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INVITED COMMENTARY

# Timing for treatment of HCV recurrence after liver transplantation: the earlier the better

Francesco Paolo Russo, Alberto Zanetto & Patrizia Burra

Multivisceral Transplant Unit, Padua University Hospital, Padua, Italy

**Correspondence**
Prof. Patrizia Burra MD, PhD, Department of Surgery, Oncology and Gastroenterology, Head of Multivisceral Transplant Unit, Padua, Italy.
Tel.: 0039 0498212897;
fax: 0039 0498218727;
e-mail: burra@unipd.it

Commentary to "Simple prediction of long-term clinical outcomes in patients with mild hepatitis C recurrence after liver transplantation."

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The manuscript by Gambato *et al.* [1] in this issue reports the results from a large cohort of patients with mild hepatitis C (HCV) recurrence after liver transplantation (LT) followed up in a single referral center. The long-term graft and patient survival, the progression of liver disease stratified by liver stiffness measurement (LSM), and the rate of cirrhosis development as well as the related risk factors were investigated. The authors showed that HCV-related graft loss is exceptional in patients who are classified as having a mild HCV. However, a subset of patients (15%) developed cirrhosis due to HCV progression. Donor age ≥50 years and AST ≥ 60 IU/L 1 year after LT were independently associated with the risk of progression to cirrhosis (46% at 5 after LT in case of both risk factors).

Although we are now facing a "new era" of direct antiviral agents (DAA) that is already changing the approach to HCV burden in both the pre- and post-LT settings, there is extra value by this paper. Some arguments supporting this statement are going to be highlighted exemplarily in the following by addressing the current state and challenges in the field of antiviral therapy for HCV recurrence.

Liver transplant population has always been considered as a special population, not only because of SVR rates that were lower in comparison with pretransplant setting, but also for other aspects (i.e., immunosuppressive therapy, renal function, drug–drug interactions).

During the "Stone Age," combined peg-interferon (IFN) and weight-based ribavirin (RBV) was the standard-of-care treatment for patients with established HCV recurrence after LT [2].

Fibrosis progression in HCV transplant recipients is associated with very early activation of hepatic stellate cells, a process that appears to be partially independent from necro-inflammatory activity [3]. For this reason, when to start antiviral therapy (AT) has been always a controversial subject. In the IFN era, preemptive AT, defined as therapy started quite early after LT (<12 weeks) and before histological disease recurrence is present, was not recommended, as the efficacy has been demonstrated by several studies to be rather poor [4]. The preemptive strategy, however, might eventually be




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**Table 1.** "DAA in the setting of post-transplant recurrence."

| Authors | Drugs | Genotype | Patients (*n*) | SVR12 | Notes |
|---|---|---|---|---|---|
| Charlton M [8] | SOF, LDV ± RBV 12 or 24 w | 1–4 | No cirrhosis (111), CP A (51) CP B (52) CP C (9) FCH (6) Most of them previously treated (including PI) | No cirrhosis and CP A: 96%/98% CP B: 85%/88% CP C: 60%/75% FCH: 100%/100% | At baseline, 14% had NS5A RAV. Relapse occurred in 7% of patients with baseline RAVs as compared to 4% in patients without. No relapses in 24 W |
| PungpapongS [11] | SOF, SIM + RBV for 12 w (80%) SOF, SIM for 12 w (20%) | G1a: 74 patients (60%) G1b: 43 patients (35%) | 123 | 90% | Well tolerated, except one death, possibly due to drug-related lung injury. |
| Poordad F [12] | SOF, DAC, RBV 12 w | 1 (77%) | 53 30% cirrhosis, 58% previously treated | 94% G1: 94% G3: 91% | Among three patients who relapsed, all were observed to have NS5A variants |
| Kwo P [13] | Paritaprevir/r, dasabuvir, ombitasvir, and RBV 24 w | G1a: 29 (85%) G1b: 5 (15%) | Fibrosis ≤ 12 months post-LT Naive post-transplant | 97% | No death, graft loss or rejection episode. IS adjustment requested |
| Brown SR [14] | SOF, SIM + RBV for 12 w (78%) SOF, SIM for 12 W (11%). 15 pts 24 w | G1a: 87 (57.6%) G1b: 42 (27.8%) | 151 Treatment-naïve: 66 (43.7%) Priori PI failure 11 (7.3) | 88% | 3 pts died due to aspiration pneumonia, suicide, and multiorgan failure, 1 pt experienced liver transplant rejection. |
| Punzalan CS [15] | SOF + SIM for 12 w | G1a: 33 (79%) G1b: 8 (19%) | 42 Prior HCV treatment: 11 (26%) pre-OLT 9 (21%) post-OLT | 95% No advanced fibrosis: 97% Advanced fibrosis: 87.5% | Adjustments of FK similar to usual practice. Most patients (74%) tolerated the AT well with minimal side effects. No rejection. |
| Gutierrez JA [16] | SOF + SIM for 12 w | G1a: 35 (57%) G1b: 26 (43%) | 61 Nonresponder or relapse to prior treatment 42 (69%) Metavir: F0-F2 38 (62%) F3-F4 23 (38%) | 93.4% G1b: 100% G1a: 89%. Metavir F3-F4 associated with diminished efficacy in Gt1a | Incidence of AEs was low. No severe AE occurred. |
| Saab S [17] | SOF + SIM for 12 w | Gt1 | 30 patients Treatment-naïve 10/30 (33.3%) Fibrosis stage* 0/1/2/3/4 13 (46.4%) / 2 (7.1%) 2 (7.7%) / 6 (23%) / 5 (19%) *Two patients did not have biopsies. | 93% | No death, graft loss or rejection episode. Adjustment in FK required in 10 patients |

