Liver, Pancreas and Biliary Tract

Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: Potent antiviral activity but no clinical benefit if treatment is given late

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ABSTRACT

Background: We evaluated efficacy and safety of sofosbuvir and daclatasvir ± ribavirin in liver transplant recipients with severe recurrent hepatitis C.

Methods: Patients included in an international compassionate use programme for treatment with sofosbuvir and daclatasvir ± ribavirin for 24 weeks were prospectively studied. Serum hepatitis C virus RNA was measured at treatment weeks 4, 12, and 24 and during follow-up at weeks 4, 8, and 12.

Results: Twelve patients (3 with fibrosing cholestatic hepatitis and 9 with cirrhosis; median model for end-stage liver disease score 20) received sofosbuvir 400 mg/day ± daclatasvir 60 mg/day, and 6 patients (50%) also received ribavirin 200–800 mg/day. Nine patients completed 24 weeks of treatment (75%), and all had undetectable hepatitis C virus RNA at week 24; 3 patients died (25%, liver failure, gastrointestinal bleeding and sepsis); 4 patients experienced severe liver disease-related adverse events. Post-treatment hepatitis C virus RNA was available for 5 patients (week 8, n = 2; week 4, n = 3) and was undetectable in all cases. Mean Child–Pugh score and albumin level improved significantly at week 24. No changes in immunosuppressant doses were needed.

Conclusion: All-oral sofosbuvir plus daclatasvir combination shows high virological efficacy in liver transplant recipients and does not interact with immunosuppressants. All adverse events were unrelated to study drugs. These data strongly suggest that this combination must be initiated before decompensation.

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1. Introduction

Hepatitis C virus (HCV) infection is one of the leading indications for liver transplantation (LT) worldwide [1,2]. Unfortunately, post-transplant recurrence of hepatitis C is almost universal, causing diminished post-transplantation survival compared to patients without HCV infection. Approximately 30% of HCV transplanted patients develop acute severe recurrent hepatitis progressing rapidly to liver cirrhosis [3,4], and from 5% to 7% experience fibrosing cholestatic hepatitis (FCH), which will rapidly lead to death in the majority of patients [5]. Treatment of recurrent HCV infection with pegylated interferon (Peg-IFN) and ribavirin after LT is associated with low rates of sustained virological response (SVR), usually in the range of 15–35%, and with significant adverse effects [6]. The advent of triple treatment schedules with the addition of first-generation protease inhibitors (PI), such as boceprevir or telaprevir, to Peg-IFN and ribavirin backbone, has slightly improved the therapeutic efficacy compared to dual therapy, but at the cost of additional, and often severe, adverse events [7]. Moreover, triple therapy with PIs is not feasible in LT recipients with advanced HCV-related recurrent disease.

Sofosbuvir is a potent oral nucleotide analogue inhibitor of HCV polymerase activity, recently licensed by the Food and Drug Administration and by the European Medicines Agency for the
treatment of HCV infection in combination with other antiviral drugs. The administration of sofosbuvir in association with ribavirin in liver transplant recipients with recurrent HCV infection has been reported to increase SVR to rates as high as 70% [8,9]. Daclatasvir is a potent oral NS5A inhibitor, currently under investigation in combination with other antivirals [10]. The association of sofosbuvir and daclatasvir has been shown to have very high antiviral efficacy when administered, with or without ribavirin, to previously naïve or non-responder patients with chronic HCV infection [11]. Recently, a single experience of administration of sofosbuvir in combination with daclatasvir in a LT recipient with severe recurrent cholestatic hepatitis C has been reported, showing a favourable outcome and the lack of drug interactions with calcineurin inhibitors (CNI) [12]. The purpose of this study was to evaluate the virological and clinical efficacy and safety of the combination of sofosbuvir and daclatasvir, with or without ribavirin, in a wider population of LT recipients with advanced disease due to recurrent HCV infection.

2. Patients and methods

2.1. Study design

This study was performed within the framework of two compassionate use programs of oral antivirals for LT patients with severe recurrence of HCV infection. Six hepatology centres participated in the study, including three Italian, one German, one Austrian and one in the United States. Written informed consent, approved by the Ethical Committees, was obtained for each patient.

