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EDITORIAL

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Persistence of Virologic Response after Liver Transplant in Hepatitis C Patients Treated with Ledipasvir/Sofosbuvir Plus Ribavirin Pretransplant

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In the field of hepatitis C treatment, currently almost all past issues are solved, including treatment of special populations. Nevertheless, some aspects remain unanswered, such as the controversial decision to treat pre *vs.* post-liver transplantation (LT), the "point of no return" for improvement of hepatic function after antiviral treatment, and optimizing treatment outcomes in some subgroups like genotype 3 infection in hemodialysis patients.

We read with interest the article by Eric M. Yoshida, *et al.,* which is a *post-hoc* analysis of the persistence of viral response (pTVR) after LT in patients included in the SOLAR trials[1,2] who received antiviral treatment and subsequently underwent LT. In the study by Yoshida, *et al.,* all 17 were decompensated cirrhotic patients (Child B or C) with median MELD score of 16 who started treatment with Ledipasvir/Sofosbuvir plus ribavirin (RBV) before LT. Of these, 10 patients completed their planned treatment duration before LT, while 7 underwent LT before completing the 12 or 24 weeks of planned antiviral treatment. Seventy-six percent of patients completed at least 12 weeks of antiviral treatment. As a result, all 17 patients achieved pTVR, although one died shortly after LT (unrelated to study drugs), leading to a 94% rate of pTVR-12.

The most obvious advantage for treating patients before LT is to prevent HCV recurrence in the post-transplant setting. Nevertheless, not many studies have examined this issue. In the interferon era, only one randomized controlled trial of treatment with pegylated interferon plus RBV for patients in the waiting list for LT was performed,[3] with only 22% and 29% pTVR, for genotypes 1/4/6 and genotypes 2/3, respectively. The only factor that emerged as predictor of pTVR was the number of weeks the patient remained with undetectable viral load before LT (> 16 weeks). In the direct antiviral agent (DAA) era, a study by Curry, *et al.*[4] examined the results of the administration of Sofosbuvir plus RBV in compensated cirrhotic patients listed for hepatocellular carcinoma (HCC); 70% of patients achieved pTVR. Once again, the number of consecutive days (> 30 days) with HCV RNA target not detected prior to transplant appeared to be the strongest predictor of post-transplant viral response. In other words, the amount of time the patient remains with undetectable HCV viral load before LT seems to be an important factor in order to prevent recurrence of HCV in the liver graft. There are no specifically designed studies to examine this issue with 2 or more DAAs, but existing data of treatment in compensated and decompensated cirrhotic patients with several DAA combinations show sustained viral response (SVR) rates over 90% with viral negativity achieved in most cases within the first month of treatment initiation, suggesting that the required duration of HCV undectectability could be even shorter. However, this question remains to date unanswered. The current study is interesting as it provides data related to patients successfully treated with ledipasvir/sofosbuvir ± RBV in the pretransplant setting who present no HCV recurrence post-transplant.

An alternative for patients not finishing the established duration of therapy before transplantation is to "bridge" treatment, i.e. to continue therapy during the peritransplant period. To date, two studies summarizing limited data of patients treated before, during and after transplantation are available.[5,6] Both studies, one based on sofosbuvir plus RBV and the second based on several DAA combinations, have shown that this is a feasible and effective strategy.

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An interesting and still controversial issue is whether antiviral treatment might avoid transplantation in HCV-infected patients with decompensated cirrhosis. All 17 decompensated patients in the SOLAR study underwent LT, suggesting that not all patients improve to a point where transplantation is prevented. However, even in these cases, it is likely that the condition of the patient is globally improved leading to better post-transplant outcomes. Nevertheless, the particularities of each waiting list (WL) are different and must be taken into account. For example, in settings where donors are scarce, a MELD improvement may result in worse patient access to LT (the so-called "MELD purgatory").

In our center around 40% of waitlisted patients have HCV infection, with or without HCC. In the last three years, almost 50 patients in the WL for LT have received antiviral treatment and 30% of these have been delisted after confirming clinical and laboratory data improvement.[7]

In essence, although more studies are needed to determine the optimal timing of treatment with DAA combinations before LT, this is clearly an interesting strategy which may ultimately lead not only to prevention of viral recurrence but also to clinical improvement and potentially avoidance of LT. Given the rapidity at which DAA-based antiviral treatment is being applied in patients with advanced liver disease, at least in the western world and in countries with access to LT, it is unlikely that studies specifically designed at determining the best timing of treatment initiation will be undertaken, and studies like the one by Yoshida, *et al.* published in this issue will help understanding the benefits and limitations of such a strategy.

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