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Review

Modelling Recurrent Primary Biliary Cholangitis and Primary Sclerosing Cholangitis as Infectious Diseases Following Liver Transplantation

Victor Dong, Aldo J. Montano-Loza, Andrew L. Mason *

Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton, AB, Canada; E-Mails: vdong@ualberta.ca, montanol@ualberta.ca, andrew.mason@ualberta.ca

* **Correspondence:** Andrew L. Mason; E-Mail: andrew.mason@ualberta.ca

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Abstract

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are idiopathic and progressive autoimmune hepatobiliary disorders that lead to liver failure and a need for liver transplantation in a proportion of individuals with poorly controlled disease. It is currently thought that an environmental agent triggers disease in a genetically susceptible host and to date, xenobiotics, bacteria and a human betaretrovirus have all been linked with PBC. However, there is no consensus on which agents predominates. These disease processes are poorly understood and there are disparate hypotheses concerning the pathogenesis. One theory suggests that the disease is mediated by autoimmunity, whereas others have speculated that they are infectious disease processes that only manifest in individuals with diminished immunity. Clinically, the triggers of disease are difficult to study because of the indolent onset and chronic nature of the disorders. Notably, observations from liver transplantation provide a unique insight into the development of PBC and PSC. Both biliary disorders may reoccur in up to 30%-50% of patients following liver transplantation and many of the factors that influence recurrence have been well described. Prior to transplantation, immunosuppression is not routinely used to treat PBC and PSC because specific treatments have not been shown to have utility or have caused undue side effects. Following

transplantation, recurrence occurs earlier and tends to be more aggressive in those treated with more potent immunosuppressive agent such as tacrolimus as compared to cyclosporine, which also has broad antiviral activity. The development of cholestasis within the first year following liver transplantation was found to be predictive of recurrence years later, a finding that parallels observations in patients with recurrent viral hepatitis following liver transplantation. Herein, we discuss the observations from liver transplant recipients with recurrent autoimmune liver disease and model our findings in comparison with patients that develop recurrent infectious disease. These studies help provide a framework and understanding of the processes associated with autoimmune liver diseases in general.

Keywords
Primary biliary cholangitis; recurrent disease following liver transplantation; human betaretrovirus

1. Introduction

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are considered autoimmune conditions and comprise around 5% of all liver disorders [1]. Presentation can consist of fatigue, sicca syndrome, abdominal pain, jaundice, and pruritis and lab work may indicate either a cholestatic or hepatocellular profile. PBC and PSC are also associated with elevations in different immunoglobulins as well as the presence of autoantibodies. Histologically, there is the presence of immune cells and inflammatory damage to the liver parenchyma and biliary system [1]. Despite being considered autoimmune liver diseases, PBC and PSC have not been shown to respond to immunosuppressants. This suggests the possible presence of another underlying etiology for these hepatobiliary disorders.

Studies have linked environmental exposures including bacteria, xenobiotics, and viruses to PBC [2]. PBC has also been linked to a human betaretrovirus (HBRV) suggesting an infectious etiology as a potential cause [2]. Bolstering this idea, there have been studies showing biochemical response in PBC patients treated with antiretroviral therapy [3]. More recently, given the link between inflammatory bowel disease (IBD) and PSC, studies have looked at the gut microbiome and its links to PSC. Preliminary studies are starting to suggest the presence of a distinct intestinal microbiome in PSC patients characterized by an overabundance of potentially pathogenic bacteria [4]. Multiple studies have also demonstrated biochemical response in PSC patients treated with different antibiotics, suggesting that infection may play a role in the development of PSC [5]. All of this goes towards suggesting that an infectious etiology may underlie the pathogenesis of both PBC and PSC.

2. Primary Biliary Cholangitis

PBC is an autoimmune disorder of the liver characterized by the destruction of small intrahepatic bile ducts. Serologically, IgM is often elevated and the presence of anti-mitochondrial antibody (AMA) is seen in 80% to 95% of patients with PBC [6]. Other autoantibodies including

antinuclear antibody (ANA), anti-Sp100, and anti-gp210 are also commonly seen in PBC patients [7]. Classically, liver biopsy appearance in PBC patients demonstrates an inflammatory infiltrate, with granulomatous destruction of intrahepatic bile ducts that consists of lymphocytes, plasma cells, macrophages, and polymorphonuclear cells [6]. The immune mediated destruction of bile ducts with demonstrable humoral and cellular autoimmunity helps to support the notion that PBC has an autoimmune pathogenesis [8].