2.2. Patients

The study included liver transplant recipients with severe disease recurrence due to persistent genotype 1 or 4 HCV infection, in whom PEG-IFN-based therapy was unfeasible and an interferon-free antiviral treatment with sofosbuvir and daclatasvir was indicated. Patients were enrolled between August and November 2013. All patients had a fibrosis stage ≥3 according to the Metavir scoring system [13]. All patients continued their previous immunosuppression therapy during the study.

2.3. Antiviral therapy

All patients received oral sofosbuvir 400 mg, and daclatasvir 60 mg, once daily, either with or without ribavirin. Ribavirin was not prescribed when haemoglobin level was <9 g/dL or glomerular filtration rate (GFR) <30 ml/min. In other cases ribavirin doses were adjusted to renal function parameters and haemoglobin level. The intended duration of antiviral therapy was 24 weeks. To assess efficacy, plasma viral load (VL) was monitored using the Abbott Real Time HCV assay (Abbott molecular, USA; lower limit of detection 12 IU/ml), at baseline and then at weeks 4, 8, 12, and 24 and at 4, 8, and 12 weeks post-treatment. HCV genotyping was performed using phylogenetic analyses of NS5B region.

Rapid virological response (RVR) was defined as an undetectable VL at treatment week 4.

End-of-treatment virological response (ETR) was defined as an undetectable VL at treatment week 24.

Sustained virological response (SVR12) was defined as an undetectable VL 12 weeks after the end of treatment.

2.4. Safety assessments

Data on clinical and biochemical parameters were collected monthly during treatment. GFR was estimated from serum creatinine using the modification of diet in renal disease (MDRD-4) formula [14]. The plasma concentrations of immunosuppressive drugs were determined weekly in the first month and monthly thereafter, the dosing regimens were adjusted to within the optimal therapeutic ranges (5–10 ng/ml for tacrolimus, 50–150 ng/ml for cyclosporine). Ribavirin dose reductions were performed depending on clinical conditions and physician choice. The investigators managed any adverse events according to the Division of AIDS tables for grading and severity of Adults and Paediatrics adverse events [15].

2.5. Statistical analysis

Continuous variables were expressed as medians, means and ranges, and categorical variables as percentages. The Mann–Whitney test was used to compare continuous variables. Student’s t-test was used to compare means with a normal distribution. A p value of <0.05 was considered to be significant. All analyses were performed using SPSS 20 statistical software (SPSS Inc., Chicago, IL).

3. Results

Twelve patients (58% males, mean age 58 ± 7 years) were enrolled, including 3 with evidence of rapidly progressing FCH. Individual baseline features are reported in Table 1. Patients were treated with sofosbuvir and daclatasvir 3–60 months after LT (mean 20 ± 17 months). Most patients had been non-responders to pre-LT treatment with Peg-IFN plus ribavirin, but only one had received standard dual therapy after LT due to early severe disease recurrence.

Six patients were treated with sofosbuvir and daclatasvir (50%) and 6 received also ribavirin (50%). The mean ribavirin dose was 400 ± 250 mg/day (range, 200–800 mg/day). All patients completed at least 4 weeks of therapy, 3 died within the first 12 weeks of treatment.

Table 1 Characteristics of the 12 patients at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Calcineurin inhibitor n (%)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>8 (66)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Others IS n (%)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0</td>
</tr>
<tr>
<td>Dual therapy post-LT n (%)</td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>0</td>
</tr>
<tr>
<td>Relapser</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>0</td>
</tr>
<tr>
<td>HCV genotype n (%)</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>7 (58)</td>
</tr>
<tr>
<td>1b</td>
<td>4 (34)</td>
</tr>
<tr>
<td>4</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Fibrosis stage F4 n (%)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>FCH n (%)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL), median (min–max)</td>
<td>6.8 (1–25)</td>
</tr>
<tr>
<td>ALT (IU/ml) median (min–max)</td>
<td>97 (34–376)</td>
</tr>
<tr>
<td>INR mean ± SD</td>
<td>1.54 ± 0.5</td>
</tr>
<tr>
<td>Creatinine (mg/dL) mean ± SD</td>
<td>1.90 ± 0.9</td>
</tr>
<tr>
<td>Haemoglobin (g/dL) mean ± SD</td>
<td>10.3 ± 1.6</td>
</tr>
<tr>
<td>Platelets (&gt;10^11 μL) mean ± SD</td>
<td>92 ± 52</td>
</tr>
<tr>
<td>HCV RNA (log10 IU/ml) mean ± SD</td>
<td>5.95 ± 1.3</td>
</tr>
<tr>
<td>MELD score at baseline mean ± SD</td>
<td>22 ± 9</td>
</tr>
<tr>
<td>Child–Pugh score at baseline mean ± SD</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Months between LT and antiviral therapy mean ± SD</td>
<td>20 ± 17</td>
</tr>
</tbody>
</table>

