Prevention of hepatitis C recurrence by bridging sofosbuvir/ribavirin from pre- to post-liver transplant: A real-life strategy

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Prevention of hepatitis C recurrence by bridging sofosbuvir/ribavirin from pre to post liver transplant: a real life strategy

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Abbreviations:

Direct-acting antiviral (DAA)

Hepatitis C virus (HCV)

Liver transplant (LT)

Sofosbuvir/Ribavirin (SOF/R)

Hepatocellular carcinoma (HCC)

Sustained virological response (SVR)

Model for End Stage Liver Disease (MELD)

Low limit of quantification (LLOQ)

Intention to treat (ITT)

Child-Pugh (CP)

Mycophenolate mofetil (MMF)

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Key Points

- HCV post-transplant reinfection reduces recipient survival.
- Sofosbuvir/Ribavirin before liver transplant can avoid HCV reinfection in patients with at least 4 weeks of HCV-RNA suppression before transplant.
- In patients with end-stage HCV liver disease treated by sofosbuvir-regimens and showing HCV-RNA still positive or negative for less than 4 weeks at transplant, a feasible approach is to continue therapy after transplant (bridging therapy), achieving HCV-free liver in 94% of treated recipients.
- Although more effective combo DAA-regimens and shorter treatment duration will minimize the need of such approach, it may be cost-effective in patients with anticipated liver graft availability and suboptimal virological response.

ABSTRACT

Background and aims: Hepatitis C virus (HCV) reinfection following liver transplant (LT) is associated with reduced graft and patients survival. Before transplant, Sofosbuvir/Ribavirin (SOF/R) treatment prevents recurrent HCV in 96% of those patients achieving viral suppression for at least 4 weeks before transplant. We evaluated whether a bridging SOF-regimen from pre to post-transplant is safe and effective to prevent HCV recurrence in those patients with less than 4 week HCV-RNA undetectability at the time of transplant. Material and Methods: From July 2014 SOF/R was given in 233 waitlisted HCV cirrhotics with/without hepatocellular carcinoma (HCC) within an Italian Compassionate Program. One-hundred were transplanted and 31 patients (31%) treated by SOF/R bridging therapy were studied . Results: LT indication in bridge subgroup was HCC in 22 and decompensated cirrhosis in 9. HCV-genotype was 1/4 in 18 patients. SOF 400 mg/day and R (median dosage 800 mg/day) were given for a median of 35 days before LT. At transplant time, 19 patients were still HCV-RNA positive (median HCV-RNA 58 IU/ml). One recipient had a virological breakthrough at week 4 post-transplant; one died, on treatment, 1-month post-transplant for sepsis and 29/31 achieved a 12-week sustained virological response (94%). Acute cellular rejection occurred in 4 recipients. On September 2016, 30 recipients (97%) are alive with a median follow-up of 18 months (range 13-25). Conclusions: In patients with suboptimal virological response at LT a bridging SOF/R regimen helps avoiding post-transplant graft reinfection.

INTRODUCTION

Safe and highly effective oral direct-acting antiviral (DAA) regimens now available to treat hepatitis C virus (HCV) have revolutionized the management of both liver transplant (LT) candidates and recipients **[1-4]**. A major breakthrough of all oral regimens was the chance to treat cirrhotic patients with impaired liver function before LT, in order to prevent HCV

