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Recurrence of primary sclerosing cholangitis, primary biliary cholangitis and auto-immune hepatitis after liver transplantation

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A B S T R A C T

Liver transplantation is a well-accepted treatment for decompensated chronic liver disease due to primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC) and auto-immune hepatitis (AIH). Survival after liver transplantation is generally good with 1 and 5-year survival rates around 90% and 70–85%. After transplantation, however, these diseases recur in 8.6–27% (rPSC), 10.9–42.3% (rPBC) and 7–42% (rAIH), and this poses significant challenges in terms of management and graft outcome in these patients. In this review we discuss the incidence, clinical presentation, challenges in diagnosis, reported risk factors and impact on post-transplant outcomes of recurrence of PSC, PBC and AIH after liver transplantation. We also discuss some of the limitations of current investigations and formulate idea's for future research objectives.

Liver transplantation is a well-accepted treatment option for end-stage liver disease due to auto-immune hepatitis (AIH), primary biliary cholangitis (previously named primary biliary cirrhosis; PBC) [1] and primary sclerosing cholangitis (PSC). These diseases are often collectively referred to as autoimmune liver diseases, although autoimmunity per se does not explain these diseases fully. Of the three, AIH is the most classical autoimmune disease, with a striking female predominance (ratio 7:1), hypergammaglobulinemia, strong association with autoantibodies (antinuclear antibodies (ANA) or anti-smooth muscle (SMA) in type I AIH and anti-liver kidney microsomal type 1 antibody (anti-LKM-1) or anti-liver cytosol type 1 antibody (anti-LC-1) in type II AIH), association with other autoimmune diseases and good clinical, serological and histological response to anti-inflammatory drugs such as corticosteroids and azathioprine [2]. PBC shares several autoimmune features including autoreactivity against specific mitochondrial self-antigens (E2 domain of pyruvate dehydrogenase complex, PDC-E2), seropositivity for anti-mitochondrial antibodies (AMA) in >90% of patients, female overrepresentation (ratio 10:1) and significant overlap with other systemic autoimmune disorders. Despite this, PBC has not been shown to respond to any anti-inflammatory drugs. PSC is the least typical autoimmune disease of the three. Although in genome-wide association studies (GWAS) risk loci hosting genes involved in innate and acquired immune responses (mostly, the human leukocyte antigen (HLA) complex) are overrepresented, non-specific perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are sometimes expressed and a strong association with inflammatory bowel disease (present in 80% of patients) exists, PSC is characterized by male predominance (ratio 2:1), absence of disease-specific serology and complete lack of response to immunosuppression.

In Europe and the United states, these immune-mediated liver diseases together constitute approximately 12–24% of all indications for liver transplantation [3,4]. In general, post-transplantation outcomes are favorable with reported 1 and 5-year survival rates around 90% and 70–85%, respectively [4]. However, graft survival and quality of life can be severely affected by recurrence of the primary liver disease in the graft. In this review, we will discuss the incidence, clinical presentation,

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challenges in diagnosis, reported risk factors and impact on post-transplant outcomes of recurrence of PSC, PBC and AIH after liver transplantation.

Recurrence of primary sclerosing cholangitis

Primary Sclerosing Cholangitis (PSC) is a chronic liver disease, characterized by diffuse inflammation of the intra- and extra-hepatic biliary tree. PSC results in progressive fibrosis, liver cirrhosis, cholangiocarcinoma (CCA) and, in the absence of liver transplantation (LT), death [5,6]. PSC affects young adults (mean age 40) and is most prevalent in the northern hemisphere with rates of 6 (North-America) to 16 (Northern Europe) cases per 100.000 [7,8,9]. There is a clear association with Inflammatory Bowel Disease (IBD), as up to 80% of patients affected by PSC has developed or will develop IBD. The natural history is progressive with median transplantation-free survival of 9–12 years after diagnosis [6,10–14]. There is no medical cure and hence in Northern Europe, PSC is a leading LT indication. On average, patients receive their first transplant at an age between 40 and 50 years which occurs after a mean time of 9 years after diagnosis. The established indications for LT are comparable to other chronic liver diseases resulting in end-stage cirrhosis. Allocation algorithms, e.g. MELD score, are used to deal with the discrepancy in donor organ need and availability. For PSC patients with a fulminant disease without the complications of cirrhosis, e.g. recurrent bacterial cholangiosepsis, refractory ascites and/or refractory hepatic encephalopathy, non-standard exceptions points can be considered. Intrahepatic CCA is considered a contraindication for LT in the majority of transplant centers. For perihilar CCA, liver transplantation can be performed in highly selected patients using specific protocols of which the Mayo protocol combining neo-adjuvant chemoradiation with LT is the best described with excellent results [15–17]. As immunosuppressive therapies and post-LT care in general were optimized in the recent decade, outcome post-transplant is good with 87.2%, 78.2% and 70.3% survival at 1, 5 and 10 year, respectively, based on an ELTR data analysis of 4617 PSC patients transplanted between 1980 and 2015 in Europe.

