BRIEF REPORT

Successful Pre- and Posttransplant Sofosbuvir-Based Anti-Hepatitis C Virus Treatment in Persons Living With Human Immunodeficiency Virus Infection

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This retrospective study reports the data of sofosbuvir-based anti-hepatitis C virus treatment in 24 candidates and 24 recipients of liver transplantation coinfected with human immunodeficiency virus. Sustained virologic response was cumulatively 85% (90% and 100% in those treated with optimal schedules pre- and posttransplant, respectively).

Keywords. HCV; HIV; liver transplantation; NS5A inhibitors; sofosbuvir.

In persons living with human immunodeficiency virus (PLWHIV), orthotopic liver transplantation (OLT) has produced excellent results when liver disease was not due to active hepatitis C virus (HCV) infection [1]. Human immunodeficiency virus (HIV)/HCV-coinfected patients with decompensated cirrhosis have lower survival rates (less than 1 year), mainly because of higher mortality while on the list [2]. A meta-analysis of all the reported series demonstrated that in HCV/HIV-coinfected persons, survival at 5 years is 50%–55%, which is poorer than in HCV-monoinfected patients, mainly due to the more aggressive recurrence of HCV and consequent graft loss and death [1].

The most effective factor influencing OLT outcome is successful treatment of HCV recurrence [1]. Interferon (IFN)-based therapies in coinfected OLT candidates and recipients showed low efficacy and high toxicity [3]. In contrast, sofosbuvir (SOF)-based therapies have showed high efficacy and tolerability in both OLT candidates and recipients [4]. So far, small series data in HIV/HCV-coinfected persons have been published, cumulatively reporting treatment in 13 OLT candidates and 48 recipients [5–10]. The aim of this study was to assess the impact of SOF-based anti-HCV, all oral treatment on OLT in PLWHIV.

METHODS

This retrospective, multicenter study involved 5 Italian Liver Transplant Centers with an active program of OLT in PLWHIV. All HIV/HCV-coinfected patients on the waiting list for OLT or already transplanted who consecutively started any IFN-free SOF-based therapy from June 2013 to January 2016 were included. Indications for OLT were HCV-related decompensated cirrhosis with a model for end-stage liver disease (MELD) above 15 or hepatocellular carcinoma (HCC) within the Milan criteria.

Treatment combinations changed over time according to drug availability: SOF was available for compassionate use since 2013, and daclatasvir (DCV) was available for compassionate use since December 2014. Thereafter, marketed SOF was available for clinical use since December 2014, and marketed DCV was available for clinical use since February 2015; SOF/ledipasvir (LDV) fixed-dose combination was available since May 2015.

Sustained virologic response at 12 weeks (SVR12) was defined by undetectable HCV-ribonucleic acid (RNA) 12 weeks after treatment withdrawal. The rate of SVR12 was assessed with an intention-to-treat (ITT) SVR12 approach, defined as the rate of SVR12 among all the patients who took at least 1 dose of SOF. In addition, a modified ITT (mITT) SVR12 was assessed, defined as the rate of SVR12 among the patients who took at least 1 dose of SOF, excluding those who stop the scheduled regimen for nonvirological reasons.

Hepatitis C virus genotype was assessed by Inno LIPA HCV 2.0; HCV-RNA was measured with Cobas TaqMan versus 2 Roche Diagnostics or Abbott RealTime HCV assay. Next-generation sequencing (detection threshold: 15%) to identify treatment-emergent substitutions in NS3, NS5A, and NS5B HCV genomic regions was performed in case of virological failure.

Hepatitis C virus RNA as well as liver function tests (including international normalized ratio, bilirubin, albumin, and creatinine) were performed at baseline, every 4 weeks during the treatment, at the end of therapy, and 4 and 12 weeks after treatment withdrawal. Human immunodeficiency virus RNA and T lymphocyte $CD4^+$ and $CD8^+$ cell counts were measured at baseline and every 12 weeks thereafter.

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Levels of immunosuppressive drugs were monitored during treatment according to local protocols. The study was conducted in accordance with the ethical standards of the Helsinki Declaration, informed consent was obtained from each participant, and the study was approved by the local ethical committee of each participating center.

RESULTS

Study Population

Forty-eight patients were included in this study: 24 treated while on the waiting list and 24 after OLT. Patients' demographic and clinical features are summarized in Table 1.

