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INVITED COMMENTARY

Living donor liver transplantation in HCV-infected patients: improvement of the donor risk–recipient benefit ratio is around the corner

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Living donor liver transplantation (LDLT) has been a welcome alternative to deceased donor liver transplantation (DDLT), increasing the availability of donor livers overall and improving survival in individual patients [1, 2]. In experienced centers, operative outcomes of LDLT are almost comparable with DLDT [3, 4]. However, LDLT comes with substantial donor morbidity and, although rarely, acute hepatic insufficiency in the donor requiring transplantation and even donor death has been described [5]. From an ethical perspective, we must continually strive to improve the donor risk–recipient benefit ratio of LDLT. Currently, the most common indication for adult liver transplantation is complications from chronic hepatitis C virus (HCV) infection. HCV recurrence postliver transplant is almost universal and associated with poor graft and patient survival. The development of severe fibrosis or cirrhosis is accelerated after transplantation and the current antiviral treatment is not successful. This poses a major issue for the transplant community whether LDLT should be performed in HCV infection.

Indeed, in this issue of Transplantation International, Akamatsu *et al.* [6] show that the leading cause of post-transplant death in a group of HCV-infected LDLT recipients was recurrent hepatitis C. The authors retrospectively evaluated 514 HCV-positive patients who underwent LDLT between 1998 and 2012 in one of 12 surveyed institutions in Japan. Median follow-up time was 3.5 years (range 0.4–13). During the follow-up time, 142 (28%) patients died of which 42 deaths (30%) were attributed to recurrent HCV. Another 22 (15%) deaths were due to recurrent hepatocellular carcinoma. This study highlights that preventing HCV recurrence-related deaths is the most important step in improving donor risk–recipient benefit ratio in LDLT.

Moreover, the authors found that donor age (>40 years), nonright liver graft, acute rejection episode, and the absence of a sustained virologic response (SVR) were independently associated with post-transplant mortality. Of all these four factors, the absence of SVR had the highest hazard ratio (5.52; range 3.32–8.06).

Sustained virologic response is a surrogate marker to determine the effectiveness of antiviral treatment. Whether SVR also improves (long term) outcome in liver transplant recipients remains debatable. The non-SVR group is presumably biased by having included patients that were too sick to undergo treatment: patients with advanced liver disease at the start of treatment who are more likely to be intolerant to treatment with interferon (IFN) and/or ribavirin and patients who may have died of non-HCV-related complications before treatment could have been initiated or finished. The impact of SVR on survival may therefore be overestimated. Nonetheless, as HCV recurrence is a major cause of graft loss and death, prevention of graft reinfection seems the most feasible approach to improve outcome. The most effective way of decreasing HCV recurrence-related death and graft loss post-transplant is successful pretransplant antiviral treatment. Unfortunately, HCV is worldwide still under diagnosed and subsequently undertreated. Of the 514 patients, Akamatsu and colleagues describe only 45% received antiviral treatment pretransplant. This highlights again the need of timely diagnosis of HCV infection and early intervention to prevent severe liver disease. Specifically, post-transplant HCV IFN-based treatment comes with considerable side effects, requiring dose reductions (40% in this study) and preemptive discontinuation (42% in this study) of antiviral medication. Improving tolerability of antiviral treatment will improve adherence and therefore SVR rates in liver transplant recipients. In this light, the current developments in the HCV field are very promising. Most recently, at the 49th meeting of the European Association for the Study of the Liver (EASL), results of trials in liver transplant patients showed (preliminary) SVR12 results of up to 96% [7, 8], comparable with nontransplant recipients. Even in patients with severe recurrent HCV post-treatment, treatment with DAAs in a compassionate use program led to SVR12 in 62%, although some patients in this study also received IFN at physician's discretion [9]. Treatment with DAAs in LT patients was, like in nontransplant patients, highly tolerable with few (severe) DAA-related side effects. There are still issues regarding availability (due to cost and registration delay), drug–drug interactions (with calcineurin inhibitors) and determining the best retreatment regimen for patients who relapse on DAA treatment. Larger studies need to confirm the long-term benefit of DAA treatment in liver transplant patients. In the end, when, due to IFN-free DAA treatment, SVR rates in transplant recipients rise and treatment burden decreases, it will be inevitable that SVR indeed proves to be a surrogate marker associated with improved outcome after liver transplantation. This will further improve the donor risk–recipient benefit ratio of LDLT in HCV recipients and support the current clinical practice to use living donor liver (preferably nonright) grafts if cadaveric donor livers are not available in time. But more importantly, HCV-infected patients need to be identified before they require liver transplantation. When low side effect – high SVR DAAs, become available to the world population, in the coming decades, we can expect a major decrease in liver transplantation for chronic HCV. Ultimately, liver transplantation for chronic HCV will be a rarity. This will reduce the risk of the living donor too.

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