SD, standard deviation; IS, immunosuppressant drugs; LT, liver transplant; HCV, hepatitis C virus; FCH, fibrosing cholestatic hepatitis; MELD, model for end-stage liver disease; INR, international normalized ratio; ALT, alanine aminotransferase.
treatment (25%) and 9 patients have currently completed 24 weeks of treatment and are undergoing follow up.

At baseline all patients had high levels of viraemia (mean HCV RNA: 5.95 ± 1.3 log10 IU/ml) and median MELD score was 20 (Table 1).

3.1. Virological response

Serum HCV RNA was undetectable in 9 patients at week 4 of treatment (75%), and in all 10 patients who reached week 12, regardless of the pre-treatment viral load.

All 9 patients (100%) who reached week 24 of treatment had undetectable HCV RNA, of whom 5 (55.6%) received a ribavirin-containing regimen.

Presently, post-treatment virological data are available for 5 patients (week 8, n = 2 and week 4, n = 3), all of whom have undetectable HCV RNA.

3.2. Safety

No adverse events directly attributable to either sofosbuvir or daclatasvir were noted during the study. No difference in haemoglobin levels at weeks 4, 12 and 24 was observed in the group of patients receiving ribavirin compared to those who did not (data not shown).

3.2.1. Mortality

Three patients (25%) died during antiviral therapy. One patient died at week 4 due to rapidly progressive liver failure, one at week 8 due to uncontrollable gastrointestinal bleeding and one at week 10, due to a septic shock resulting from an underlying fasciitis. All three patients had advanced disease at the beginning of antiviral therapy, with MELD scores of 40, 24 and 33, respectively. One of the patients who died had symptoms and signs of FCH. All three patients had undetectable HCV RNA at last assessment. The individual characteristics of these patients are reported in Table 2.

In patients who completed the treatment, mean Child–Pugh score and serum albumin concentration showed a significant improvement at treatment week 24 vs. baseline, while mean MELD score did not improve significantly (Table 3).

3.2.2. Severe adverse events

Several clinically relevant and potentially life-threatening complications occurred, although these were unlikely to be directly related to the antiviral treatment. One patient developed recurrent spontaneous bacterial peritonitis, one patient experienced a severe episode of pneumonia and two required the insertion of a transjugular intrahepatic portosystemic shunt (TIPS), one for recurrent upper gastrointestinal bleedings and one for refractory ascites. Both these patients currently have undetectable HCV RNA off-treatment, but have developed difficult-to-manage hepatic encephalopathy, despite the apparent improvement in liver function.

Severe adverse events occurred in 3 patients receiving sofosbuvir + daclatasvir only, and in 1 patient receiving sofosbuvir + daclatasvir + ribavirin.

Five patients (41.7%) did not develop severe adverse events (SAE). These included two patients in Child–Pugh stage C, two in stage B and one in stage A. The median MELD value of these patients was 17 (range 8–32).

3.2.3. Immunosuppression

No modifications of tacrolimus, everolimus or cyclosporine dosages were needed during antiviral treatment. Plasma concentrations of tacrolimus were 7.7 ± 4.9 ng/ml at baseline, 6.2 ± 2.6 at week 4, 4.5 ± 1.3 at week 12 and 3.67 ± 0.7 at week 24, respectively. Tacrolimus plasma levels did not differ significantly between baseline and weeks 4, 12 and 24.

4. Discussion

Severe HCV recurrence is one of the main factors limiting the success of liver transplant for HCV-related end-stage liver disease, as up to 30% of transplanted patients develop cirrhosis within 5 years after transplantation [3,4]. Regrettably, only few patients can tolerate treatment with interferon-based regimens and response rates are low. As many as 20–40% of patients withdraw from dual antiviral therapy due to the frequent development of adverse events [6].

