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12 Weeks of a Ribavirin-Free Sofosbuvir and Nonstructural Protein 5A Inhibitor Regimen Is Enough to Treat Recurrence of Hepatitis C After Liver Transplantation

Pauline Houssel-Debry,[1] Audrey Coilly,[2-5] Claire Fougerou-Leurent,[6,7] Caroline Jezequel,[1] Christophe Duvoux,[8] Victor De Ledinghen,[9] Sylvie Radenne,[10] Nassim Kamar,[11] Vincent Leroy,[12] Vincent Di Martino,[13] Louis D'Alteroche,[14] Valérie Canva,[15] Filomena Conti,[16] Jerome Dumortier,[17] Hélène Montialoux,[18] Pascal Lebray,[16] Danielle Botta-Fridlund,[19] Albert Tran,[20] Christophe Moreno,[21] Christine Silvain,[22] Camille Besch,[23] Philippe Perre,[24] Claire Francoz,[25] Armando Abergel,[26] François Habersetzer,[27] Maryline Debette-Gratien,[28] Carole Cagnot,[29] Alpha Diallo,[29] Stéphane Chevaliez,[30] Emilie Rossignol,[6,7] Aurélie Veislinger,[6,7] Jean-Charles Duclos-Vallee,[2-5] Georges-Philippe Pageaux,[31] and the ANRS CO23 CUPILT study group

Sofosbuvir (SOF) combined with nonstructural protein 5A (NS5A) inhibitors has demonstrated its efficacy in treating a recurrence of hepatitis C virus (HCV) after liver transplantation (LT). However, the duration of treatment and need for ribavirin (RBV) remain unclear in this population. Our aim was to determine whether LT recipients could be treated with an SOF + NS5A inhibitor-based regimen without RBV for 12 weeks post-LT. Between October 2013 and December 2015, 699 LT recipients experiencing an HCV recurrence were enrolled in the multicenter ANRS CO23 CUPILT cohort. We selected patients receiving SOF and NS5A inhibitor ± RBV and followed for at least 12 weeks after treatment discontinuation. The primary efficacy endpoint was a sustained virological response 12 weeks after the end of treatment (SVR12). Among these 699 patients, 512 fulfilled the inclusion criteria. Their main characteristics were: 70.1% genotype 1, 18.2% genotype 3, 21.1% cirrhosis, and 34.4% previously treated patients. We identified four groups of patients according to their treatment and duration: SOF + NS5A without RBV for 12 (156 patients) or 24 (239 patients) weeks; SOF + NS5A + RBV for 12 (47 patients) or 24 (70 patients) weeks. SVR12 values reached 94.9%, 97.9%, 95.7%, and 92.9%, respectively ($P = 0.14$). Only 20 patients experienced a treatment failure. Under multivariate analysis, factors such as fibrosis stage, previous treatment, HCV genotype, and baseline HCV viral load did not influence SVR12 rates in the four groups ($P = 0.21$). Hematological adverse events (AEs) were more common in the RBV group: anemia ($P < 0.0001$) and blood transfusion ($P = 0.0001$). *Conclusion:* SOF + NS5A inhibitors without RBV for 12 weeks constituted reliable therapy for recurrent HCV post-LT with an excellent SVR12 whatever the fibrosis stage, HCV genotype, and previous HCV treatment. (Hepatology 2018; 68:1277-1287).

Since the introduction of interferon (IFN)-free regimens, and particularly second-generation direct-acting antiviral agents (DAAs), treatment of hepatitis C virus (HCV) recurrence after liver transplantation (LT) has improved dramatically.[1,2] Several sofosbuvir (SOF)-based regimens have demonstrated their excellent efficacy and safety in treating post-LT HCV recurrence. In particular,

Abbreviations: AE, adverse events; CTP, Child-Turcotte-Pugh; DAAs, direct-acting antiviral agents; DCV, daclatasvir; EPO, erythropoietin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intention to treat; LDV, ledipasvir; LLOQ, lower limit of quantification; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NS5A, nonstructural protein 5A; PP, per protocol; RBV, ribavirin; SAEs, serious adverse events; SOF, sofosbuvir; SVR12, sustained virological response 12 weeks after the end of treatment; VF, virological failure; W, week.

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combining SOF with the nonstructural protein 5A (NS5A) inhibitors, ledipasvir (LDV) or daclatasvir (DCV), has shown remarkable efficacy post-LT.[3-7] The need for ribavirin (RBV) to achieve successful treatment post-LT has also been studied.[8-10] The conclusion of these studies was that SOF/NS5A without an RBV regimen displayed broadly similar efficacy to SOF/NS5A with RBV in the LT setting. However, these studies focused either on the impact of RBV-free treatment or on that of the duration of treatment post-LT. As a result, questions regarding both the use or not of RBV, and the duration of treatment with an RBV-free regimen, were still unresolved.