reinfection which is a major determinant of anticipated graft loss and early mortality **[5-7].** Sofosbuvir (SOF) a nucleotide analogue inhibitor of the HCV-RNA-dependent RNA polymerase (NS5B) (Gilead-Sciences, Foster City, CA), has been approved in 2013 **[8**]. It was the first drug investigated in association with Ribavirin (R) before and after transplant, providing convincing proof that a 24-48 week course can eliminate HCV infection in two-thirds of the patients **[9-10**]. Prevention of graft HCV reinfection was investigated by Curry **[9**] in a phase 2 study in patients listed for well-compensated cirrhosis and hepatocellular carcinoma (HCC). Overall, sustained virological response (SVR) was achieved in 70% of the 43 transplanted patients who achieved HCV-RNA below the lower limit of quantification at the time of LT**,** yet SVR peaked to 96% in the subset of patients with undetectable HCV-RNA for at least 4 consecutive weeks before transplant. At the same time, post-transplant efficacy and safety of SOF/R was reported by Charlton **[10**] in a multicentre open-label study including 40 HCV transplant recipients of whom 63% with compensated cirrhosis; SVR was achieved in 70% of the patients. These data were further validated by a worldwide SOF compassionate use program including 104 recipients with severe HCV recurrence and a short life-expectancy **[11**]. Noteworthy, this study confirmed the safety of SOF-therapy also in transplant recipients with advanced HCV recurrence, with more than 50% of the patients achieving HCV eradication and a significant clinical improvement in terms of reversal of ascites, encephalopathy and liver function. Subsequently, several studies on both decompensated cirrhotics and transplant recipients have shown that SOF in combination with NS5A inhibitors (Ledipasvir or Daclatasvir) is more effective with SVR rates going up to more than 80-90%, according to viral genotype, severity of disease, R use and duration of therapy **[12-15**]. Nowadays, there is still an on-going debate as to whether patients with advanced cirrhosis on the transplant list should be treated prior or after liver transplantation. Indeed, prevention of liver graft reinfection considerably facilitates post-transplant

management **[16, 17**]. However, pre-LT treatment should be reserved only for those patients with a sufficient predictable waiting-list duration, thus allowing a sufficient period to achieve SVR or at least, HCV-RNA suppression for > 4 weeks before transplant as shown by Curry with an outdated regimen based on SOF/R **[9**]. Nowadays, more effective drugs with shorter treatment duration (12 weeks) are available; however, there are no data focusing on the prevention of HCV graft reinfection with such regimens. Moreover, the waiting list time is usually unpredictable in liver transplant candidates and a finite anti-HCV treatment is a strategy difficult to follow in the real life. As a proof-of-concept study, in the frame of a National Compassionate Use Program of SOF in Italy, we therefore investigated safety and efficacy of extending SOF-based regimen from the pre-LT period over the peri and post-transplant phase in listed patients with a suboptimal HCV-RNA suppression at the time of liver offer.

MATERIAL AND METHODS

Starting from June 2014 to December 2014 Agenzia Italiana Farmaco (AIFA) and Gilead Sciences promoted a National SOF-Compassionate Use Program in patients on waiting list for LT and in those with HCV recurrence after LT (Metavir score >F2). Two hundred and thirty-three LT candidates with end-stage HCV received SOF/R within this Program **[18].** Inclusion criteria were: age > 18 years, LT waitlist for decompensated cirrhosis (Model for End-stage Liver Disease, MELD < 25) or HCC within Milan criteria. All patients gave their written consent to participate in the study which was approved by our local ethic committee (Comitato Etico Milano Area B - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Via F. Sforza n. 28- 20122 Milano).

Eligible waitlisted patients were planned to receive SOF 400 mg/day and R 600-1200 mg/day, until transplant or for a maximum of 24 weeks for HCV-2 and 48 weeks for all other genotypes.

One hundred patients received a liver graft and in 37 out of 49 transplant candidates (75%) still HCV-RNA positive or negative for less than 4 weeks at surgery, the physicians decided to continue antiviral treatment after transplant up to overall 24 weeks (Bridge Therapy) whereas 12 stopped SOF at LT time **[18].**

All patients had blood tests, HCV-RNA assessment, kidney function and clinical evaluation every 4 weeks or whenever clinically requested before transplant, whereas, during the early phase after surgery, patients followed a strict virological surveillance in addition to the scheduled protocol of Intensive Care and Surgery Units. In case of a reduction of estimated-glomerular filtrate rate under 30 ml/min SOF was temporary discontinued until regaining of kidney function. HCV-RNA assessment was performed either by Roche High-Pure-System/COBAS(®) TaqMan(®) v2.0 assay (low limit of quantification, LLOQ 15 IU/ml; Roche Diagnostics, Indianapolis, IN, USA) or by Abbott real time assay (LLOQ 12 IU/ml; Abbott Molecular Inc., Des Plaines, IL, USA).

Statistical analysis.

