INVITED COMMENTARY

Filling the gap between clinical trials and real life in the treatment of severe HCV recurrence after liver transplantation

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In this issue of *Transplant International*, Herzer *et al.* [1] report the results obtained in a real-world European cohort of 87 patients with severe recurrent hepatitis C (HCV) after liver transplantation (LT), who were treated with a compassionate use of daclatasvir (DCV) plus registered sofosbuvir (SOF), with or without ribavirin (RBV). The vast majority of patients were HCV genotype 1, although the sample included a few with genotypes 3 and 4. It is noteworthy that 37/87 patients (42.5%) had cirrhosis (and 16/37 patients [43%] had Child-Pugh B/C decompensated cirrhosis). Forty of the 87 patients (46%) had moderate or severe renal impairment (CrCl <60 ml/min/1.73 m^2). Low platelet counts (<100 × 10^9/l) and low albumin levels (<35 g/l) were identified in 27 (31%) and 13 (15%) patients, respectively. Five of the 37 cirrhotic patients (13.5%) had fibrosing cholestatic hepatitis (FCH). Excluding the five nonvirological failures (four patients with decompensated cirrhosis who died—one during and three after the treatment—of causes related to their advanced liver disease, and one patient lost to follow-up after discontinuing the treatment due to acute kidney injury with lactic acidosis), the rate of sustained virological response 12 weeks after the end of the therapy (SVR12) was 100% (80/80). During the treatment, 16/87 patients (18.4%) experienced severe adverse events (AEs) and a very small proportion of them (4/87, 4.6%) discontinued the therapy. No significant drug–drug interactions (DDIs) or episodes of acute rejection were reported.

We all agree that the "new era" of antiviral therapy associated with the recent approval of highly effective and well-tolerated regimens of direct-acting antiviral agents (DAAs) has revolutionized the approach to the burden of HCV after LT [2], and several prospective trials have already been published on this topic [3–7]. These trials were relatively small, however, and—given concerns about the impact of immunosuppression on response rates—patients were treated with RBV-containing regimens, most of them for as long as 24 weeks. Establishing the safety of DAAs in patients with advanced liver disease and/or renal insufficiency, and the related DDIs with immunosuppressants is still a challenge, although it is clearly much less so than it was in the "stone age" of interferon (IFN)-based antiviral therapy.

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Needless to say, these issues are particularly relevant in LT recipients, and it seems important to analyze large, real-world cohorts to confirm the response rates seen in clinical trials, and to address any unanswered questions. The data available on DAAs in patients with advanced liver disease after LT also remain somewhat limited [8–15], so the experience reported in this paper might partially fill this gap.

The authors conclude that the DAC/SOF antiviral regimen is effective even in a population of patients with several negative predictors of response, as mentioned above. High SVR12 rates were observed across the subgroups, regardless of the severity of patients' liver disease, the extent of their renal impairment, their HCV genotype, baseline HCV-RNA levels or prior HCV therapy. Among 29 patients with paired data for the baseline and post-treatment week 12, there were 15 (52%) who showed improvements in terms of their MELD scores (5/19 classed as Child A, 8/8 as Child B, and 2/2 as Child C), further confirming the previous report from Forns *et al.* [16] on the first compassionate use of SOF after LT, and corroborated by Manns *et al.* [5] in the SOLAR-2 post-LT cohort treated with SOF plus ledipasvir. In addition, in 85% of the patients (on small numbers 6/7) a shift from Child B/C to Child A from the baseline to post-treatment week 24 was reported.

On the other hand, although this confirmation provided by Herzer *et al.* [1] of the efficacy of DAAs in cases of severe recurrent HCV after LT is important, these encouraging results should be interpreted with caution. The SVR12 rate has been unsatisfactory in other cohorts of patients with decompensated liver cirrhosis due to HCV recurrence [3]. Apart from the virological and/or biochemical response, an overall assessment of the patient is always necessary, and the retransplantation option should always be considered first for patients who develop decompensated graft cirrhosis due to HCV recurrence [17].

Severe AEs occurred during the treatment in approximately one in five of the patients in the cohort described. Not surprisingly, most of them were related to complications of advanced liver disease (hepatic encephalopathy, bacterial peritonitis, deterioration in general physical health), infections (abdominal abscess, cholangitis, pneumonia) or renal disease (acute kidney injury, fluid overload with cardiac failure, lactic acidosis). Only three were reported as being "treatment-related": Two were cases of renal impairment, and one was a case of acute pancreatitis associated with *Clostridium difficile* colitis, acute kidney injury, and pancytopenia. It seems interesting that severe AEs were slightly more frequent among patients with cirrhosis (19% vs. 14% in the noncirrhotic group).

