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Sofosbuvir Compassionate Use Program for Patients With Severe Recurrent Hepatitis C After Liver Transplantation

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Recurrent hepatitis C virus (HCV) infection after liver transplantation (LT) is associated with accelerated progression of liver disease, frequently leading to graft loss and early death. Existing treatment options for severe recurrent HCV infection are limited by suboptimal efficacy, poor tolerability, and numerous drug interactions. We provided sofosbuvir (SOF) and ribavirin (RBV) on a compassionate-use basis to patients with severe recurrent hepatitis C, including those with fibrosing cholestatic hepatitis (FCH) and decompensated cirrhosis who had a life expectancy of 1 year or less. All patients were to receive 24-48 weeks of SOF plus RBV. Investigators could add pegylated interferon to the regimen at their discretion. Data from the first 104 patients who completed or prematurely discontinued treatment by January 1, 2014 are presented. Of the 104 patients analyzed, 52 had an early severe recurrence (diagnosed <12 months after LT) and 52 had cirrhosis (diagnosed >12 months after LT). Twelve patients who underwent retransplantation were excluded from our efficacy analysis. Of the 92 patients assessed, 54 (59%) achieved sustained virological response (SVR) at 12 weeks after the end of treatment, with a higher rate (73%; 35 of 48) in patients with early severe recurrence. Of the 103 patients assessed for clinical outcome, 59 (57%) reported clinical improvement at the last study visit, 23 (22%) were unchanged, 3 (3%) had a worsened clinical status, and 13 (13%) died. Overall, 123 serious adverse events (SAEs) occurred in 49 patients (47%). SAEs associated with hepatic decompensation were the most frequent, with 26 SAEs occurring in 19 patients (18%). *Conclusion*: SOF and RBV provide high rates of SVR in patients with severe recurrent HCV, including patients with early severe recurrence, FCH, and cirrhosis. (HEPATOLOGY 2015;61:1485-1494)

The leading indication for liver transplantation (LT) in North America and Western Europe is liver disease resulting from chronic infection with hepatitis C virus (HCV).[1,2] For patients with detectable serum levels of HCV RNA at time of transplantation, recurrence of HCV infection is immediate and universal.[3,4] Recurrent HCV infection after transplantation is generally aggressive, and progression to

Abbreviations: ACH, acute cholestatic hepatitis; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMF, bone marrow failure; CH, cholestatic hepatitis; CHC, chronic hepatitis C; CTP, Child-Turcotte-Pugh; DCV, daclatasvir; ESR, erythrocyte sedimentation rate; FCH, fibrosing cholestatic hepatitis; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; IFN, interferon; ILTS, International Liver Transplantation Society; INR, international normalized ratio; IQR, –; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NS, not significant; OLT, –; Peg-IFN, pegylated IFN; RBV, ribavirin; SAEs, serious adverse events; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; SVR4, SVR at 4 weeks; SVR12, SVR at 12 weeks.

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cirrhosis and decompensation is more rapid than in patients with HCV who have not been transplanted.[5,6] Patients at higher risk of graft loss include those who develop acute cholestatic hepatitis (ACH), including fibrosing cholestatic hepatitis (FCH) and those with early severe recurrence (significant fibrosis ≥F2 during the first 12 months after LT).[2,7] FCH, an especially severe type of recurrence, is infrequent (approximately 5% of hepatitis C recurrence after LT), but invariably leads to liver failure in a matter of months.[1,8] By the fifth postoperative year, one third of LT recipients with HCV infection have either died, experienced allograft loss, or developed cirrhosis.[9] Once decompensation occurs, prognosis is poor and survival is usually less than 1 year.[10]

Treatment options for patients with recurrent HCV after transplantation are limited. For patients with severe recurrence, interferon (IFN)-based regimens are difficult to tolerate and have disappointing efficacy with hard-to-manage drug interactions.[11] Triple-therapy regimens with protease inhibitors have been shown to improve efficacy, but exacerbate the side effects of treatment and are complicated to administer with immunosuppressive drugs.[12] Retransplantation, which is often the only remaining option, is constrained by an ongoing shortage of donor organs and is associated with long-term outcomes that are significantly worse than after primary transplantation.[13] Therefore, there is a great need for a more-potent as well as more-tolerable regimen without drug interactions for LT recipients with recurrent HCV.