Strictly speaking, PBC is an autoimmune disease because patients make an immune response to self-proteins. However, the assumption that the disease process is mediated through the autoimmune attack has not been shown experimentally. For example, the autoimmune studies conducted in patients with PBC and corresponding models have not met the criteria for proof of an autoimmune causality. Witebsky criteria are loosely based on Koch's postulates and were created to directly link the autoimmune responses with the disease process [9]. Clinically, we know that humoral autoimmunity is not required to develop PBC because levels of AMA do not reflect the ongoing disease process. Patients without AMA can develop PBC, whereas a proportion of patients with AMA do not [10]. Furthermore, immunosuppression has proven to be of little utility for PBC patients, whereas bile modulation therapy with ursodeoxycholic acid and more recently with the potent FXR receptor agonist obeticholic acid, have become the standard of care [11]. Nevertheless, the common perception remains that PBC patients have autoimmune destruction of bile ducts [8] but this assumption is prevalent (and rarely challenged) even though pertinent validation is lacking.

2.1 Role of Human Betaretrovirus in PBC

It is currently thought that environmental agents trigger PBC in susceptible individuals. Studies have linked environmental exposures including bacteria, xenobiotics, and viruses to the development of PBC [2]. A human betaretrovirus (HBRV) resembling mouse mammary tumor virus was characterized in patients with PBC in 2003, suggesting an infectious etiology as a potential cause [2, 12, 13]. Bolstering this idea, there have been studies showing biochemical response in PBC patients treated with antiretroviral therapy [3, 14, 15]. Using the gold standard methodology for detecting retroviral infection, the majority of PBC patients were shown to have definitive evidence of HBRV infection with the demonstration of proviral integrations in cholangiocytes and peri-hepatic liver nodes [16]. However, a stumbling block in the investigation of HBRV is that good serological assays to detect viral infection are not available for diagnostic purposes or epidemiological studies. In fact, viremia can only be detected in 15-25% of PBC patients by PCR, ELISA assays have a low frequency of positivity (15%) and the virus is difficult to detect in the liver, whereas lymphoid tissue is the dominant reservoir of infection [13, 17]. However, HBRV has met criteria for Koch's postulates *in vitro* as it has been shown to trigger a disease specific phenotype of PBC. HBRV infection of normal cholangiocytes promotes the expression of the usually sequestered mitochondrial antigens on the biliary epithelium cell surface [13, 18]. It is thought that the exposure of the autoantigens to the immune system is responsible for the production of AMA. The immune response to HBRV suggests that viral infection may trigger autoimmunity by bystander activation by attracting an immune response to mitochondrial autoantigens aberrantly expressed on the cell surface [2, 12].

Following the discovery of the HBRV, treatment protocols with antiretroviral therapy were pursued in animal models of PBC with betaretrovirus infection [19, 20] and in patients with PBC [14]. Initial studies assessing lamivudine monotherapy in PBC patients showed limited responses, whereas the use of combination lamivudine and zidovudine therapy provided clinical improvements in liver biochemistry and the necro-inflammatory scores on liver biopsy in PBC patients [21]. The follow up randomized controlled trial did not meet the established endpoints even though patients on therapy developed a 20% reduction in alkaline phosphatase over 6 months of treatment [22]. A follow up randomized controlled trial using an HIV protease inhibitor with reverse transcriptase inhibitors (lopinavir boosted with ritonavir, with combination emtricitabine and tenofovir) was terminated early due to the development of GI side effects in the majority of PBC patients. In the long term extension study, however, those who tolerated the combination antiretroviral therapy developed sustained and clinically meaningful reductions in hepatic biochemistry coupled with reduction in HBRV levels in blood [15]. This study stands as a proof of principal that HBRV may play an active role in the development of PBC, even though the HIV protease inhibitors will have no role in the treatment of PBC. Additional diagnostic assays to detect HBRV infection will be required, however, to diagnose infection and conduct large scale epidemiology studies to evaluate the prevalence of HBRV in populations with liver disease.