Since the widespread adoption of DAAs, their ease of use (especially when compared with "old" IFN-based regimens) has meant that clinicians involved in HCV antiviral therapy are becoming less and less familiar with the management of AEs. Transplant hepatologists should nonetheless remember that when a cirrhotic status develops, superimposed conditions such as infections and/or renal impairment [18] capable of causing a sudden clinical deterioration can occur regardless of a patient's HCV status [19].

Currently used all-oral, IFN-free regimens achieve SVR rates in excess of 90%, and 12-week periods of treatment for the majority of patients [2]. Whether or not to add RBV should be considered patient by patient, depending on the risk–benefit ratio in terms of a slight improvement in efficacy and/or short-lived treatment versus a worse safety profile and/or quality of life. Nowadays, adding RBV amounts to over-treating most patients because it is hard to tell from various baseline factors which patients really need it [20]. In HCV-positive LT recipients, the benefit of administering RBV has not been clearly demonstrated by randomized trials [3,5,7,21]. The role of RBV in the management of HCV remains an open issue. In this study, the benefit of RBV cannot be examined properly because of the nonrandomized setting and the relatively limited number of patients given RBV (25/87, 29%). What is more, the authors did not report any virological failures among patients treated with the DAC/SOF combination alone. Side effects (and hemolytic anemia in particular) are more common in LT patients and may also be associated with dose reductions or discontinuation of the drug(s). Antiviral treatment schedules without RBV (and with a demonstrated efficacy for recurrent HCV) are consequently needed. Together with the data coming from the ANRS ("*Agence Nationale de Recherches sur le Sida et les hepatites virales*") [22], the results of this study may suggest that RBV be considered as an optional addition in the case of 24-week courses of treatment. The very small numbers discussed here cannot justify this approach as yet, however.

After hepatic metabolism, RBV is excreted by the kidney, so renal function needs to be monitored with particular care when RBV is administered. In this study, only 4/87 (5%) patients showed grade 3 or 4 increases in creatinine levels, while the overall median creatinine clearance (CrCl) level remained stable during the treatment. Renal impairment is a frequent complication in

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cirrhosis [23] and the risk is commonly exacerbated by LT, with its prevalence increasing from 10–20% before to 40–50% after LT [24,25]. The lack of clinically relevant interference with renal function is therefore quite important from the clinical perspective.

Sofosbuvir is the backbone of the combination therapy for several approved all-oral HCV regimens. It is largely metabolized to the pharmacologically active metabolite GS-461203, and ultimately dephosphorylated to the inactive metabolite GS-331007. Renal clearance is the main route for the elimination of SOF, via GS-331007, and—compared with patients whose renal function was normal—the SOF AUC was found 170% higher, and the GS-331007 AUC 450% higher in patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 [26]. The administration of SOF (or any regimens containing SOF) is consequently not recommended for patients on hemodialysis or with an eGFR <30 ml/min/1.73 m^2. Unfortunately, patients with a CrCl <30 ml/min were excluded from the present study, so data are lacking on this highly selected (but still important) group. Guidance on SOF dose adjustments for the transplant population in the event of advanced kidney dysfunction will be extremely useful.

Drug–drug interactions pose a challenge in daily practice when it comes to treating HCV recurrence [4]. Further clinically significant DDIs are also expected to be discovered in the near future in relation to the recent introduction of DAAs [27]. The potential for DDIs (particularly with immunosuppressants) should therefore be considered in all patients undergoing treatment with DAAs. Regarding this specific concern, no clinically significant DDIs were observed (and no cases of acute rejection were reported) in the present series.

Last but not least, it remains to be seen whether this LT population with very advanced liver disease) will remain a substantial part of our clinical practice in future. In the main, such patients will be treated either before or very soon after LT. Our current approach is to treat patients within the first 3–6 months, when the risk of surgical complications or early rejection fades, renal function has stabilized, and severe HCV recurrence can still be avoided in most cases. Hopefully, there will be a substantial reduction in the burden of HCV-related disease over the next twenty years [28], and recurrent cirrhosis will no longer be a major health issue.

To sum up, HCV infection significantly impairs patient outcomes after LT, carrying lower survival rates than in patients without HCV infection [29]. Antiviral therapy is the only available tool for delaying the progression of liver disease, and viral clearance improves long-term graft and patient survival [30]. Our aim must therefore be to achieve the highest possible SVR rate. Real-world experiences do confirm that great improvements have been made in our capacity to cure HCV infection—even in the LT population with advanced liver disease—which remains a unique high-risk group. But all patients must have access to treatment as soon as possible after transplantation (including F0 patients), without resorting to further compassionate treatment programs.

In conclusion, we believe that HCV recurrence must be treated early after the transplant, as soon as a patient's condition has stabilized and irrespective of the severity of any fibrosis.

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Conflicts of interest

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