Sofosbuvir (SOF) is a potent inhibitor of the HCV nonstructural 5B polymerase. SOF has been approved in combination with ribavirin (RBV), with or without pegylated IFN (Peg-IFN), for treatment of chronic hepatitis C (CHC) genotypes 1-6.[14-16] SOF has pangenotypic activity, a high genetic barrier to resistance, and a favorable safety profile. Most adverse reactions reported in clinical studies with SOF have been attributable to the concurrent use of Peg-IFN or RBV.[17] SOF plus RBV for up to 48 weeks is indicated for patients with HCV and hepatocellular carcinoma (HCC) awaiting LT.[14,18] In addition, 24 weeks of treatment with SOF and RBV resulted in a 70% sustained virological response (SVR) at 12 weeks after the end of treatment (SVR12) rate in LT recipients with advanced fibrosis or cirrhosis, the majority of whom were previous nonresponders to Peg-IFN treatment.[19]

Treatment guidelines recently issued jointly by the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the European Association for the Study of the Liver include recommendations for patients who develop recurrent HCV infection after LT: 12-24 weeks of SOF and simeprevir (SIM) or daclatasvir (DCV) with or without RBV for patients with HCV genotype 1 and 24 weeks of SOF and RBV for patients with HCV genotype 2 or 3.[20] There are case reports of the successful use of SOF and RBV and SOF and DCV in treating patients with FCH after LT.[21-23] To date, there have been no reports of SOF-based treatment in large, prospectively assembled cohorts of patients with FCH and/or severe rapid recurrence with cirrhosis.

We conducted a compassionate-use program in which SOF and RBV were provided to patients with aggressive recurrent HCV and no other treatment options. The aim of this report is to present the available efficacy and safety data for patients who completed or prematurely discontinued treatment before January 1, 2014.

Patients and Methods

Patients. To be eligible for this program, patients were required to have undergone LT and have a life expectancy of 1 year or less owing to hepatic failure if left untreated. This included patients who had ACH, severe hepatitis C recurrence, and end-stage liver disease. Individual requests from physicians that included patient medical history, laboratory values, clinical

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assessments, and liver biopsy reports were submitted to the sponsor for review and approval. SOF was supplied under approved individual emergency investigational new drug applications submitted according to local country regulations by the treating physicians.

Study Design. There was no planned number of patients or sites. All patients received 400 mg of SOF daily plus RBV (dosing as determined by the investigator) for 24 weeks. Treatment could be extended beyond 24 weeks (up to 48 weeks total) on a case-by-case basis, subject to approval by the sponsor. Peg-IFN could be added to SOF plus RBV at the discretion of the investigator, based on the patient's medical history and ability to tolerate the side effects of IFN treatment. The use of colony-stimulating agents and erythropoiesis-stimulating agents was allowed as clinically indicated. Investigators were requested to collect safety labs, including complete blood count, comprehensive profiles, and international normalized ratio (INR) values at screening, baseline, and monthly during treatment as well as at post-treatment week 4, 12, and 24. Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores were calculated according to local references and provided by the investigator at time points requested above. HCV-RNA testing was done at each site's local laboratory and reported by spreadsheets to the sponsor along with the clinical and laboratory data above. Drug resistance was not assessed.

Definitions. Patients who received SOF in this compassionate-use program were divided into two groups according to their pattern of HCV recurrence: (1) those with early aggressive recurrent hepatitis during the first year after transplantation and (2) those who had compensated or decompensated liver disease and were at least 1 year from transplantation.

Patients in the early aggressive recurrent hepatitis group included patients with FCH, cholestatic hepatitis (CH), and early severe recurrence.

For the definition of FCH, we used the following criteria set forth by the International Liver Transplantation Society (ILTS)[3]: (1) HCV recurrence must have occurred more than 1 month (but within 6 months) post-transplantation; (2) the patient must have serum bilirubin levels greater than 6 mg/dL; (3) characteristic histological state with ballooning of hepatocytes predominantly in the perivenular zone (not necrosis or fallout), periportal or pericellular/sinusoidal fibrosis, prominent cholestasis, paucity of inflammation, and variable degrees of cholangiolar proliferation without bile duct loss; (4) very high serum HCV-RNA levels; and (5) absence of surgical biliary complications (normal cholangiogram) and absence of evidence for hepatic artery thrombosis. Patients with CH were those who did not fulfill all the ILTS criteria for FCH, but had at least elevated levels of serum bilirubin, gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP), as well as a liver biopsy showing acute cholestatic injury. Patients with early severe recurrence were those with significant fibrosis ($\geq$F2) or increased hepatic venous pressure gradient ($\geq$6 mmHg) developed before the first year after LT.[2,7]

Patients in the second group included those with compensated cirrhosis (Metavir F4 by liver biopsy) or decompensated liver disease (ascites, hepatic encephalopathy [HE], variceal bleeding, or jaundice) at least 1 year from transplantation.

Classification of patients was performed on the basis of a chart review by two of the authors (X.F. and T.B.S.). Investigators were contacted if biopsy reports were not conclusive, laboratory data were missing, or if the narratives were not sufficiently clear to classify patients.