Data were expressed as counts and percentages for quantitative variables and as median and range for discrete variables. Significance of differences in the distribution of quantitative and qualitative variables were assessed with Student's t-test or Fisher's exact test as appropriate. All p-values were two-tailed and a level of 0.05 was considered statistically significant. Statistical analysis was performed with STATA (Stata Statistical Software: Release 7.0

Collage Station, TX: Stata Corporation). The SVR rate was calculated by an intention to treat (ITT) analysis.

RESULTS

Patients

We restricted the analysis to 31 out of 37 LT candidates who received bridge therapy, because 6 were add-on Daclatasvir or Simeprevir after transplant or received a liver graft from HCV positive donors and by consequence they prolonged post-transplant therapy. Twenty-six subjects were men (84%) and the median recipient age was 53 years (range 40-65). LT indication was HCC in 22 (71%) and decompensated cirrhosis in 9 (29%). HCV-genotype was 1 or 4 in 18 patients (58%), HCV-2 in 5 (16%) and HCV-3 in 8 (26%). At start of antiviral therapy median overall MELD and Child Pugh (CP) scores were 12 and 7, respectively, and HCV-RNA was 355.058 IU/ml (range 4860-3.358.164) **(Table 1).**

Virological and clinical assessment

At transplant, 23 patients received Tacrolimus and 8 Cyclosporine, 9 were added on Mycophenolate Mofetil (MMF) early after surgery; donor age was 60 years (range 14-84). Nineteen patients were still viremic with a median viral load of 58 IU/ml (range 12-2584), and 12 were HCV-RNA negative for a median of 9 days (10 with HCV-RNA undetectable and 2 detectable but <LLOQ). The median DAA treatment duration before transplant was 35 days (range 2-98). Twenty one out of 31 patients were treated for more than 28 days before transplant; 10 of them (48%), were still HCV-RNA positive at transplant and one developed HCV recurrence post-transplant.

Post-transplant, antiviral treatment was started in Intensive Care Unit (through the nasogastric tube) in the majority of transplant recipients but 13 patients (42%) transiently discontinued SOF/R: first day after surgery in 7; 2-4 days in 4 (glomerular filtration rate <30 ml/min) and 15 and 24 days in the remaining 2 recipients. The first of these last two patients (bar 6 from the Figure 1 top) affected by HCC (MELD-8, CP-5) and HCV genotype 3 was treated for 10 days before transplant and HCV-RNA level at surgery was 18 IU/mL. After transplant he experienced a graft and kidney dysfunction due to a bacterial infection and remained in the intensive care unit for 24 days without antiviral therapy. HCV-RNA became positive and fluctuated around the cut-off level of detection. SOF/R was restarted at day 25 post-surgery, HCV-RNA returned undetectable after 30 days and became persistently negative from the day 84. The second patient was affected by HCV genotype 1b and HCC (MELD-8, CP-5), (bar 13 from the Figure 1 top); he was treated for 32 days before transplant and HCV-RNA was 35 IU/mL at surgery. After transplant, he experienced an arrhythmia and was treated with iv amiodarone; SOF was stopped for 15 days. He restarted SOF at day 16 and became HCV-RNA negative after few days (Figure 1).

R was given post-transplant in 29 out of 31 patients at a median dosage of 600 mg/day (200-1000 mg/day). The median SOF/R treatment duration after transplant was 119 days (range 10-170 days). The median overall duration of SOF-treatment before and after transplant was 168 days (range 40-170 days).

One recipient, HCV genotype 4 and affected by HCC, still viremic at LT, showed HCV-RNA levels < LLOQ early post-LT but developed a virological rebound at week 4 and discontinued SOF/R; later-on the patient developed a cholestatic recurrent hepatitis C successfully treated at month 6 post-LT with 12 weeks of SOF/Ledipasvir/R; one recipient, HCV-RNA negative post-transplant, died at week 4 for sepsis and multi organ failure, and 29/31 SOF-treated recipients remained persistently HCV-free (94%) **(Table 2).** Thirty

recipients are alive (97%) after a median post-transplant follow-up of 18 months (range 13-25) and all of them are HCV-free **. Figure 1** shows the virological status during SOF-therapy before and after transplant in each studied patient.

