH, Lammert F, Lazaridis KN, Mason AL. The genetics of complex cholestatic disorders. Gastroenterology 2013;144:1357-1374.
2) Montano-Loza AJ, Bhanji RA, Wasilenko S, Mason AL. Systematic review: recurrent autoimmune liver diseases after liver transplantation. Aliment Pharmacol Ther 2017;45:485-500.
3) Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A protects against primary biliary cirrhosis recurrence after liver transplantation. Am J Transplant 2010;10:852-858.
4) Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A inhibits in vitro replication of betaretrovirus associated with primary biliary cirrhosis. Liver Int 2010;30:871-877.
5) Kogiso K, Egawa H, Teramukai S, Taniai M, Hashimoto E, Tokushige K, et al. Risk factors for recurrence of primary biliary cholangitis after liver transplantation in female patients: a Japanese multicenter retrospective study. Hepatol Commun 2017; doi:10.1002/hep4.1037.
6) Egawa H, Sakisaka S, Teramukai S, Sakabayashi S, Yamamoto M, Umeshita K, et al. Long-term outcomes of living-donor liver transplantation for primary biliary cirrhosis: a Japanese multicenter study. Am J Transplant 2016;16:1248-1257.
7) Carbone M, Mells GF, Alexander GJ, Westbrook RH, Heneghan MA, Sandford RN, et al. Calcineurin inhibitors and the IL12A locus influence risk of recurrent primary biliary cirrhosis after liver transplantation. Am J Transplant 2013;13: 1110-1111.
8) Nakamura M, Nishida N, Kawashima M, Aiba Y, Tanaka A, Yasunami M, et al. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. Am J Hum Genet 2012; 91:721-728.
9) Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, Bain VG, Tandon P. Risk factors for recurrence of autoimmune hepatitis after liver transplantation. Liver Transpl 2009;15:1254-1261.
10) Bosch A, Dumortier J, Maucor Boulch D, Conti F, Morard I, Rubbia-Brandt L, et al. Long-term administration of ursodeoxycholic acid prevents recurrence of primary biliary cirrhosis after liver transplantation. J Hepatol 2015;62(Suppl 2):S783.