Study Assessments. Although no formal study visits were planned, investigators were asked to provide data on safety and efficacy to the sponsor on an ongoing basis, including laboratory assessments (HCV RNA, chemistry, hematology, MELD, and CTP scores) and narratives describing changes from baseline in patient status at treatment weeks 4, 12, 24, 36, and 48 as wells as post-treatment weeks 4, 12, and 24. Investigators were asked to assess clinical status at the last study visit. Improvement was defined as a significant decrease in HE, improvement or disappearance of ascites, or improvement in liver-related laboratory values as determined by the investigator. Improvement of ascites was defined as its disappearance or a significant reduction in the need for diuretic therapy or paracentesis. Improvement of HE was defined as its disappearance or a significant reduction in the number of episodes, as well as a significant reduction of therapy as determined by the investigator. Serious adverse events (SAEs) were to be reported by the investigator to the U.S. Food and Drug Administration or country-specific regulatory agency and the sponsor.

Statistical Analysis. No sample-size calculations were performed, and no inferential statistics or statistical comparisons were planned. The presentation of efficacy and safety data are descriptive. Categorical variables are depicted as n (%), and quantitative variables are shown as median (25-75th percentiles). Categorical variables were compared using the chi-square (χ^2) or Fischer's exact test, and quantitative variables were compared by the *t* test or McWhitnney's test (if

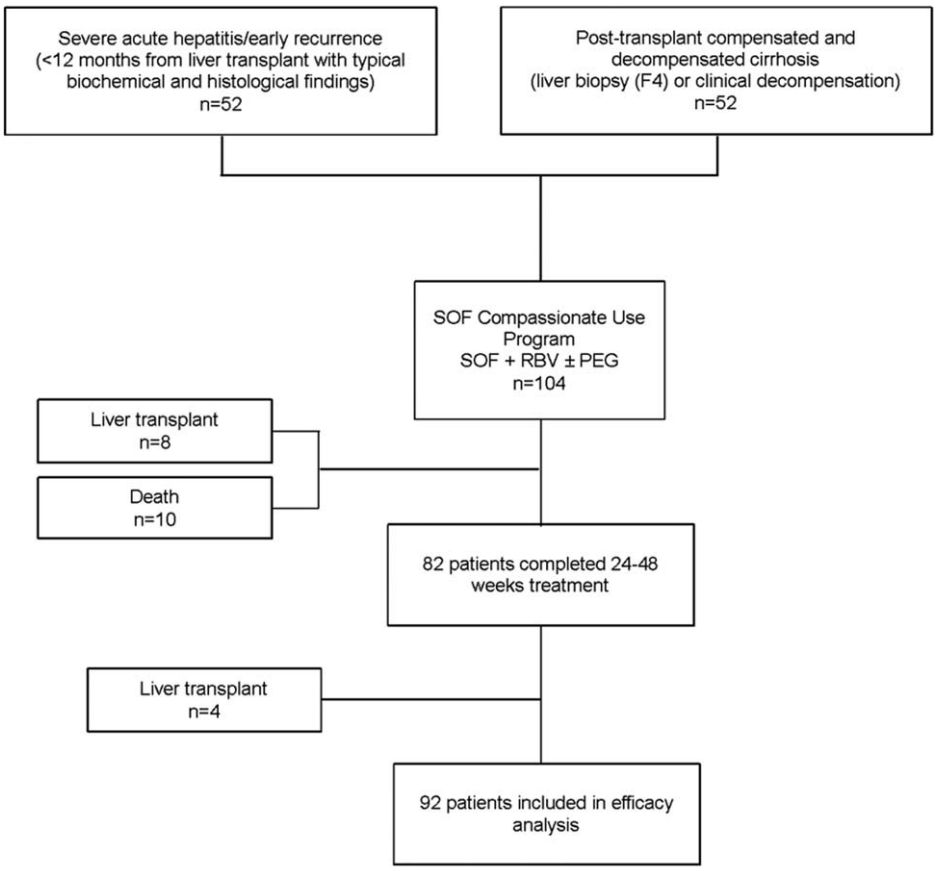

Fig. 1. Patient disposition.

unpaired data) or by the *t* test or Wilcoxon's test (if paired data), using SPSS software (v 18; SPSS, Inc., Chicago, IL).

Results

Patient Disposition

Patient disposition is depicted in Fig. 1. We include in the safety analysis all 104 patients who had completed or discontinued treatment by January 1, 2014. Of these 104 patients, 77% (80 of 104) received SOF and RBV and 23% (24 of 104) received SOF, RBV, and Peg-IFN. Of the 104 patients, 82 completed at least 24 weeks of treatment, 63 with SOF and RBV, and 19 with SOF, RBV, and Peg-IFN. Three of the eighty-two patients who completed treatment died, 4 underwent retransplantation after completing treatment (but preceding the 12-week follow-up visit), and 5 were lost to follow-up. Of the 22 patients who did not complete planned treatment (17 of whom were receiving SOF and RBV and 5 of whom were receiving SOF, RBV, and Peg-IFN), 8 underwent liver retransplantation, 10 died, 3 discontinued treatment because of adverse events (AEs), and 1 was not adherent to treatment and was a nonresponder. We include in the efficacy analysis 92 patients, excluding the 12 who underwent retransplantation before the SVR12 assessment.