Adverse events

Twelve patients experienced anemia before and/or after transplant: 7 (23%) required erythropoietin and 4 (13%) received blood transfusions; 12 (39%) patients experienced asthenia/fatigue/nausea or headache during therapy before or after transplant; neutropenia was transiently observed in 3 (10%) patients and in 2 cases was judged SOF-related ; 6 (19%) patients developed a transient episode of acute kidney injury early after surgery and 3 (10%) experienced paroxysmal atrial fibrillation treated in one of them with intravenous bolus of amiodarone and transient discontinuation of SOF and in the other two with beta-blockers. Three patients (10%), all treated with Cyclosporine monotherapy and HCV-free, showed a liver graft dysfunction with features of acute cellular rejection at histology, between 4 and 6 months after LT and were switched to Tacrolimus with recovery in 2 out of 3. The remaining patient showed a severe long-lasting liver dysfunction with cholestatic/hepatitic profile, requiring add on MMF and 2 cycles of intravenous steroid pulses with later on clinical-biochemical remission. One patient was re-transplanted during SOF treatment, 2 weeks after the first transplant, owing to an early allograft dysfunction; SOF was withdrawn but he remained persistently HCV-RNA-free thereafter. Another patient, HCV-free after surgery died at week 4 post-transplant for sepsis and multi organ failure.

DISCUSSION

DAA have rekindled the development of strategies to prevent HCV-reinfection after transplant who previously failed for the poor tolerability and efficacy of IFN-based regimens

in the transplant setting **[19, 20].** Using a SOF/R regimen up to the time of transplant, Curry et al **[9]** showed that 96% of patients remained HCV-free post-transplant, in case of HCV-RNA suppression for at least 4 weeks before transplant. On the contrary, HCV reinfection occurred in the large majority of those showing less than 4 weeks of HCV-RNA undetectability. The strong message arisen from this study was to treat patients on waiting list for an adequate period of time. However, a major limit is that the exact timing of liver transplant after listing is unknown at individual level. In our real life series, 31 cirrhotics treated by SOF/R on waiting list without an adequate HCV suppression at the transplant time, received a SOF-bridging therapy post-transplant for up to 6 months and by this approach the large majority of them remained HCV-free following transplant (SVR 94% by ITT). Therefore, by this strategy we reached the objective to prevent HCV reinfection in the subset of cirrhotic, at high risk of recurrence (<4 weeks of HCV-RNA negativity before LT) as suggested in the Curry's study **[9].** Noteworthy, this is the first cohort study reporting a SOF/R use in the immediate post-LT period, confirming that this regimen is well tolerated and effective as we previously described in a case report **[16, 17].** A similar policy was also reported in two studies using different DAA pre-transplant. The first **[11]** included 12 retransplanted recipient on SOF-therapy; 6/12 continued therapy after surgery achieving HCV eradication in 5 cases. The other was a SOF/Daclatasvir-based phase 2 study on 60 decompensated cirrhotics where 3 patients still viremic at LT, received a treatment extension for 12 week after LT and remained HCV-free during follow-up **[14]**. Most of our treated transplant candidates were patients with a low MELD score and HCC (71%), hence similar to those enrolled in Curry's study **[9]**, suggesting that a good liver function may favour the use of antiviral therapy before and after transplant. However, in our cohort a SOF-induced HCV eradication was achieved in both compensated and decompensated patients.

We acknowledge that our therapeutic strategy requires expert management and intensive monitoring of patients by the hepatologists and surgeons, we also realize that this strategy might be less appealing and more time consuming than universal treatment of HCV post-LT. Still we think that there are benefits associated with prevention of HCV recurrence that can provide a rationale for bridging therapy in HCV LT recipients. Indeed, our therapeutic strategy, which keeps patients HCV-free immediately following liver surgery, simplifies the management of the complications which can occur after LT (graft rejection, biliary complications, kidney impairment, cytomegalovirus and/or bacterial infections) **[21]**. Furthermore, HCV reinfection is also associated with worsening of extra-hepatic manifestations such as diabetes and kidney damage that together with immunosuppressive drugs toxicity , negatively affect the short and long-term outcome of HCV recipients **[22, 23]**. This is all the more relevant in areas such as ours where in the last decade, the median donor age increased up to 60 years in more than 50% of cases, leading to a more severe HCV recurrence **[24]**. We cannot exclude that using regimens with higher potency and improved barrier to resistance than SOF/R could further improve the efficacy, while allowing for shorter treatment duration before LT. This concept although not proven in listed liver transplant candidate, is indirectly supported by the two multinational trials in USA, Europe and Middle East, SOLAR-1 and SOLAR-2, and other clinical and real-life studies in Europa and USA confirming the high efficacy and safety of 12-24 weeks of the NS5A inhibitors plus SOF in cirrhotics with decompensated disease (Child B and C) **[4, 12-14, 25-26]**.