Treatment

The suboptimal regimen of SOF and ribavirin (RBV) was used in 10 patients pre-OLT and 9 patients post-OLT. The remaining patients were treated with SOF in combination with an NS5A inhibitor, with or without RBV: in the pre-OLT setting, 12 used DCV and 2 used LDV; in the post-OLT setting, 9 used DCV and 6 used LDV. Only 7 patients were treated for 12 weeks (2 in the pretransplant cohort), and the remaining 41 patients were treated for at least 24 weeks (in 3 candidates, the therapy lasted until OLT). The antiretroviral regimens were mostly based on integrase inhibitors (79.2%), and 40% were on tenofovir disoproxil fumarate. Twelve of 48 (25%) subjects were switched

Table 1. Characteristics of the Study Population and Treatment Response in 48 HIV-HCV-Coinfected Patients Treated Pre- and Postliver Transplant

Characteristics	Patients Treated Pretransplant (N = 24)	Patients Treated After Transplant (N = 24)
Age year median (IQR)	51 (50–52)	52.5 (49–54)
Gender, male N (%)	18 (75%)	20 (83%)
HCV Genotype		
1a	11	8
1b	4	6
2	1	0
3	4	3
4	4	7
HCV-RNA $\log_{10}$ IU/mL median (IQR)	5.64 (4.48–6.02)	6.81 (6.04–7.08)
Experienced		
PEG-IFN + RBV	15 (62%)	17 (71%)
PEG-IFN + RBV + NS3I	0	1 (4%)
Time from OLT weeks, median (IQR)	–	49 (5–142)
CD4 cell/mm^3 median (IQR)	356 (239–497)	342 (236–580)
HIV-RNA undetectable N (%)	24 (100%)	22 (92%)
Cirrhosis n (%) with HCC N (%)	24 (100%) 6 (25%)	12 (50%)
MELD median (IQR)	16 (12–20)	8 (6–10)
MELD >18	7 (29%)	1 (4%)
Child Pugh B	16 (67%)	5 (21%)
Child Pugh C	4 (25%)	2 (10%)
Immunosuppression based on tacrolimus N (%)	–	19 (79%)
ART, N (%)		
Including INSTI	17 (71%)	21 (87%)
Including tenofovir	10 (42%)	9 (37%)
Anti-HCV treatment used		
SOF + RBV	10 (40%)	9 (37%)
SOF + DCV ± RBV	12 (50%)	9 (37%)
SOF/LDV ± RBV	2 (10%)	6 (25%)
Duration of SOF 12/24/>24 weeks	3/18/3	4/20/0
SVR12 ITT (overall)	19/24 (79%)	22/24 (92%)
SVR12 mITT (overall)	19/22 (87%)	23/24 (96%)
SOF + RBV SVR ITT	7/10[3a] (70%)	8/9 [3a] (89%)
SOF + RBV SVR mITT	7/10[3a] (70%)	8/9 [3a] (89%)
SOF + DCV ± RBV ITT	11/12[2b] (92%)	8/9 [4c] (89%)
SOF + DCV ± RBV mITT	11/11 (100%)	8/8 (100%)
SOF/LDV ± RBV ITT	1/2[1d]	6/6 (100%)
SOF/LDV ± RBV mITT	1/1	6/6 (100%)

Abbreviations: ART, antiretroviral therapy; DCV, daclatasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase inhibitors (raltegravir and dolutegravir); ITT, intention to treat; IQR, interquartile range; LDV, ledipasvir; MELD, model for end-stage liver disease; mITT, modified intention to treat (nonvirological failure excluded); NS3i, first-generation NS3 inhibitors (ie, boceprevir or telaprevir); OLT, orthotopic liver transplantation; PEG-IFN, pegylated interferons alpha 2a or 2b; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response (ie, HCV-RNA undetectable 12 weeks after anti-HCV treatment withdrawal).

Note: Reasons for nonresponse were as follows: [a], virological relapse; [b], HCC progression withdrawn from waiting list and stopped anti-HCV at 12 weeks with relapse; [c], death due to graft dysfunction (vanishing bile duct syndrome) with undetectable HCV-RNA on treatment; [d], death due to intracranial bleeding with undetectable HCV-RNA on treatment.

from previous anti-HIV treatment before starting anti-HCV therapy because of potential drug-drug interactions. The immunosuppressive treatment included tacrolimus in 19 OLT recipients (79.2%) and cyclosporin in 5 (20.8%).