Baseline Characteristics

Demographic and clinical characteristics of the 104 patients overall and by subgroups are provided in Table 1. Fifty-two patients were categorized as having early severe recurrent hepatitis in the first year after transplantation and 52 were classified as compensated/decompensated with cirrrhosis. Overall, most patients were male (73%) and most had HCV genotype 1 (82%). Median age was 55 (range, 16-76). Mean baseline bilirubin and INR were elevated, whereas mean albumin and platelet counts were below normal levels. Patients with severe recurrent HCV in the first year after transplantation had significantly higher mean total bilirubin, alanine aminotransferase/aspartate

Table 1. Baseline Demographic Characteristics of the Entire Cohort and by Time of Diagnosis (Early Recurrence vs. Established Cirrhosis)

Characteristic	Overall (N = 104)	Acute Hepatitis and Early Severe Recurrence (N = 52)	Compensated and Decompensated Cirrhosis (N = 52)
Age, years (IQR)	55 (51-60)	54 (50-60)	56 (51-64)
Male, n (%)	76 (73)	39 (75)	37 (71)
Genotype, n (%)			
1a	36 (35)	22 (42)	14 (27)
1b	49 (47)	23 (44)	26 (50)
2	1 (1)	1 (2)	0
3	7 (7)	1 (2)	6 (12)
4	7 (7)	5 (10)	2 (4)
>1	4 (4)	0	4 (8)
HCV RNA, $\log_{10}$ IU/mL (IQR)	6.2 (5.3-7.0)	6.7 (5.5-7.5)	5.8 (5.1-6.4)
Months from OLT (IQR)*	16.8 (18-54)	8.4 (4.8-12.7)	53.1 (33.1-92.1)
Bilirubin, mg/dL median (IQR)	3.1 (1.3-9.7)	4.7 (1.5-19.2)	1.9 (1.2-4.8)
Albumin, g/dL median (IQR)	3.1 (2.7-3.5)	3.1 (2.6-3.6)	3.1 (2.7-3.5)
INR median (IQR)	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.4 (1.2-1.6)
Platelet count $\times 10^3$/mL median (IQR)	75 (52-119)	91 (59.3-134.5)	69 (50.3-99.3)
ALT, U/L median (IQR)	71.0 (39.3-167.0)	102.0 (38.5-200.8)	60.0 (39.5-101.3)
AST, U/L median (IQR)	124.5 (70.8-210.5)	145.5 (93.5-339.0)	101.0 (62.3-180.0)
ALP, U/L median (IQR)	164.0 (117.5-263.3)	190.0 (124.5)	148.0 (362.5)
GGT, U/L median (IQR)	144.0 (64.0-426.5)	383.0 (121.0-915.5)	112.7 (45-148.0)
Hemoglobin, g/dL median (IQR)	10.9 (9.6-12.5)	10.9 (9.4-12.2)	11.0 (9.8-12.9)
Creatinine, mg/dL median (IQR)	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.4)
CTP (IQR)	8 (7-10)	N/A	8.0 (7-10)
MELD (IQR)	15 (11-21)	16 (10-22)	14 (11-19)
Antiviral regimens used			
SOF+RBV alone, n/N (%)	80/104 (77)	36/52 (69)	44/52 (85)
SOF+RBV+Peg-IFN, n/N (%)	24/104 (23)	16/52 (31)	8/52 (15)
Median duration of SOF, weeks (range)	24 (1-56)	24 (1 dose-48)	24 (1-56)
Median duration of Peg-IFN, weeks (range)	24 (3-26)	24 (3-26)	24 (6-24)

*Time from LT to diagnosis was used to characterize patients into groups. However, time of initiation of therapy was counted in the months from transplantation in this table.

Abbreviation: IQR, interquartile range.

aminotransferase (ALT/AST), ALP, and GGT levels than the patients with cirrhosis ($P < 0.05$ in all cases). Owing to the nature of this compassionate-use program, there was no collection of concomitant medications or immunosuppression.

Efficacy

Overall. The SVR12 rate, excluding patients who underwent retransplantation (n = 12), was 59% (54 of 92) (Table 2). Patients who received SOF-RBV had an SVR12 rate of 56% (39 of 70) and those receiving SOF-Peg-IFN-RBV had an SVR12 rate of 68% (15 of 22; $P = 0.3$).

Investigators were asked to assess the clinical status of their patients at the last study visit in relation to baseline for all who received at least 1 dose of SOF. Of the 103 patients with available data, 59 (57%) were categorized as having an improved clinical status, 23 (22%) had unchanged clinical status, and 21 (21%) had worsened clinical status or had died (Table 3; Fig. 2). Overall, liver function tests (including bilirubin and INR) improved significantly over time during therapy (Fig. 3).

