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INVITED COMMENTARY

HCV treatment in liver transplantation: timing is the challenge

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Hepatitis C infection is one of the most common causes of chronic end-stage liver disease, with its sequelae decompensated liver cirrhosis and hepatocellular carcinoma. Both are currently the most important indications for liver transplantation [1]. Unfortunately, almost all patients with detectable HCV RNA at the time of transplantation will have recurrent hepatitis C in their graft [2]. Although spontaneous clearance can occur during primary infection [3], under immunosuppressive therapy this is rather rare [4]. Moreover, recurrent hepatitis C after liver transplantation follows a more rapid course, with the development of liver cirrhosis in approximately 20-40% of the patients within 5 years [5] and causing significant graft loss and even death.

Until recently, the only possible treatment was (peg) interferon-based antiviral therapy. It has been clearly shown that obtaining sustained virological response even in the cirrhotic stage is associated with improved survival by a decrease in both all-cause and liver-related mortality [6]. In the setting of liver transplantation, the efficacy is significantly less due to poor tolerance and the occurrence of (severe) complications [7]. However, with the introduction of all oral interferon-free direct antiviral therapy this is past history and hepatitis C in the setting of liver transplantation can now be treated as in all other patients, obtaining similar results.

In most countries where liver transplantation is being performed, hepatitis C after liver transplantation is being regarded an indication for antiviral therapy with high priority. Both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases/Infectious Diseases Society of America advocate the use of direct antiviral agents (DAAs) after liver transplantation and have designed specific guidelines for the post-liver transplant setting [7–9].

With the approval of NS3/4a protease inhibitors (simeprevir, paritaprevir), NS5a polymerase inhibitors (daclatasvir, ombitasvir, ledipasvir), NS5b polymerase inhibitors (sofosbuvir, dasabuvir) and more to come, all patients after liver transplantation can now be treated, with almost similar high cure rates as in the non-liver transplant setting [10–13]. All DAA combinations are well tolerated, without any severe complication. In the setting of liver transplantation, important drug–drug interactions are to be expected, in particular because the

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calcineurin inhibitors tacrolimus and cyclosporin are the cornerstone of immunosuppressive regimens. However, with careful monitoring of blood levels and anticipating dose adjustments, significant clinical problems can be prevented. All potential drug–drug interactions are described on the "Liverpool" website including recommendations [14].

Although the outcome of hepatitis C treatment has improved considerably, some challenges still remain; the most important are the treatment of patients with liver cirrhosis and decompensated liver cirrhosis, with genotype 3 infection and with coexistent renal insufficiency. The timing of antiviral therapy is for patients in the liver transplant setting of particular importance: Can it still be done before or should it always be after transplantation, and what would then be the optimal timing? When treatment is still feasible before liver transplantation, preliminary data show that one of five patients can be delisted [15]; long-term outcome of these patients is not yet known. Continuing cohort studies suggest that antiviral therapy might be futile in those with portal hypertension (as reflected by thrombocytopenia), high MELD scores (>14) and/or low albumin levels [16,17]. In addition, rapid and extensive recurrent hepatocellular carcinoma might be a specific newly recognized risk for those previously treated for hepatocellular carcinoma [18].

In the postoperative phase, it is the question whether the patient should be treated as soon as possible or in a steady clinical situation, that is after fading of the early-postoperative risks (surgical complications, infections, rejection, etc.). However, in particular those patients with high viral load, genotype 1 infection, females, older donor age, being treated for cytomegalovirus or for acute rejection, have a high risk for rapidly progressive recurrent hepatitis C [19]. But how can we distinguish high risk in the individual patient?

It might well be that the combination of only two genetic markers identifies those patients at high risk of early reduced liver graft survival, and thus could become an important tool for decision making whether to treat early or later after liver transplantation. In this issue of *Transplant International, Romagnoli R et al. [20]* describe the role of the expression of HLA variants and the interleukin-28B (IL28B) C/C genotype (rs12979860) in the prediction of the outcome of liver transplantation in HCV recipients. Among 449 patients with a median follow-up of 10 years, graft survival in HLA-DRB1*11-positive recipients was significantly longer than in HLA-DRB1*11-negative recipients; the difference amounted 17% after 10 years. Graft survival was also influenced by the IL28B genotype of both recipient and donor, being better in C/C recipients and with non-C/C donors; the outcome was significantly worse in non-C/C recipients transplanted with a C/C donor. Compared with the HCV recipients exhibiting all other genetic combinations, patients lacking both these markers experienced a significant survival disadvantage as early as the first post-transplant year, the 1-year risk of graft loss being increased by 68% (hazard ratio 1.68). This suggests that both HLA-DRB1*11 and IL28B genotype should be known before transplantation: Patients lacking both markers should undergo antiviral therapy as soon as possible after transplantation (within 3 months?), whereas others probably can wait until their clinical course has completely stabilized.

Antiviral therapy of hepatitis C has come to a stage where almost all patients can be cured. Results in patients after liver transplantation, in the interferon era regarded as difficult to treat, are more or less similar. Some patients are, however, at increased risk of the development of severe rapidly progressive recurrent hepatitis C shortly after transplantation. The important work of Romagnoli *et al.* indicates that the combined genotyping of HLA-DRB1*11 and IL28B is necessary to make a proper decision to treat early (as soon as possible) or later (after complete stabilization). Although confirming results should be awaited, liver transplant centers should already seriously consider to genotype all HCV patients pretransplant.

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