3. Primary Sclerosing Cholangitis

PSC is considered an autoimmune biliary disease characterized by inflammation and destruction of the intrahepatic and extrahepatic bile ducts. This can eventually lead to irreversible scarring of the liver [4]. Evidence to support the autoimmune nature of the disorder includes the close association with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC), and the presence of several autoantibodies. Antineutrophil cytoplasmatic antibodies with a perinuclear staining pattern (p-ANCA) is the most prevalent serum autoantibody and can occur in over 90% of patients with PSC [23]. ANA can also be seen in close to 80% of PSC patients and anti-smooth muscle antibodies (anti-SMA) are detected in up to 83% of patients with PSC [23]. In addition, IgA antibodies to glycoprotein 2 (anti-GP2 IgA) were recently found in the serum of PSC patients 46.7% to 71.5% of the time and was associated with large bile-duct involvement and increased mortality [24]. PSC patients may also have increased levels of IgG4 in 10% to 12% of cases [25]. The finding of such autoantibodies in patients with PSC lends support to the notion that PSC has autoimmune features.

Despite the thought that PSC is an autoimmune disorder, because of its close association with UC, researchers have been looking at the interplay between the gut microbiome and PSC more recently. PSC patients have been found to have a significant decrease in diversity of the gut microbiota [26]. The intestinal microbiome in PSC patients have an overabundance of *Escherichia*, *Enterococcus*, *Fusobacterium*, *Lactobacillus*, *Veillonella*, *Blutia*, *Barnesiellacea*, *Lachnospiraceae*, and *Megasphaera* genera [27]. Within the intestinal microbiome of PSC patients, there is reduced concentrations of *Clostridiales II*, *Prevotella* and *Roseburia*, and Bacteroides [28]. *Escherichia*, *Veillonella*, *Lachnospiraceae*, and *Megasphaera* have genes that encode for copper amine oxidase proteins that are substrates for vascular adhesion protein-1, which plays a critical role in lymphocyte trafficking between the intestine and liver [29].

Not only is the altered gut microbiome thought to be a factor in PSC development, but it is also felt that colonic bacterial and endotoxin translocation to the liver is involved in the pathogenesis of PSC [30]. As the bacteria and endotoxins get transferred to the canaliculi, pathogen recognition receptors on cholangiocytes get activated resulting in proinflammatory responses [31]. These findings suggest that the gut microbiota may be an important factor in the pathogenesis of PSC and that an infectious etiology may contribute to the development of PSC.

Due to the suggestion of intestinal microbiome alteration and dysfunction as a possible underlying etiology of PSC, numerous studies have looked at the role of antibiotics in the treatment of PSC. The use of oral vancomycin in PSC has been evaluated in multiple studies as initial studies reveled significant hepatic biochemical and symptomatic improvements in a small case series of children with PSC [32]. Once vancomycin was stopped in this study, patients worsened in terms of their liver biochemistry and their symptoms recurred [32]. Oral vancomycin was also shown in a randomized control trial comparing it to metronidazole to result in a significant decline in serum alkaline phosphatase (ALP) after 12 weeks of therapy [33]. Metronidazole has also been looked at for the treatment of PSC as an add-on therapy to ursodeoxycholic acid (UDCA). In a trial comparing metronidazole and UDCA to UDCA alone, the addition of metronidazole resulted in a more significant reduction in serum ALP compared to use of UDCA alone, suggesting beneficial effect of the antibiotic [34]. These studies go towards suggesting an infectious contribution to the pathogenesis of PSC.