Efficacy in Patients <12 Months Post-Transplantation. The SVR12 rate in patients with early severe recurrent hepatitis who did not undergo retransplantation was 73% (35 of 48). Of the 13 patients who did not achieve SVR12, 6 died, 4 relapsed, 2 were lost to follow-up, and 1 discontinued because of an SAE. Of the patients who received SOF+RBV and those that received SOF+RBV+IFN, 74% (25 of 34) and 71% (10 of 14), respectively, achieved SVR12. Median duration of SOF therapy was 24 weeks (range, a single dose to 48 weeks). RBV was required to be dosed with SOF, so, although use of RBV was not collected, the sponsor assumed that the median duration of RBV was the same as SOF. Among the 11 subjects given Peg-IFN, the median duration of Peg-IFN was 24 weeks (range, 3-26).

Among the 52 patients with early severe recurrent hepatitis, 36 (69%) were judged by investigators to have improved clinical status at the last study visit, 9 (17%) had unchanged clinical status, and 7 (13%) either worsened or died (Fig. 2).

Levels of total bilirubin, albumin, INR, and MELD over time for patients with early severe recurrent

Table 2. Response (HCV RNA <25 IU/mL) During and After Treatment

	Overall (N = 104)	Acute Hepatitis and Early Severe Recurrence (N = 52)	Compensated and Decompensated Cirrhosis (N = 52)
During treatment, % (n/n) %*			
At week 4	56/104 (54)	24/52 (46)	33/51 (65)
At week 12	82/104 (79)	42/50 (84)	40/49 (82)
At week 24	76/96 (73)	38/48 (79)	38/47 (81)
In post-treatment follow-up, n (%)			
At week 4 (SVR4)	62/93 (67)	38/48 (79)	24/46 (52)
At week 12 (SVR12)	54/92† (59)	35/48† (73)	19/44† (43)
Virological failure (%)			
On-treatment failure	0	0	0
Relapse	19/92 (21)	4/48 (8)	15/44 (34)
Lost to follow-up	2/92 (2)	2/48 (4)	0
Discontinuation because of SAE	3/92 (3)	1/48 (2)	2/44 (5)
Discontinuation because of nonadherence	1/92 (1)	0	1/44 (2)
Death	13/92 (14)	6/48 (13)	7/44 (16)

*HCV RNA <25 IU/mL response during treatment is in patients for whom HCV-RNA results are available.

†Twelve patients underwent LT during the study and were not included in the efficacy analysis; 4 with acute hepatitis and early severe recurrence and 8 with compensated and decompensated cirrhosis.

hepatitis are provided in Fig. 3A. Serum total bilirubin levels, which are a hallmark of severe cholestatic disease, decreased significantly from 4.7 to 0.7 g/dL (84% decline) from baseline to follow-up week 12. Albumin values increased from 3.1 to 4 g/dL whereas INR level remained unchanged. Overall median MELD scores decreased from 16 to 8 ($P = 0.001$).

Ten patients met the ILTS definition for FCH. Eight of the ten FCH patients cleared the virus and were HCV-RNA negative 12 weeks after the end of treatment and 2 underwent retransplantation. Of the 8 FCH patients who did not undergo retransplantation, 7 were judged to have improved clinically and 1 remained stable at the end of observation. Laboratory values improved dramatically in this group of patients: Median bilirubin values at baseline, at weeks 12 and 24 on treatment, and 12 weeks post-treatment were 10, 1.5, 0.86, and 0.9 mg/dL, respectively. The same figures for GGT were 690, 127, 55, and 30 IU/L, respectively, and for albumin 3, 3.3, 3.8, and 4.4 g/dL, respectively.

Efficacy in Patients >12 Months Post-LT. The SVR12 rate in the 44 patients with cirrhosis who did not undergo retransplantation was 43% (19 of 44). Of the 25 patients who did not achieve SVR12, 15 relapsed, 7 died, and 3 discontinued treatment prematurely (2 SAEs and 1 noncompliance). Of the patients who received SOF and RBV and those who received SOF, RBV, and Peg-IFN, 43% (16 of 37) and 43% (3 of 7) achieved SVR12, respectively. The median duration of SOF dosing was 24 weeks (range, 1 dose to 56 weeks). In the 8 subjects receiving Peg-IFN, median duration of IFN therapy was 24 weeks (range, 6-24).