used with the new-generation antivirals to prevent the spread of the virus in the entire body and organs, as they are widely better tolerated compared with IFN regimen.

Novel treatments for HCV infection are highly efficacious but costly. Thus, many insurers/drug regulatory agencies cover therapy only in advanced fibrosis stages.

The role of LSM in stratifying the risk of progression was considered in the paper by Gambato *et al.* Interestingly, in patients with mild HCV recurrence LSM 1 year after LT was low, but its progressive increase (slope) throughout the first 2 years after transplantation proved very helpful to identify individuals at risk of cirrhosis. The same group [5] has previously evaluated the value of transient elastography to assess clinical outcomes in HCV after LT. In HCV-infected patients, cumulative probabilities of liver decompensation 5 years after LT were 8% for patients with LSM <8.7 kilopascals (kPa) versus 47% for patients with LSM ≥ 8.7 kPa ($P < 0.001$). Five-year graft and patient cumulative survival were 90% and 92% in patients with LSM < 8.7 kPa ($P < 0.001$) and 63% and 64% in patients with LSM ≥ 8.7 kPa, respectively ($P < 0.001$). No association between outcomes and LSM at 12 months was documented in patients without HCV infection. Therefore, the authors conclude that LSM 1 year after LT is a valuable tool to predict HCV-related outcomes in recurrent HCV and can be used in clinical practice to identify the best candidates for antiviral therapy. We certainly agree that LST could be very useful in the setting of HCV recurrence as noninvasive tool. However, in the perspective of treating HCV recurrence as soon as possible, it would have been very remarkable to evaluate the impact of LSM increase promptly after LT (i.e., 3 months versus 6 months after LT).

However, it is our opinion that all patients with HCV recurrence after LT should be considered for AT. As a matter of fact, apart from the fact that new DAA AT is highly effective and extremely well tolerated, this "360°" approach for HCV recurrence is justified for at least two reasons.

Because the two forms of severe HCV recurrence – early severe recurrent HCV, including FCH, and cirrhosis as a result of recurrent chronic disease more than 1 year after LT – have somewhat distinct clinical characteristics, as analyzed by Forns *et al.* [6] comparing outcomes in these two groups of patients. In this study, patients with early recurrent hepatitis were more likely to achieve SVR12 (73%) than those with established cirrhosis (43%). Moreover, a greater proportion of patients with early recurrent hepatitis showed clinical improvement with respect to ascites and hepatic encephalopathy than patients with decompensated cirrhosis (69% vs. 45%, respectively). These results suggest that early treatment of patients with recurrent HCV infection after LT may offer an advantage over waiting until a patient develops more advanced fibrosis. However, in a simulated model (nontransplant setting) [7], treating HCV infection at early stages of fibrosis appeared to improve health outcomes and to be cost-effective but incurred substantial aggregate costs.