4. Liver Transplantation and Autoimmune Liver Disease

A commonality with all autoimmune liver diseases, including PBC, autoimmune hepatitis (AIH) and PSC, is that all three disorders reoccur following LT [35, 36]. This observation supports the hypothesis that these autoimmune diseases may have a persistent infectious component at the time of transplantation. In support of this notion, the use of more potent immunosuppression regimens appears to hasten the onset of recurrent disease in the setting of LT. For example, liver transplant recipients with PBC have an increased probability of developing earlier and more severe recurrent disease with the use of the more potent calcineurin inhibitor, tacrolimus as compared to cyclosporin [37, 38]. Similar observations have been made in patients with PSC following transplantation, where the use of tacrolimus is associated with an increased prevalence of *de novo* IBD [39, 40]. Furthermore the use of tacrolimus, as compared to cyclosporine, has been linked with the development of *de novo* AIH; a hepatitis syndrome with autoimmune features occurring in LT recipients without a prior diagnosis of AIH [41]. One could argue that the development of recurrent disease occurring with more potent immuno-suppression favors the reappearance of an infection rather than the development of recurrent autoimmune process, which should theoretically be dampened to a greater extent with higher levels of immunosuppression.

A review of our experience with managing LT recipients with viral hepatitis sheds some light on understanding the process of recurrent autoimmune liver disease post LT. Over the last 3 decades, we have learned to be more sparing with immunosuppression because of the development of fibrosing cholestatic hepatitis, mediated by uncontrolled viral replication on the background of uninterrupted, high potency immunosuppression [42, 43]. Indeed, recurrent viral infection was universal in LT recipients without access to directly acting antiviral regimens available today, and as a result disease progression with viral hepatitis was often accelerated by prolonged

immunosuppression [42, 43]. The extent of HCV viral load prior to LT was shown to a reliable predictor of severity of recurrent infection, whereas patients with lower viral loads developed mild recurrent disease without biochemical hepatitis [44]. There was also considerable debate on how best to recognize and manage acute recurrent HCV Infection with the accompanying presence of alloreactivity [42]. Over the years, mild rejection occurring with recurrent HCV infection was either ignored or treated with a small adjustment of tacrolimus levels to prevent immune reconstitution and activation of biochemical hepatitis [45].

Factors that predict recurrent autoimmune liver disease have also been documented to a degree. With regards to severity of disease prior to LT, patients with AIH have been found to be more likely to develop recurrent disease if they had raised IgG levels, elevated AST/ALT and histological evidence of moderate to severe inflammatory activity [46]. Similar pre-LT data have not been gathered for PBC and PSC. However, comparable to observations with LT recipients with viral hepatitis, the development of recurrent PBC and PSC following LT is augmented by more robust immunosuppression, supporting the idea that both disorders may be linked with infectious disease [36, 47]. Accordingly, we recently conducted studies to address the hypothesis that PBC and PSC patients may develop evidence of recurrent disease soon after LT by assessing hepatic biochemistry in the first 12 months of LT [48, 49], and herein we provide a brief synopsis of our findings.

4.1 Recurrent PBC Following LT

Recurrent PBC (rPBC) is diagnosed by liver histology compatible with PBC along with biochemical cholestasis. AMA do not factor into making a diagnosis as 70% of PBC patients remain AMA positive following LT, whereas less than half of these patients actually develop rPBC. We reported our experiences nearly 10 years ago from the University of Alberta program showing that 13% of patients developed rPBC at 5 years and 29% at 10 years [37]. Similar to experiences from many other centers, we found that the use of tacrolimus and mycophenolate mofetil was associated with a higher risk of rPBC recurrence, whereas cyclosporine reduced the risk of PBC recurrence [37]. Because of our interest in the retroviral hypothesis for the development of PBC, we evaluated whether cyclosporine had antiviral activity against HBRV and observed reduced betaretrovirus production from infected cells treated with cyclosporine but not tacrolimus *in vitro* [50]. These data were consistent with prior studies showing that cyclosporine inhibited cyclophilin activity required for assembly of many viral agents [50, 51]. This observation may partially explain the effects of reduced frequency of rPBC post-LT with cyclosporine therapy. However, it should be emphasized that as a less potent immunosuppressive agent, cyclosporine may lower the incidence of any infectious disease versus tacrolimus when employed following transplantation. However, this is all conjecture because studies have not been performed to evaluate the presence of HBRV in peripheral blood of patients with recurrent PBC.