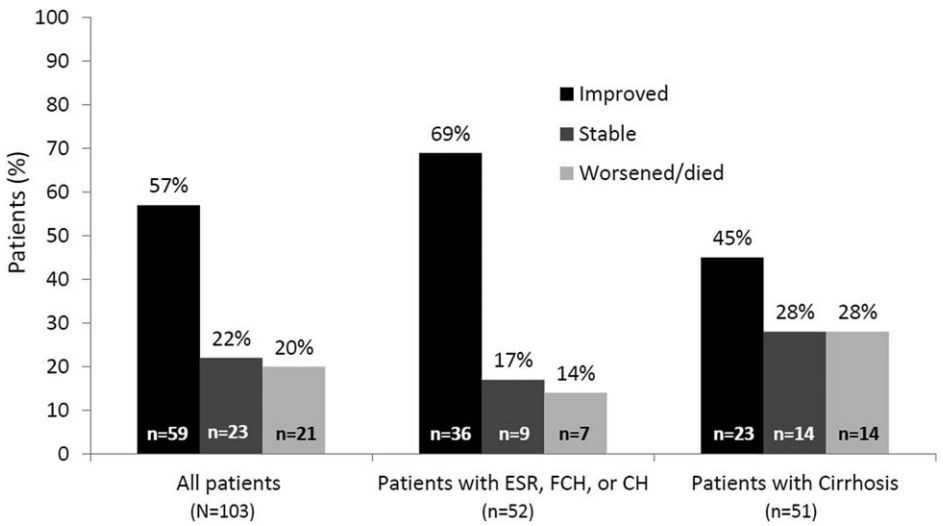

Fig. 2. Clinical outcomes in all patients and by diagnosis (early recurrence vs. established cirrhosis). Abbreviation: ESR, erythrocyte sedimentation rate.

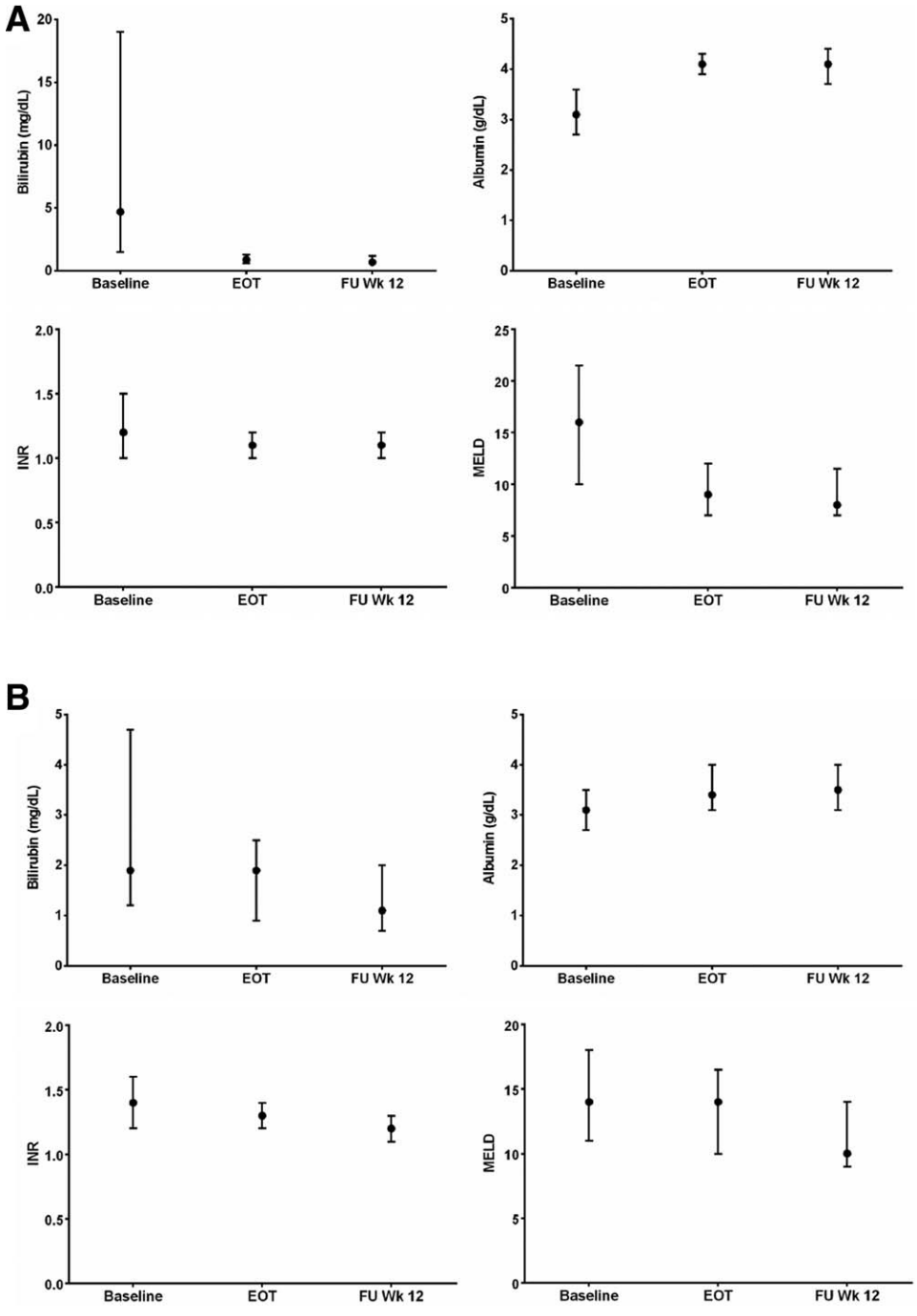

Fig. 3. Selected laboratory tests and scores over time. (A) Patients with acute hepatitis and early severe recurrence (n = 52). (B) Patients with compensated and decompensated cirrhosis (n = 52). Variables are depicted as median and 25–75 percentiles. Abbreviations: EOT, end of treatment; FU wk, follow-up week.