Unfortunately, the association of Peg-IFN and ribavirin with first-generation PI (telaprevir and boceprevir) has also proven to be largely unsatisfactory in this setting, mainly due to severe adverse events, and death, especially in patients with advanced liver disease. In addition, both drugs have significant interactions with CNI, making the management in LT recipients difficult [7].

Recently, different therapeutic regimens, including second-generation DAAs, have been employed in post-LT patients. Forns et al. [8] described a series of 104 LT patients (all genotypes), treated with sofosbuvir + ribavirin + Peg-IFN. Half of these patients had compensated or decompensated post-LT cirrhosis, while the remaining had severe cholestatic hepatitis C or early HCV related disease recurrence (Metavir F2–F3). Overall 30% of patients stopped treatment, 12.5% due to death, 11.5% due to AEs and 6.7% due to re-transplantation. Among those who completed therapy 60% improved, 20% remained stable and 20% worsened or died [8]. The EOT response was 87% with an SVR12 of 62%. In another study, Fontana et al. [12] reported the case of a LT recipient with severe cholestatic HCV who was successfully treated with the all-oral association of sofosbuvir and daclatasvir.
Since mid-2013 both Gilead Sciences and Bristol-Myers Squibb (BMS) launched compassionate use programmes with sofosbuvir and daclatasvir, respectively, which allowed to use the two drugs in combination. However, both programmes restricted the use of DAAs to LT recipients with advanced liver disease and/or with evidence of FCH, hence to patients with a very short survival expectancy, for whom no alternative treatment options were available. Several independent investigators therefore applied for the two compassionate use programmes and were able to treat transplant recipients meeting the above-mentioned characteristics with this all-oral regimen.

In the present paper, we describe the experience of six different centres in Europe and the USA with sofosbuvir + daclatasvir ± ribavirin, on effectiveness, safety and clinical efficacy of this novel drug combination. Our findings confirm a potent and rapid antiviral efficacy and show a highly favourable safety profile for this combination. However, the excellent virological efficacy in many cases was not associated with valuable clinical benefits (Fig. 1). Similarly to Forns et al. in the study on sofosbuvir + ribavirin [8], our study also showed a high mortality and SAE rate in this difficult patient population, which is likely not related to the study drugs but rather to the underlying liver disease. This strongly suggests that treatment should be started at an earlier stage in post-LT patients compared to the restrictions dictated by current compassionate use programmes.

In our study, half the patients experienced a mild recovery of liver function during treatment, as shown by the modest, though statistically significant, improvement of the Child–Pugh score after 24 weeks of therapy. This was not associated with a significant improvement in MELD score, despite the fact that serum HCV RNA was already undetectable at week 4 or 8 of treatment. In the case reported described by Fontana, the rapid and complete recovery of the patient could be explained by the fact that treatment was begun at an early stage of cholestatic hepatitis, possibly before the advent of cirrhosis. These findings suggest that treatment should be started at an early stage of HCV recurrence after LT to obtain the greatest benefit, and that use in advanced liver disease should be discouraged.

In our study 6 patients did not receive ribavirin, while the remainder received a low dose (median 300 mg/day, range 200–800 mg/day). There was no difference in early antiviral effect of therapy between the two groups, supporting the view that ribavirin is not needed when sofosbuvir and daclatasvir are used in combination, as also suggested by Fontana et al. [12]. However, a longer follow-up will be needed to confirm that ribavirin does not increase antiviral efficacy in this setting.

Another clinically relevant finding of our study is that no adjustments in immunosuppressants drugs dosage were required during treatment, thus confirming that both sofosbuvir and daclatasvir have no relevant interactions with CNI and mTOR inhibitors (such as everolimus).

In conclusion, although our relatively small series and the short duration of post-treatment follow-up are two major limitations, we believe that the preliminary data collected in this international multicentre experience are sufficient to state that sofosbuvir plus daclatasvir combination therapy exerts potent antiviral effects in LT recipients with severe HCV-related recurrent disease, and is apparently safe and free of interactions with immunosuppressants drugs. Yet, despite this favourable profile, severe disease complications and deaths occur frequently in this population. These data strongly suggest that this antiviral combination must be initiated before the onset of cholestasis or liver decompensation.
Conflict of interest
None declared.

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