To better understand mechanisms involved in rPBC, we conducted a larger retrospective, multi-center study involving 785 patients undergoing a liver transplant for PBC [38]. We observed a steady increase in probability of rPBC over time from 22% at 5 years to 55% at 20 years. Once again, we confirmed that the use of tacrolimus was associated with increased frequency rPBC, whereas cyclosporine was protective. This study was sufficiently powered to demonstrate that rPBC led to diminished survival, whereas prior studies had reported increased graft loss only, likely

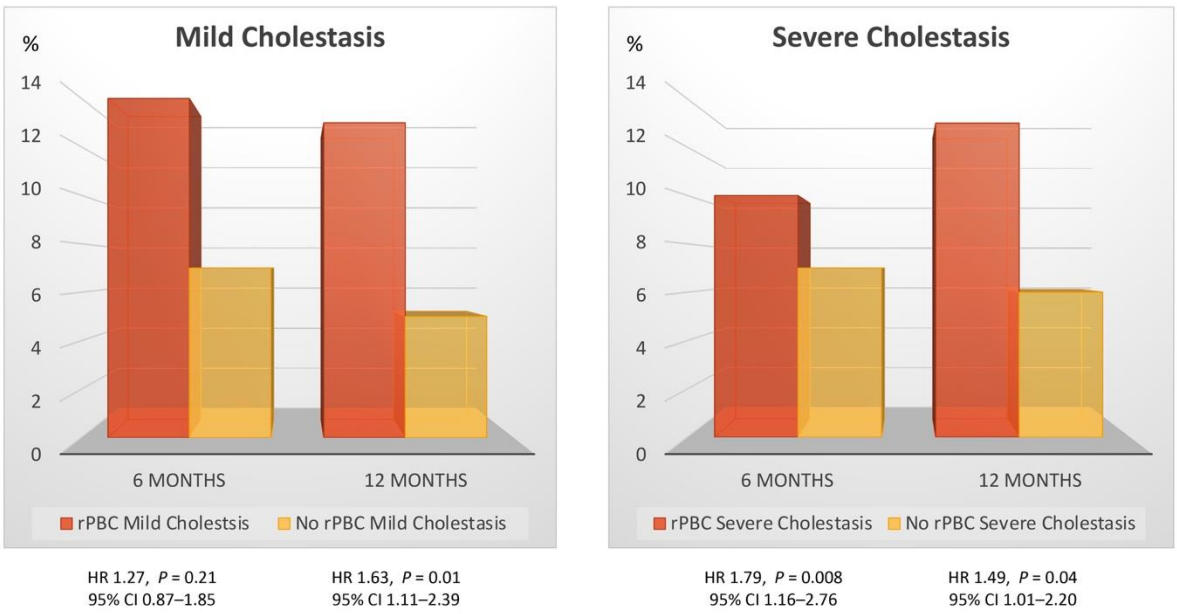
due to smaller sample size and length of follow up [36]. These data bring up the question of whether cyclosporin should be used as primary immunosuppression for patients with PBC. However, ease of use of tacrolimus and availability of other treatment modalities for PBC have superseded. In fact we have adopted the policy of using prophylactic UDCA directly following LT to prophylaxis against rPBC [52] and other second line experimental therapies to treat rPBC [14].

The second novel finding in this study of rPBC was that patients younger than 60 years old at the time of LT were more likely to develop recurrent disease [38]. These data are consistent with observations from prognostic studies of PBC patients prior to transplantation, where patients with younger onset of disease were also shown to be at increased risk for a more rapid progression to LT [53]. It is not immediately clear why those who develop PBC at a younger age develop accelerated disease. Based on our current understanding of the etiology of PBC, if an earlier onset of disease worsens prognosis, then younger patients must have a combination of (i) increased genetic susceptibility and/or (ii) a greater environmental exposure. If we were to model this on an infectious disease hypothesis, one could argue that patients with early onset PBC are genetically less able to contain an infection, which then causes a more penetrant disease. It is anticipated that construction of genetic risk scores from the genome wide association study data and creation of biomarkers that better evaluate the infectious disease process may address this question in the future [12, 54].