Of the 51 patients in whom investigators assessed clinical status at the last study visit, 23 (45%) had clinical improvement, 14 (27%) had unchanged clinical status from baseline, and 14 (27%) worsened or died.

Levels of total bilirubin, albumin, INR, and MELD over time are provided in Fig. 3. Between baseline and follow-up week 12, median total bilirubin values decreased from 2.0 to 1.1 g/dL (not significant; NS). Albumin values increased from 3.1 to 3.5 g/dL ($P = 0.042$), INR decreased from 1.4 to 1.2 (NS), and MELD scores decreased from a median of 14 to 10 (NS).

Outcomes in Patients Who Underwent Transplantation. Twelve patients enrolled in the program underwent LT, either after the completion of treatment (n = 4) or while on treatment (n = 8). Of the 4 patients who completed at least 24 weeks of treatment before transplantation (all of whom received SOF and RBV), 2 achieved SVR12 after transplantation (1 stopped

Table 3. Clinical Outcomes by Diagnostic Category

	Acute Hepatitis and Early Severe Recurrence (N = 52)	Compensated and Decompensated Cirrhosis (N = 51)
Improved (%)	36 (69)	23 (45)
Stable (%)	9 (17)	14 (27)
Worsened/died (%)	7 (13)	14 (27)

treatment at the time of transplantation with HCV RNA undetectable and 1 achieved SVR at 4 weeks [SVR4] before transplantation) and 2 had recurrent infection after transplantation (1 achieved SVR4 before transplantation and 1 underwent transplantation 10 days after the end of treatment with HCV RNA undetectable).

Of the 8 patients who were transplanted while on treatment, 6 achieved SVR12 after transplantation. One of the six patients received 10 weeks of treatment before transplantation and stopped treatment on the day of transplant; the other 5 continued treatment into the post-transplantation period. Duration of treatment before transplantation for these patients ranged from 1 to 8 weeks, and all 5 continued treatment post-transplantation for an average of 6 months. Five of these six patients received SOF and RBV, and 1 received SOF, Peg-IFN, and RBV. Of the 2 patients who were transplanted while on treatment and subsequently experienced post-transplantation recurrence of infection, 1 received treatment with SOF and RBV for 3 weeks before transplantation and 1 week after transplantation before stopping because of an AE. The second patient received 4 weeks of treatment with SOF, Peg-IFN, and RBV before transplantation and had recurrence of infection 2 weeks after transplantation.

Safety

Overall, 123 SAEs occurring in 49 patients (47%) were reported. Not surprisingly, given that this was a population of patients with progressive liver disease and a life expectancy <1 year, SAEs associated with hepatic decompensation were the most numerous, with 26 SAEs occurring in 19 patients (18%).

Infections and anemia were reported in 17 and 10 patients, respectively, including one report each of pancytopenia, autoimmune hemolytic anemia, aplastic anemia, and medullary aplasia/bone marrow failure (BMF). Dose modifications and interruptions were not captured as part of this program. Nine patients experienced renal failure/dysfunction (6 acute renal failure, 1 acute-on-chronic renal failure, 1 renal insufficiency, and 1 acute kidney infection).

Among the 24 patients who received Peg-IFN in addition to SOF and RBV, 5 (21%) developed infections that were classed as SAEs: 2 patients with ascites developed spontaneous bacterial peritonitis (1 resolved and 1 died), 1 patient developed a *Staphylococcus aureus* infection and died, 1 had sepsis of unknown origin, which resolved, and 1 developed cytomegalovirus (CMV) pneumonitis, which subsequently resolved.

For those 80 patients who did not receive Peg-IFN, 14 SAEs of infection in 13 patients (16%) were reported: 5 developed spontaneous bacterial peritonitis (all resolved), 3 developed sepsis (1 resolved and 2 died), 3 developed CMV infections (2 resolved and 1 died), 1 had pseudomembranous colitis (resolved), 1 tuberculosis (resolved), and 1 developed pleural empyema (died).

Six SAEs in 5 patients (5%) were considered related to study drug by the investigator: ascites, diabetes, neutropenia (2), hemophagocytic syndrome, and medullary aplasia/BMF. Eight SAEs led to early treatment discontinuation in 6 patients (6%); neutropenia (2), HCC, deep vein thrombosis, renal failure and sepsis, renal insufficiency, and subcutaneous infection of the hand. There were no SAE reports of calcineurin inhibitor toxicity or rejection.

There were 8 deaths (8%) during treatment or within 30 days of last dose (the 5 additional deaths occurred greater than 30 days after the cessation of treatment during the follow-up period), mainly related to progression of liver disease, severe infections or sepsis, pulmonary conditions, and renal failure.