Before the DAA era, eradication of HCV post-LT proved difficult because of previous treatments and previous failures, fibrosis stage, and immunosuppressive therapy.[11] RBV combination regimens for 24 weeks were often proposed and even considered to be the reference HCV treatment in this so-called difficult-to-treat population. However, the use of RBV can be complex in LT recipients. Anemia is its principal adverse effect and is common because of the associated treatments required post-LT (antiviral agents, antibiotics, and immunosuppressive therapy such as mycophenolate). RBV is often tapered or discontinued in order to enhance safety and treatment adherence.[12]

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ARTICLE INFORMATION:

From the [1]Hepatology and Liver Transplant Unit, Pontchaillou University Hospital, Rennes, France; [2]Hepatobiliary Center, AP-HP Paul Brousse Hospital, Villejuif, France; [3]Paris Sud University, Paris Sud Saclay University, UMR-S 1193, Villejuif, France; [4]INSERM, Unité 1193, Villejuif, France; [5]DHU Hepatinov, Villejuif, France; [6]Pharmacology Unit, CHU Rennes, Rennes, France; [7]INSERM, CIC 1414 Clinical Investigation Centre, Rennes, France; [8]Hepatology Unit, Henri Mondor Hospital, AP-HP, Créteil, France; [9]Hepatogastroenterology Unit, Haut Leveque Hospital, Bordeaux, France; [10]Hepatology Unit, HCL, Hôpital de la Croix-Rousse, Lyon, France; [11]Nephrology and Organ Transplantation Unit, CHU Rangueil, INSERM U1043, IFR-BMT, Paul Sabatier University, Toulouse, France; [12]Hepato-Gastroenterolgy Unit, Pôle Digidune, CHU Grenoble, Grenoble, France; [13]Hepatology Unit, CHRU Jean Minjoz Franche Comté University, Besançon, France; [14]Hepatogastroenterology Unit, CHU Tours, Tours, France; [15]CHRU Lille, Hepatology Unit, Claude Huriez Hospital, CHRU Lille, Lille, France; [16]Hepatology and Liver Transplant Unit, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [17]Liver Transplant Unit, Digestive Diseases Federation, Edouard Herriot Hospital, Hospices Civils de Lyon Université Claude Bernard Lyon 1, Lyon, France; [18]Hepatology Unit, CHU Rouen, Charles Nicolle Hospital, Rouen, France; [19]Hepatogastroenterology Unit, CHU Timone, Marseille, France; [20]Hepatogastroenterology Unit, Nice University Hospital, INSERM, U1065, Equipe 8, Nice Sophia Antipolis University, Faculty of Medicine, Nice, Cedex 2, Nice, France; [21]Hepatogastroenterology Unit, CUB Hôpital Erasme, Brussels University, Bruxelles, Belgique; [22]Hepatogastroenterology Unit, CHU Poitiers, Poitiers, France; [23]Liver Transplant and Digestive Surgery Unit, Strasbourg University, Strasbourg, France; [24]Infectious Diseases Unit, CHD Vendée, La Roche sur Yon, Strasbourg, France; [25]Hepatology Unit, Beaujon Hospita, Assistance Publique-Hôpitaux de Paris, Clichy, France; [26]Hepatogastroenterology Unit, CHU Estaing Clermont-Ferrand, Clermont-Ferrand, France; [27]Universitary Hospitals of Strasbourg, Inserm U 1110, LabEx HepSYS, Strasbourg University, Strasbourg, France; [28]Hepatogastroenterology Unit, CHU Limoges, Limoges, France; [29]Unité de recherche Clinique et Fondamentale sur les Hépatites Virales, ANRS (France REcherche Nord&sud Sidahiv Hépatites), Paris, France; [30]Virology Unit, French National Reference Center for Viral Hepatitis B, C and delta French National Reference Center for Viral Hepatitis B, C and delta, Hôpital Henri Mondor, Université Paris 12, Paris, France; [31]Liver transplant and Hepatogastroenterology Unit, CHU Saint-Eloi, Montpellier University, Montpellier, France.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Pauline Houssel-Debry, M.D.
Hepatology and Liver Transplant Unit
Pontchaillou University Hospital
Rue Henri Le Guilloux
35000 Rennes, France
E-mail: pauline.houssel-debry@chu-rennes.fr
Tel: +00 33 2 99 28 96 54

However, with second-generation DAAs, these practices now need to be re-evaluated.

We report here on our multicenter experience, which included a large number of patients who received SOF and NS5A inhibitor combination therapy, with or without RBV, for 12 or 24 weeks to treat a recurrence of HCV post-LT. The primary aim of this study was to determine which patients could be treated with SOF + NS5A inhibitor-based regimens without RBV for 12 weeks post-LT.

