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Liver transplantation in autoimmune liver diseases

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Liver transplantation is indicated for terminal phases of autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Indications for transplantation in autoimmune liver diseases are similar to those used in other acute or chronic liver diseases. Therapeutic advances have reduced the need for transplantation for autoimmune hepatitis and primary biliary cirrhosis but not for primary sclerosing cholangitis. Overall, outcomes of transplantation for autoimmune liver diseases are excellent. However, recurrence of autoimmune liver diseases in the allograft has variable impacts on graft and patient survivals. Treatment of recurrent diseases requires changes in immunosuppression or addition of ursodeoxycholic acid. Among autoimmune liver diseases, only autoimmune hepatitis occurs *de novo* in recipients transplanted for other diseases. Patients transplanted for autoimmune hepatitis or primary sclerosing cholangitis are at risk for reactivation or *de novo* onset of ulcerative colitis. Better understanding of the pathogenesis of recurrent autoimmune liver diseases is needed to devise effective means of prevention and treatment.

Introduction

Orthotopic liver transplantation (OLT) is a lifesaving procedure for patients with irreversible liver damage caused by acute or chronic liver diseases [1]. Among the childhood and adult hepatobiliary diseases that may require OLT, 3 have a putative autoimmune pathogeneses: autoimmune hepatitis

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(AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Among these 3, only AIH may present as acute liver failure (ALF) and require urgent OLT [2,3]. The indications for OLT are similar for patients with chronic AIH, PBC and PSC and for patients with other chronic liver diseases resulting in decompensated cirrhosis, liver failure or hepatic malignancy. Currently, autoimmune liver diseases (AILDs) are the primary indications for approximately 24% of total OLTs (Fig. 1). Overall, graft and patient survivals after OLT for AILDs are excellent (Fig. 2), but recurrent diseases can negatively impact both. Recurrent AIH, PBC or PSC occurs after OLT, despite immunosuppression potent enough to prevent rejection and the lack of HLA-matching of the allograft required for recipient T cell recognition of allograft autoantigens presented by self-HLA molecules [4,5]. Among the AILDs, only AIH occurs *de novo* in patients transplanted for other diseases. Patients with AIH or PSC also have an increased risk of recrudescent or *de novo* ulcerative colitis after OLT.

The purposes of this review are to: (1) discuss the indications and outcomes of OLT for adult patients with AIH, PBC and PSC; (2) review our current knowledge of the frequencies and impacts recurrent AILDS or *de novo* AIH in the allograft; and (3) discuss the risk factors for ulcerative colitis after OLT in patients with AIH and PSC. Emphasis is placed on key issues that require more research in the hope that a better understanding of the pathogenesis of the primary and recurrent AILDs will lead to more successful therapies to prevent the need for OLT and to prevent or control recurrent diseases after OLT.

The liver as an immunological organ

OLT does not require HLA matching for success, which is attributed to nature of the immunosuppressive microenvironment of the liver allograft [6,7]. Thus, matching of HLA loci between donor and recipient occurs only by chance [8]. The liver allograft is a microenvironment in which the host immune system can react against alloantigens, including HLA molecules, “minor” transplantation antigens of the donor and potentially liver-specific autoantigens [6]. Donor antigen-specific activation of naïve and effector T cells of the host within the allograft reduces the repertoire of alloreactive T cells capable of mediating rejection [7]. Passenger leucocytes in the allograft also reduce host alloreactivity by migrating to lymphoid tissues and inducing apoptosis of alloreactive naïve host T cells [7]. AILDs mediated by effector T cells presumably require a break in tolerance to autoantigen(s) presented to CD4 and CD8 T cells as processed peptides in the antigen-binding grooves of self-HLA molecules [5]. Thus, in the absence of HLA matching in OLT, recurrence of AIH, PBC or PSC in HLA-mismatched allografts of recipients transplanted for these diseases seems paradoxical [5]. Definition of the precise mechanisms of pathogenesis in recurrent AILDs is the highest research priority in the field.

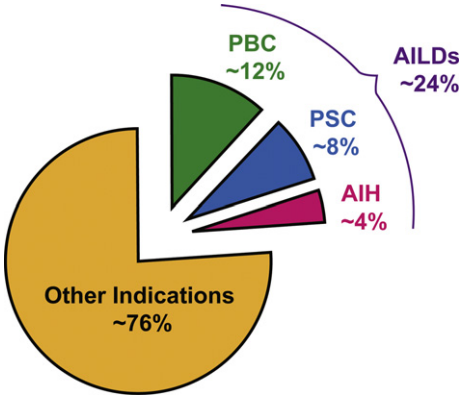

Fig. 1. The Frequency of Orthotopic Liver Transplantation for the Autoimmune Liver Diseases Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis and Autoimmune Hepatitis Abbreviations: AILDs, Autoimmune Liver Diseases; PBC, Primary Biliary Cirrhosis; PSC, Primary Sclerosing Cholangitis; AIH, Autoimmune Hepatitis.