Discussion

In this compassionate-use program in patients with severe hepatitis C recurrence after LT, including patients with FCH and decompensated cirrhosis, 24-48 weeks of treatment with SOF and RBV with and without Peg-IFN resulted in SVR12 in a majority of patients. This population of patients, who have generally exhausted available treatments and are expected to die in a matter of months, are in urgent need of new treatment options besides retransplantation, the benefits of which are generally short-lived without eradication of HCV. Our findings suggest that SOF plus RBV may provide a safe, effective salvage treatment for this population. Though there are ample data reporting the safety and efficacy of SOF-based antiviral therapy in patients with cirrhosis, the safety and efficacy in patients with liver failure and decompensated cirrhosis has not hitherto been reported on in any context. The results of this study are unique in many respects and have broad implications.

The most important observation in this study is that SOF-based antiviral therapy is broadly safe and substantially effective in patients with severe recurrence

of hepatitis C infection after LT. 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 transplantation—have somewhat distinct clinical characteristics, it was interesting to compare outcomes in these two groups of patients. Early severe recurrent hepatitis is often associated with rapid progression to death or graft loss unless HCV replication can be controlled or eliminated.[3] In our study, patients with early recurrent hepatitis were more likely to achieve SVR12 (73%) than those with cirrhosis (43%). This finding is somewhat surprising in light of the higher level of immunosuppression given to early LT recipients, compared to stable long-term LT recipients. Furthermore, previous studies have demonstrated the difficulty of administering IFN-based therapies to LT recipients early on after LT.[2,24] Interestingly, the kinetics and extent of viral suppression was similar at week 4 in the early recurrent and late recurrent patients in this study (Table 2). Moreover, a greater proportion of patients with early recurrent hepatitis showed clinical improvement with respect to measures of liver-related laboratory values, ascites, and HE than patients with decompensated cirrhosis (69% vs. 45%, respectively). These results suggest that early treatment of patients with recurrent HCV infection after transplantation may offer an advantage over waiting until a patient develops advanced fibrosis. Early fibrosis developing during the first months after transplantation might be more likely to regress than established cirrhosis. The pattern of fibrous tissue deposition at this early stage post-LT is quite different from that in patients with CHC, where portal fibrosis expands into the sinusoids. In patients with established cirrhosis, old fibrous septa contain high-density fibrillar collagens (I and III) and proteoglycans, as well as an increase in extracellular matrix cross-linking. The latter may indicate greater difficulty with respect to fibrosis regression.[25] Moreover, the presence of portal hypertension may also be relevant in fibrosis irreversibility, given that the latter is associated with an inflammatory state of the endothelium that activates hepatic stellate cells.[26] This may, in part, explain why hepatic function did not improve in some patients despite viral clearance, at least during the first months after SVR. It is possible that a longer follow-up might be necessary to observe an amelioration in liver function and clinical outcomes (liver decompensation episodes). Nevertheless, it is also possible that, at very late stages of cirrhosis, improvement of liver function will not occur. In support of this, the use of lamivudine rescue therapy in patients with decompensated HBV cirrhosis and high bilirubin and creatinine levels was associated with poor short-term outcomes.[27] Overall, liver function tests improved significantly in both groups of patients with multiple fold decreases in bilirubin in the early recurrent HCV group, increases in albumin, and decreases in MELD scores.

Although uncommon—occurring in less than 5% of patients with recurrent hepatitis C—FCH is a formidable clinical challenge in the early post-LT setting. Therapeutic options for this rapidly progressive and frequently fatal condition are needed. Several recent case studies have shown the feasibility of successful HCV treatment with protease inhibitor regimens, but the AEs associated with these combinations limit their use in this setting. Our findings suggest that treatment of this very aggressive form of hepatitis C with SOF and RBV may prove life-saving, and that full recovery of liver function is possible even in patients with very advanced liver disease. The SVR12 rate of 80% in our small cohort of patients with FCH is considerably higher than that reported in previous studies using IFN-based therapies.[28]

Although SOF-based therapy was well tolerated in these very sick patients, including those with MELD scores as high as 43 and for whom compassionate-use approval meant that they had no other standard therapeutic options, a number of patients died (13%). The majority of patients who died succumbed to disease progression and resulting complications. None of the deaths were attributed to treatment.

The number of patients treated in this compassionate-use protocol is not sufficiently large to settle a number of important questions, such as the role of Peg-IFN, differences in outcome by HCV genotype, optimal duration of SOF, and factors predictive of treatment success or failure. Moreover, the patient subgroups were not prespecified at the outset. The approval of new direct-acting antiviral therapies is likely in the short and medium term. The impending availability of newer agents does not diminish the importance of this study, particularly given that SOF will likely remain a cornerstone therapy for many patients.

In conclusion, our findings suggest that a 24- to 48-week course of SOF and RBV may be a promising rescue therapy for LT recipients with severe and refractory recurrent HCV. Further studies in this population involving SOF in combination with other antiviral agents, including SIM, DCV, and ledipasvir are ongoing.

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