Hepatitis C Virus Virologic Response

The SVR12 was achieved by 41 of 48 subjects (85.4%): 19 of 24 (79.2%) pre-OLT and 22 of 24 (91.7%) post-OLT. There were 4 virological failures: 3 relapses in the pre-OLT group and 1 relapse in the post-OLT group; all of these patients were treated with a dual SOF and RBV regimen and were infected by HCV genotype 1. Results are reported in detail in Table 1.

Cumulatively, 19 patients started a suboptimal therapy according to the EASL guidelines (SOF + RBV): in these individuals, ITT SVR12 and mITT SVR12 rates were both 79% (both 70% pre-OLT and 89% post-OLT). In the remaining 29 patients treated with optimal combinations according to the EASL guidelines, ITT SVR12 was 90% and mITT SVR12 100% (both in pre-OLT and post-OLT).

No clear indications about when to stop treatment after OLT were available during the majority of pre-OLT treatments. Therapy was initiated while patients were on the waiting list and completed according to the programmed schedule after OLT in 4 patients, and all patients achieved SVR. In 1 patient, SOF and RBV treatment was stopped on the day of liver transplantation after 20 weeks of treatment and 12 weeks after his first undetectable HCV-RNA, but this patient relapsed after OLT. No resistance-associated substitutions were registered after treatment failure.

Safety

During and after anti-HCV treatment, no HIV breakthroughs were observed; however, in 1 patient, a treatment failure was registered after OLT. Likewise, no clinically significant decrease in T lymphocyte CD4$^+$ cell count was noted.

No serious treatment-related adverse events were recorded. Ribavirin was given with an escalating schedule starting from 600 mg daily in 37 of 48 subjects: 5 of 37 showed anemia (hemoglobin, <10.5 g/dL). Infections, either bacterial or viral, were observed in 4 subjects: 1 had herpetic cheratitis, 1 had sepsis, 1 had prostatitis, and 1 had a urinary tract infection.

Liver-related complications were seen in 3 individuals: 1 developed spontaneous bacterial peritonitis, 1 developed hepatic encephalopathy, and 1 developed jaundice (even

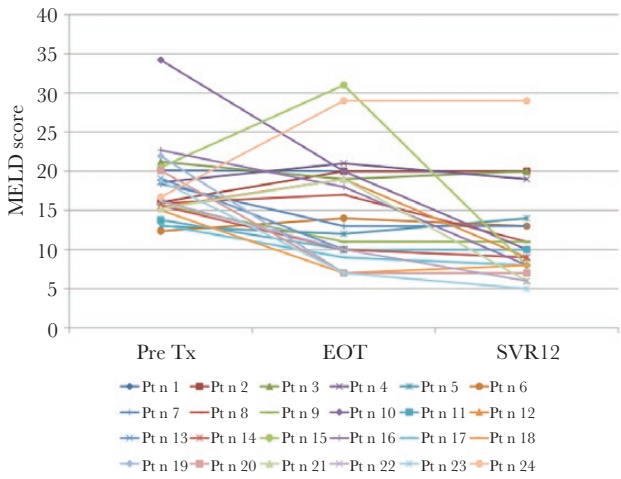

Figure 1. Model for end-stage liver disease (MELD) scores measured pretreatment (Pre Tx) at the end of treatment (EOT) and 12 weeks after treatment end of treatment (12 weeks post-EOT) in the 24 patients treated while on the waiting list for liver transplantation. SVR12, sustained virologic response at 12 weeks.

Table 2. Flow Diagram for the Cohort of HIV-HCV-Coinfected Patients Treated Pretransplant

All Patients		24					
Treatment		SOF ± RBV 24 Weeks		SOF + DCV ± R 12–24 Weeks		SOF + LDV ± RBV 12–24 Weeks	
Number of patients		10		12		2	
Treatment response		SVR 24: 7	NR: 3	SVR24: 11	D/O: 1[a]	SVR 24: 1	D/O: 1[b]
Patients status on January 31, 2017 (median follow up after treatment withdrawal up 18 months, IQR 14–20 months)	Death						1[b]
	Transplant without HCV recurrence	7		5		1	1[b]
	Transplant with HCV recurrence		1				
	SVR24 and delisted alive with MELD <10			6			
	NR and delisted		1[c]		1[a]		
	NR and on the waiting list with MELD >15		1				

Abbreviations: DCV, daclatasvir; D/O, drop out; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; LDV, ledipasvir; MELD, model for end-stage liver disease; NR, nonresponder; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR24, sustained virologic response 24 weeks posttreatment withdrawal.