Secondly, treating HCV infection during the first week after LT (i.e., within 30 days) could be useful to prevent HCV extrahepatic dissemination. It is well known that HCV infection is associated with injury of organs other than the liver, which is thought to contribute to increased rates of morbidity and all-cause mortality [8]. Extrahepatic manifestations (EHMs) of HCV infection are variegated because they include mixed cryoglobulinemia (MC), lymphomas, membranous glomerulonephritis, porphyria cutanea tarda (PCT), lichen planus, thyroiditis, sicca syndrome, polyarthritis, diabetes mellitus (DM), cardiovascular diseases, and neurocognitive impairment. MC is the dominant EHM because it can be detected in half of all HCV-infected patients, yet less than 5% of the affected subjects develop a cryoglobulinemic syndrome. In this setting, early HCV eradication through AT protects against the clinical consequences of such EHMs as cryoglobulinemic vasculitis, glomerulonephritis and polyneuropathy, lymphoma, and diabetes, and we think that deferral of HCV infection treatment favors the onset of irreversible organ injury [9].

With all current oral HCV therapies, SVR rates in LT recipients appear comparable to nontransplant patients (Table 1) [10–17].

In summary, it is important to maximize the treatment in that specific setting. Viral eradication post-LT improves long-term graft and patient survival and reduces the need for re-LT. Our aim has to be to use the most effective treatment that provides the highest SVR rate. IFN-free regimens appear to be highly effective in LT recipients; therefore, all patients should have access to AT as soon as possible, independently from fibrosis severity.

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## REFERENCES


1. Gambato M, Crespo G, Torres F, *et al.* Simple prediction of long-term clinical outcomes in patients with mild hepatitis c recurrence after liver transplantation. *Transpl Int* 2016; **29**: 698.
2. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. *J Hepatol* 2008; **49**: 274.
3. Russo MW, Firpi RJ, Nelson DR, Schoonhoven R, Shrestha R, Fried MW. Early hepatic stellate cell activation is associated with advanced fibrosis after liver transplantation in recipients with hepatitis C. *Liver Transpl* 2005; **11**: 1235.
4. Chalasani N, Manzarbeitia C, Ferenci P, *et al.* Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology* 2005; **41**: 289.
5. Crespo G, Lens S, Gambato M, *et al.* Liver stiffness 1 year after transplantation predicts clinical outcomes in patients with recurrent hepatitis C. *Am J Transplant* 2014; **14**: 375.
6. Forns X, Charlton M, Denning J, *et al.* Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology* 2015; **61**: 1485.
7. Chahal HS, Marseille EA, Tice JA, *et al.* Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a US treatment-naive population. *JAMA Intern Med* 2016; **176**: 65.
8. Vigano M, Colombo M. Extrahepatic manifestations of hepatitis C virus. *Gastroenterol Clin North Am* 2015; **44**: 775.
9. Makara M, Sulyok M, Csacsovszki O, Sulyok Z, Valyi-Nagy I. Successful treatment of HCV-associated cryoglobulinemia with ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin: a case report. *J Clin Virol* 2015; **72**: 66.
10. Charlton M, Everson GT, Flamm SL, *et al.* Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015; **149**: 649.
11. Pungpapong S, Aqel B, Leise M, *et al.* Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology* 2015; **61**: 1880.
12. Poordad F, Schiff ER, Vierling JM, *et al.* Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY-1 study. *J Hepatol* 2015; **62**: S261.
13. Kwo PY, Mantry PS, Coakley E, *et al.* An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014; **371**: 2375.
14. Brown RS Jr, O'Leary JG, Reddy KR, *et al.* Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: real world experience from HCV-TARGET. *Liver Transpl* 2015; **22**: 24.
15. Punzalan CS, Barry C, Zacharias I, *et al.* Sofosbuvir plus simeprevir treatment of recurrent genotype 1 hepatitis C after liver transplant. *Clin Transplant* 2015; **29**: 1105.
16. Gutierrez JA, Carrion AF, Avalos D, *et al.* Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. *Liver Transpl* 2015; **21**: 823.
17. Saab S, Greenberg A, Li E, *et al.* Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. *Liver Int* 2015; **35**: 2442.