Recurrence of Nonviral Liver Diseases After Liver Transplantation

Ivo W. Graziadei, MD[a,b,*]

KEYWORDS

• Immunosuppression • Graft survival • Liver cirrhosis • Posttransplant management

KEY POINTS

- There is compelling evidence that nonviral diseases recur after liver transplantation (LT), with incidence rates ranging from 10% to 50%.
- In most patients, recurrent diseases do not negatively impact patient and graft survival.
- Recurrent alcoholism also jeopardizes the long-term outcome of LT recipients.

INTRODUCTION

Liver transplantation (LT) has become a well-accepted treatment modality for patients with acute or chronic liver failure, as well as hepatocellular carcinoma. LT does not only improve survival but also the quality of life. Mainly due to advances in surgical techniques and development of new, more potent immunosuppressive as well as anti-infective drugs, the outcome of LT recipients has dramatically improved over the past decades, leading to an increased number of long-term survivors after LT.[1,2]

Many diseases causing acute or chronic liver failure, however, may recur after LT and may negatively affect patient and graft survival. The incidence rates and the impact on patient and graft survival mainly depend on the indication for LT. In particular, recurrent hepatitis C infection is almost universal, leading to rapid fibrosis and graft loss in a significant number of patients within 5 to 10 years after LT.[3,4] With the increasing number of long-term survivors of LT recipients transplanted for nonviral diseases, in particular autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), alcoholic liver disease (ALD), and nonalcoholic

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[a] Department of Internal Medicine II (Gastroenterology and Hepatology), Medical University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria; [b] Department of Internal Medicine, District Hospital Hall, Milserstraße 10, A-6060 Hall, Austria
* Department of Internal Medicine, District Hospital Hall, Milserstraße 10, A-6060 Hall, Austria.
E-mail address: ivo.graziadei@i-med.ac.at

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steato-hepatitis (NASH), it became evident that disease recurrence is a clinically important and prognostically relevant issue in the long-term management of these patients.

The aim of this review is to examine the current knowledge of recurrent nonviral liver diseases after LT with special emphasis on diagnosis, risk factors, therapy, and impact on patient and graft survival.

AIH, PBC, AND PSC

In contrast to patients with AIH, there is almost no effective medical treatment available for patients with PBC and PSC to cure or at least positively influence the natural history of these diseases. Consequently, LT is the only potentially curative therapeutic option for patients with liver cirrhosis secondary to PBC and PSC. End-stage liver disease due to AIH, PBC, and PSC accounts for 3% to 8% of the indications for LT according to the United Network of Organ Sharing (UNOS) and the European Liver Transplant Registry (ELTR). The long-term outcome of these patients is excellent, with actuarial 5-year and 10-year survival rates higher than 70%, 5 and 10 years after LT.[5–11] In contrast to the recurrence of viral hepatitis, which is well accepted, the recurrence of AIH, PBC, and, in particular, PSC has been a constant subject of debate with respect to diagnostic criteria and impact on long-term outcome.

AIH

Recurrence of AIH in the allograft was first described by the King's College group in 1984[12] and, subsequently, confirmed by several other reports. However, there are no standard criteria to diagnose AIH recurrence. Most investigators based their diagnosis on increased serum transaminases, positive autoantibody titers greater than 1:40, in particular antinuclear antibodies (ANAs), hyper-gamma-globulinemia, and characteristic histologic features of (peri)portal and lobular hepatitis with lymphoplasmacellular infiltration in the absence of acute cellular rejection or viral infection.[13,14] The exact differentiation between acute rejection and recurrent AIH, however, is particularly challenging. Also, markers that are helpful in the pre-LT diagnosis of AIH, such as elevated liver transaminases associated with hyper-gamma-globulinemia and the presence of autoantibodies may persist after LT without any specific diagnostic relevance for recurrent AIH.

Recurrence rates between 16% and 43% have been reported for patients transplanted for AIH-related cirrhosis. In a recent review article, including 25 publications, 23% of patients developed a recurrent disease after a median interval of 26.4 months (range: 14–55 months) after LT.[15] Pathologic findings seemed to be the most appropriate diagnostic markers. Interestingly, in one article, histologic abnormalities characteristic for recurrent AIH were found on protocol liver biopsies in the absence of elevated biochemical liver tests, demonstrating the importance for late-protocol biopsies in these patients.[16]

Results regarding possible risk factors for AIH recurrence are controversially discussed in the literature. Some investigators have shown an increased frequency of recurrent disease in HLA-DR3–positive recipients, whereas others have failed to observe this association.[7,8,17,18] HLA antigen mismatch and numbers of acute cellular rejections did not differ between patients with or without recurrent disease. In addition, no difference in AIH recurrence was found with the use of cyclosporine A or tacrolimus for immunosuppression, as well as pretransplant or posttransplant overall dose and duration of corticosteroid treatment.[15]