Unfortunately, PSC recurs in 8.6–27% of patients post-LT within a median of 4.7 years [14,18–22] (Table 2). Recurrence carries significant morbidity and mortality and often requires retransplantation, aggravating the already overtaxed waiting list due to scarcity of organs. The etiopathogenesis of recurrent PSC (rPSC), similarly to the primary disease, is poorly understood but mostly is multifactorial combining genetic predisposition with immunologic and environmental factors [23], as shown in Fig. 1. Below we will discuss all relevant cohort studies, which aimed to identify risk factors for rPSC. As all of these studies are retrospective in nature and heterogeneous in study population and sample size, the results of these studies are both overlapping and conflicting [24–26].

Diagnosis of rPSC

The biliary tree constitutes the most vulnerable structure of the liver, as bile ducts are highly dependent on preserved blood flow. Hence, these are the structures most endangered during the course of events of the transplantation surgery. During organ preservation and implantation, oxygenation of the organ is naturally compromised. After reperfusion, ischemia-reperfusion injury can further impair the bile ducts [27], and post transplantation, hepatic artery stenosis or thrombosis and chronic ductopenic rejection can lead to biliary injury. Furthermore, the bile duct anastomosis is a delicate surgical site prone for development of stenosis in up to 16.3% of LT cases [28].

rPSC is characterized by diffuse intrahepatic and/or extrahepatic non-anastomotic biliary strictures, alike PSC before transplantation, but also very comparable to other post-LT biliary complications, such as ischemic-type biliary lesions (ITBL) or secondary lesions occurring in the setting of recurrent cholangitis due to (non)anastomotic strictures. This complicates the diagnosis of rPSC. Therefore, a strict definition to distinguish rPSC from other complications, based on cholangiographic and/or hepatic histologic criteria was designed by Graziadei et al and thus far constitutes the most widely accepted definition [18] (Table 1). Within this definition, the diagnosis of PSC must be confirmed prior to liver transplant. After LT, cholangiographic features or histologic aspects characteristic for PSC must be present. Other causes that can mimic rPSC, such as hepatic artery thrombosis/stenosis, early (non)anastomotic strictures and ductopenic rejection have to be excluded.

Risk factors for rPSC

Over the last two decades, multiple single-center and a few multicenter studies have been exploring risk factors for rPSC in a retrospective manner. There is a large variability in the reported risk factors among various studies, which is explained by differences in patient populations, sample sizes, extent and depth of the collected dataset and statistical methods. For risk factor analysis, multivariable models are essential to reliably evaluate the effect of risk factors, independently from other potentially confounding factors. However, when overall sample size is small while at the same time event rates are small (which is the case in rPSC with max reported prevalence of 27%), power issues and overfitting of models may severely impact the results. Most of these are overcome by larger, preferably multicenter, studies such as those by Hildebrand et al. ($n = 305$) [12] and Ravikumar et al. ($n = 565$) [13]. Table 3 summarizes the reported risk factors, including those related to IBD, rejection, donor-recipient (mis)match (gender, CMV, HLA, related donor), organ quality, recipient factors and severity of PSC pre-transplant.

One of the most studied risk factors is IBD. It is known that both PSC and Ulcerative Colitis (UC) occur more frequently in family members of PSC patients, indicating a shared genetic component [29]. It has become clear that most PSC patients suffer from a distinct entity of intestinal inflammation, often referred to as PSC-IBD. The characteristics are an early onset of a mild (pan)colitis, predominantly right-sided with rectal sparing and sometimes back-wash ileitis [30]. Recently, major advances have been made in the understanding of the genetics of PSC and PSC-IBD. A large genome-wide association study (GWAS) has identified four new PSC risk loci, bringing the total of regions associated with disease risk to 23 [31]. The authors find that although there is correlation between risk loci of PSC and UC, the observed genetic correlation ($r_G = 0.29$) would generate a PSC UC comorbidity rate of only 1.6% and not the 60%, as is clinically observed. They conclude that genetic predisposition is clearly not the only factor explaining the association between both diseases, and other (environmental) factors play a role.

While the PSC is removed by transplantation, at least initially, the diseased colon remains. Several studies investigating post-transplant outcomes found that an active IBD (inflamed colon) after LT is a risk factor for rPSC, whereas colectomy appeared to be protective [12–14,20], indicating that the gut-liver axis continues to play a role post transplantation. One possible explanation lies in the observation that in PSC, long-lived memory T-cells, activated in the gut, aberrantly home to the bile ducts, as described by Trivedi et al. These mucosal lymphocytes express the integrin $\alpha 4\beta 7$ and chemokine CCR9, molecules that address