The alternative option of DAA treatment after transplant in HCV-reinfected recipients, is today also recommended since many DAA-regimens have been proved safe and effective post-transplant with SVR rates going up 90% according to viral genotype **[4, 12-15**]. However, we emphasize that both CNI toxicity and HCV itself can induce renal injury after transplant and even as many DAA regimens are available for genotype 1 and 4, no alternative

SOF-sparing regimens are available at the moment in the subgroup of HCV-genotype 3 recipients with a glomerular filtration rate of less than 30 ml/min. At present, the only option we can employ for these patients is a SOF-based regimen with an expert monitoring of kidney function as suggested by Saxena **[27].**

In summary, these preliminary data clearly indicate that bridging pre and post-transplant SOF/R dual therapy allowed us to prevent post-LT HCV recurrence in 94% of the patients, when administered selectively in case of anticipated waiting time for transplant and concomitant suboptimal virological response. We are aware that currently, SOF monotherapy is not more employed neither before or after transplant, but our series represent a proof of concept that SOF-based regimens can be safely employed during peri-transplant phase in order to avoid HCV graft reinfection in case of suboptimal viral suppression at LT. Besides confirmation from more robust studies, safety data among combination DAA regimens are also needed to fully endorse this approach in selected patients with anticipated graft availability, particularly knowing that highly effective and tolerable regimens will be available post-LT.

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Table 1: Demography of the listed patients at start of SOF-regimen

BEFORE TRANSPLANT	**Overall (N=31)**
Age, yrs*	53 (40-65)
Male**	26 (84%)
HCV genotype** 1 2 3 4	 13 (42%) 5 (16%) 8 (26%) 5 (16%)
Prior-interferon therapy**	18 (58%)
MELD*	12 (6-24)
CHILD-PUGH*	7 (5-12)
HCV-RNA, IU/mL*	355058 (4860-3358164)

*Median (range); ** N, %

Table 2: Features and outcome of listed patients treated by SOF-regimen at transplant time and after transplant

AT TRANSPLANT	**Overall (N=31)**
Donor Age, yrs*	60 (14-84)
MELD*	12 (7-30)
CHILD-PUGH*	7 (5-12)
SOF duration before LT, days*	35 (2-98)
Ribavirin dose, mg/die*	800 (200-1.200)
HCV-RNA undetectable HCV-RNA detectable <LLOQ	10 (32%) 2 (6%)
HCV-RNA positive	19 (61%)
HCV-RNA at LT, IU/mL*	58 (12-2584)
AFTER TRANSPLANT	
Immunosuppressive regimen -Tacrolimus -Cyclosporine	 23 (74%) 8 (26%)
Transient SOF-DC** Duration of SOF-DC, days*	13 (42%) 1 (1-24)
Treatment duration days	119 (10-170)
Ribavirin dose, mg/die*	600 (200-1000)
SVR-12 weeks (by ITT)**	29 (94%)
Biliary complication**	7 (23%)

Acute cellular rejection**	3(10%)
Re-transplant**	1 (3%)
Deaths**	1 (3%)

*Median (range); **N, %; Discontinuation =DC

Legend to figure

Figure 1. Virological status during SOF-therapy before and after transplant in each studied patient.

LLOQ, low limit of quantification; MOF, multi organ failure; SOF, sofosbuvir.

The open bars (HCV-RNA negative) include the period of treatment for each patient before and/or after transplant.

In 29/31 (93.5%) a post-treatment follow-up of 24 weeks was reached. In 2 transplant recipients SOF was discontinuated.

*1 died on-treatment, at week 4 post-transplant, for MOF; ** the other had a virological breakthrough 4 weeks post-transplant.

Virological status during SOF-therapy before and after transplant in each studied patient