Another major goal of our retrospective study was to address a simple question of whether development of cholestasis within the first year following LT heralded the onset of rPBC. This hypothesis is based on observations of LT patients with untreated viral hepatitis who may develop biochemical hepatitis on infection of the allograft [42, 43]. It is our experience that a liver biopsy diagnosis of rPBC is seldom made within the first year because patients usually have non-specific findings accompanied by a degree of alloreactivity in this period. To assess for biochemical changes, we evaluated patients for severe cholestasis (bilirubin ≥100 μmol or alkaline phosphatase > 3x the upper limit of normal) or mild cholestasis (alkaline phosphatase level >2 times the ULN or a combined elevation of both bilirubin and alkaline phosphatase levels) in the first year following LT. At 6-month post-LT, we observed that patients who subsequently developed rPBC were more likely to manifest severe cholestasis with increased mean ALP levels compared to patients with recurrent disease. By 12 months, both mild and severe cholestasis were associated with increased risk of recurrent PBC and these patients were more likely to have increased mean levels of ALT, ALP and Bili (Figure 1).

These data support the infectious disease hypothesis for PBC whereby infectious agents that cause cholestatic liver changes within the first 6 months following LT go on to trigger recurrent disease. Because more potent immunosuppression is used in the first year following LT, this would argue against the development of recurrent disease being linked with autoimmunity that would presumably be dampened down by more potent immunosuppressive regimens. Further studies to detect viral footprints of disease or better diagnostic tools to confirm the presence of HBRV infection should be performed to address this question further.

A



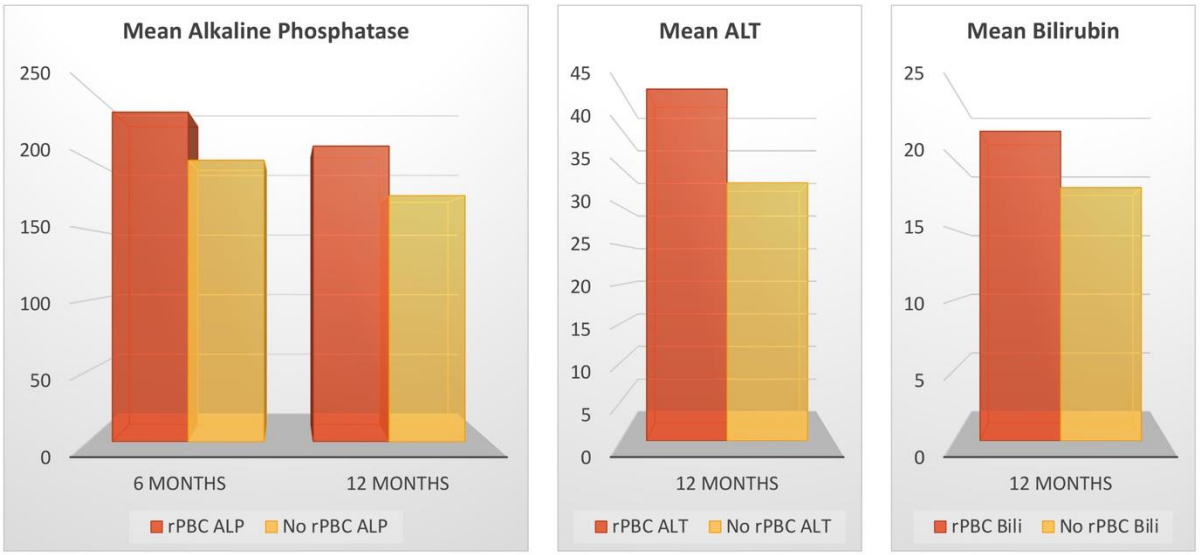
HR 1.27, $P = 0.21$
95% CI 0.87–1.85

HR 1.63, $P = 0.01$
95% CI 1.11–2.39

HR 1.79, $P = 0.008$
95% CI 1.16–2.76

HR 1.49, $P = 0.04$
95% CI 1.01–2.20

B



HR 1.12, $P < 0.001$
95% CI 1.05–1.19

HR 1.001, $P = 0.001$
95% CI 1.00–1.001

HR 1.002, $P = 0.01$
95% CI 1.001–1.004

HR 1.002, $P = 0.1$
95% CI 1.00–1.004

Figure 1 (A) Patients with rPBC had a higher prevalence of severe cholestasis at both 6 months and 12 months following LT, and mild cholestasis at 12 months following LT. [Severe cholangitis: Bili ≥100 µmol or ALP > 3x the upper limit of normal; Mild cholestasis: ALP>2 times the ULN or a combined elevation of both Bili and ALP levels]. (B) Patients with rPBC have elevated mean ALP levels at 6 months and then increased mean levels of ALT, ALP and Bili by 12 months.