[a]Withdrawn from treatment and liver transplant list 12 weeks after treatment initiation for progression of hepatocellular carcinoma relapser after anti-HCV treatment (HCV genotype 3); treated with sorafenib on January 31, 2017, 17 months after treatment withdrawal, alive without progression of hepatocellular carcinoma with detectable HCV-RNA.

[b]Treated with SOF and LDV for 12 weeks before and after transplant; died for cerebral hemorrhage 1 month after liver transplant while on SOF + LDV with on treatment response.

[c]Withdrawn from liver transplant list for "de novo" hepatocellular carcinoma outside of Milan criteria; nonresponder to SOF and RBV for 24 weeks; on January 31, 2017, 19 months after treatment withdrawal, alive and on sorafenib with progession of hepatiocellular carcinoma and liver decompensation MELD 24.

though the patient was receiving atazanavir). A renal insufficiency grade of III or more was not observed during or after treatment. Cyclosporin toxicity was observed in 2 subjects: 1 showed mild neurologic toxicity, whereas the other had seizures promptly resolved after specific treatment and cyclosporin dose adjustment.

Liver Disease-Related Outcomes

Among the 24 subjects who started the treatment while on the waiting list, 2 were withdrawn: 1 for HCC progression, and 1 for HCC "de novo" occurrence outside from the Milan criteria. None of them achieved the SVR12. Six (25%) subjects were withdrawn from the waiting list after the achievement of SVR12 because they maintained a MELD value below 15 for more than 6 months (delta MELD at SVR12 −5, interquartile range −2 to −6). Figure 1 reports change of MELD score in patients treated pretransplant before, during, and after treatment.

Fifteen patients underwent transplantation: 1 died as a result of cerebral hemorrhage and could not be considered as a candidate for viral eradication, and 12 achieved SVR12. As mentioned, 1 showed post-OLT recurrence after SOF and RBV withdrawal at transplantation. Another one did not respond to SOF and RBV and is currently on re-treatment with SOF/LDV; he is still on the waiting list. Table 2 reports the flow diagram of the 24 patients treated before liver transplantation and their status as observed on January 31, 2017. Among the 24 subjects who started treatment after OLT, 22 are still alive, and 1 died from liver failure due to vanishing bile duct syndrome after acute rejection (HCV-RNA was undetectable during his last control visit).

DISCUSSION

Sofosbuvir-based treatment was safe and effective in HCV/HIV-coinfected patients who were OLT candidates or recipients: SVR rates were higher than 90% in both settings when optimal treatment regimens were used. Data of 13 patients treated pre-OLT have been published: SVR was observed in 9 of 10 patients treated with optimal therapy (90%) and in 1 of 3 (33.3%) patients treated with SOF and RBV. Six small series reported the data of 48 patients treated post-OLT: the SVR12 rate was 90%, but it topped at 100% when evaluating only the 28 patients treated with optimal regimens [5–10]. These and our results confirm the data observed in HCV-monoinfected individuals in the same settings [4].

Twenty-five percent of OLT candidates were withdrawn from the list: this proportion is similar to that observed in other cohorts of patients treated pre-OLT [11]. In addition, the treatment schedule was completed post-OLT in 4 patients without safety or efficacy issues, confirming anecdotal data observed in persons without HIV infection [11].

Two patients of the 6 candidates with a HCC showed tumor progression. This rate was not different from that observed in untreated HCV-HIV-coinfected patients [1]. Nevertheless, taking into consideration the recently emerged data on relapse of HCC in patients treated with oral anti-HCV drugs [12], pre-OLT treatment of these patients should be considered with caution.

CONCLUSIONS

In conclusion, SOF-based anti-HCV treatment is safe and effective pre- and post-OLT, and it has the potential to improve the outcome of OLT in HCV/HIV-coinfected patients. Pre-OLT treatment should be strongly considered for HIV-infected patients because of the higher wait-list mortality due to progression of liver disease [2]; nevertheless, treatment could be delayed posttransplant in patients with HCC and compensated liver disease.

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