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

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

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List of abbreviations in order of appearance: hepatitis C (HCV), liver transplantation (LT), antiviral therapy (AT), direct antiviral agents (DAA), peg-interferon (IFN), ribavirin (RBV), sustained virological response (SVR), ledipasvir (LDV), sofosbuvir (SOF), fibrosing cholestatic hepatitis (FCH), simeprevir (SIM), daclatasvir (DCV), liver stiffness measurement (LSM)

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

Abstract

HCV is the leading cause of death from liver disease and is the most common indication for a liver transplantation. Although HCV is a widespread health problem, disease management is particularly challenging in several key subpopulations, including liver transplant recipients.

HCV recurrence after liver transplantation constituted a major challenge for the physicians during the last years. The recommended standard of care before the advent of new regimen was the treatment of confirmed recurrent disease, based either on persistent, unexplained elevated alanine aminotransferase levels or on histologically confirmed fibrosis, once rejection, biliary obstruction, and vascular damage have been ruled out. Moreover, early therapy (including interferon) has been associated with high rates of adverse effects, an increased risk of graft rejection, and higher proportions of patients requiring dose reductions.

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We are now facing a "new era" of direct antiviral agents that is already changing the approach to HCV burden in the post liver transplantation setting.

Available data on treatment of HCV recurrence with the new antiviral drugs showed sustained virological response that ranges between 60 to 100%. In this comment we have focused on both the utility of non invasive test to evaluate the fibrosis progression and on timing of antiviral therapy for HCV recurrence.

The manuscript by Gambato et al. in this issue report 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 hepatitis C. 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).

Despite we are now facing a "new era" of direct antiviral agents (DAA) that is already changing the approach to HCV burden both in the pre- and in the 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 to pre-transplant 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 (1). 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 (2). For this reason, when to start antiviral therapy (AT) has been always a controversial subject. In the IFN-era, pre-emptive 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 (3). The pre-emptive strategy, however, might eventually be used with the new-generation antivirals to prevent the spread out of the virus in the entire body and organs, as they are widely bettered tolerated compared with IFN regimen.

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

The role of liver stiffness measurement (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 (4) has previously evaluated the value of transient elastography to assess clinical outcomes in HCV after LT. In HCV 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 non-HCV patients. Therefore, the Authors conclude that LSM 1 year after LT is a valuable tool to predict HCV-related outcomes in recurrent hepatitis C 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 non invasive tool. However, in the perspective of treating HCV recurrence as soon as possible, it would have been very remarkably 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 are highly effective and extremely well tolerated, this "360°" approach for HCV recurrence is justify 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 (5) 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 (non-transplant setting) (6), 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 know 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 (7). Extrahepatic manifestations (EHMs) of HCV infection are variegate 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 (8).

With current all oral HCV therapies, SVR rates in LT recipients appear comparable to non-transplant patients. Table I (9-16).

In summary, it is important to maximize the treatment in that specific setting. Viral eradication post-LT to improve long-term graft and patient survival and reduce 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.

Table I. "DAA in the setting of post transplant recurrence"

Author	Drugs	Genotype	Patients (n)	SVR12	Notes
Charlton M (9)	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
Pungpapong S (10)	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 (11)	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 (12)	Paritaprevir/r, dasabuvir, ombitasvir and RBV 24 w	G1a: 29 (85%) G1b: 5 (15%)	Fibrosis < or equal to 2 > 12 months post-LT Naive post-transplant	97%	No death, graft loss or rejection episode. IS adjustment requested
Brown SR (13)	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 multi-organ failure, 1 pt experienced liver transplant rejection.
Punzalan CS (14)	SOF+SIM for 12 w	G1a: 33 (79%) G1b: 8 (19%)	42 Prior HCV-treatment: 11 (26%) preOLT 9 (21%) postOLT	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 (15)	SOF+SIM for 12 w	G1a:35 (57%) G1b: 26 (43%)	61 Non responder or relapse to prior treatment	93.4% G1b : 100%	Incidence of AEs was low. No severe AE

			42 (69%) Metavir: F0-F2 38 (62%) F3-F4 23 (38%)	G1a: 89%. Metavir F3-F4 associated with diminished efficacy in Gt1a	occurred.
Saab S (16)	SOF+SIM for 12 w	Gt1	30 patients Treatment naıve 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

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