4.2 Recurrent PSC Following LT

For PSC patients undergoing LT, recurrence is diagnosed in up to 35% of patients by cholangiography, as long as there are no other risk factors for biliary structuring. Multiple studies

have proposed risk factors associated with recurrent PSC post-LT. The presence of active UC post-liver transplant has been found to be significantly associated with PSC recurrence [55] and the presence of IBD in general was shown to be an independent risk factor for PSC recurrence post-LT [56]. In addition, the need for repeat LT due to recurrent PSC is probably a further risk factor for subsequent development recurrent PSC but it is a rare event [55-57]. More recently, tacrolimus and basiliximab induction have been shown to markedly increase the risk of rPSC, along with disease activity at the time of LT [47]. These data suggest the potential for an infectious agent as a risk factor for the development of PSC. Along these lines, receiving a colectomy prior to or during liver transplant has been shown to be protective against recurrence of PSC [57]. Other studies have reported that total colectomy with end ileostomy conferred a protective effect against recurrence of PSC post-liver transplant whereas colectomy with an ileoanal pouch formation did not [58]. Overall these studies that once the risk of colonic bacterial translocation is removed, recurrence of PSC is rare, which supports the notion of an underlying infectious etiology as the cause.

In patients who do develop PSC again post-liver transplant, there have been case reports suggesting that oral vancomycin may be effective in terms of treatment. In one report, oral vancomycin lead to complete normalization of liver biochemistry in an adult patient with PSC recurrence four years post-liver transplant [59]. A separate case demonstrated successful treatment of a pediatric patient who developed recurrent PSC post-liver transplant with oral vancomycin [60]. Although just case reports, they do add to the growing literature around use of antibiotics for the treatment of PSC, which again suggests a possible underlying infectious etiology in the pathogenesis of PSC.

In a prior analysis of our LT program, we had found that the presence of mild cholestasis at 3 months was predictive of recurrent disease for patients with PSC. For example, we observed that those without cholestatic liver function tests experienced a median time to recurrence of 12.9 yrs, whereas patients with mild cholestasis at 3 months developed recurrent disease with a median of 9.6 years. Based on these findings, we conducted an international multi-center that revealed that cholestasis at 12 months is highly predictive of recurrent PSC [61].

5. Prospectus

PBC and PSC are traditionally considered autoimmune disorders of the liver based on the presence of loss of tolerance to self and the presence of immune dysregulation. However, there are emerging data to suggest an infectious etiology playing a role in disease pathogenesis. The presence of HBRV in PBC and response in PBC patients to antiviral therapy and intestinal microbiome dysbiosis in PSC along with response to treatment with antibiotics provide support to the infectious nature of these conditions. Studying recurrent disease in patients following liver transplantation provides an opportunity to study acute onset disease. Such studies are needed to better understand the etiology and pathogenesis of PBC and PSC.

Author Contributions

These authors contributed equally to this work.

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Competing Interests

The authors have declared that no competing interests exist.

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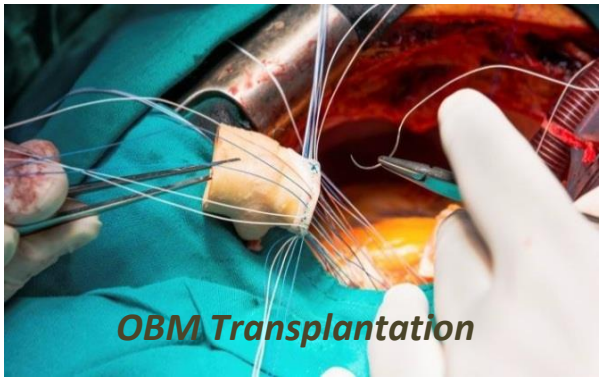

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