Patients and Methods

STUDY DESIGN AND PATIENTS

ANRS C023 CUPILT is a multicenter, prospective cohort that is being implemented in 25 French and Belgian LT centers (ClinicalTrials.gov number: NCT01944527). It is being funded and sponsored by ANRS (France REcherche Nord&Sud Sida-hiv Hépatites). To be included in the present study, patients had to have undergone an LT, presented with an HCV recurrence whatever the stage of fibrosis, and been treated with new-generation DAAs. All patients gave their written informed consent. The principal exclusion criteria were an age younger than 18 years and pregnancy.

Between October 2013 and December 2015, 699 liver recipients were enrolled in the present study, from whom we selected those receiving both SOF and NS5A inhibitors, with or without RBV, who had been followed for at least 12 weeks after treatment discontinuation. Patients were excluded if they had been diagnosed with fibrosing cholestatic hepatitis (FCH).[13]

At enrollment, fibrosis stage was established from a histological assessment (according to the METAVIR scoring system) and/or liver elastometry (such as F3 ≥9.5 kilopascals [kPa] and F4 ≥14.5 kPa). The protocol was implemented in accord with the Declaration of Helsinki and French laws on biomedical research and was approved by the "South Mediterranean Ethics Committee" (France).

Doses of medications and durations of treatment were at the discretion of each investigator. Patients received SOF and DCV or LDV at once-daily doses of 400 mg and 60 or 90 mg, respectively. When used, the dose of RBV was adjusted according to body weight, potential RBV-related hematological toxicity, and renal function in LT recipients. Treatment duration was initially planned for 12 or 24 weeks, but the investigators were allowed to extend this period if they deemed this clinically necessary. The therapeutic regimen studied was that planned at baseline.

EFFICACY ASSESSMENTS

For this study, plasma HCV-RNA levels were quantified using the Abbott Real Time HCV PCR assay (lower limit of quantification [LLOQ] of 12 IU/mL; Abbott Diagnostics, Lake Forest, IL), COBAS AmpliPrep or COBAS TaqMan (LLOQ of 15 IU/mL; Roche Molecular Systems, Pleasanton, CA). HCV RNA was monitored at baseline, during scheduled visits throughout treatment (1, 2, 3, 4, 6, 8, and 12 and, if applicable, 16, 20 and 24 weeks [W]), and then at 4, 12, 24, and 48 W after the completion of treatment. The primary efficacy endpoint was a sustained virological response 12 weeks after the end of treatment (SVR12). The intention-to-treat (ITT) population for SVR12 was defined as the group of patients who fulfilled the inclusion criteria and started treatment for HCV. The per-protocol (PP) population contained patients who completed their planned treatment. We identified four groups of patients according to their treatment regimens and duration: SOF+ NS5A ± RBV for 12 or 24 weeks. Virological failures (VFs) were also reported. Viral breakthrough and relapse were defined as plasma HCV-RNA levels higher than the LLOQ after achieving a level lower than the LLOQ, during treatment and after the end of treatment, respectively. Genotypic resistance was assessed before and after treatment in those who failed to achieve an SVR12. Sequence analysis was based on the population sequencing of three viral regions, including the NS3 protease (target of protease inhibitors), NS5A protein (target of NS5A inhibitors), and NS5B polymerase (target of SOF) coding regions. Briefly, HCV RNA was extracted using the QIASymphony DSP Virus/Pathogen kit on a QIASymphony device (QIAGEN GmbH, Hilden, Germany), according to the manufacturer's instructions. Complementary DNA synthesis was performed with the OneStep RT-PCR kit (QIAGEN GmbH) using primer sets adapted to the viral regions targeted. Nested PCR was then performed, if needed, with primers specific to genotypes 1a, 1b, 2, or 4. PCR products were purified with Amicon Ultra-0.5 mL Centrifugal Filters (EMD Millipore, Darmstadt, Germany) and sequenced with the BigDye Terminator Cycle Sequencing Kit v3.1 on an ABI Prism 3730 DNA Analyzer (Applied Biosystems, Foster City, CA).

SAFETY

The following adverse events (AEs) were recorded if they occurred after the initiation of therapy and up to 48 weeks after the end of treatment (follow-up): serious adverse events (SAEs) as defined in Supporting Appendix 1, clinical and laboratory grades 3 or 4 AEs (assessed using the INSERM-ANRS scale to score for the severity of AEs, v6 dated 9 September 2003, given in Supporting Appendix 2), and any grades of AEs involving neutrophils, platelets, prothrombin time, bilirubin, creatinine, hemoglobin, or infections.

Any decisions to reduce or discontinue RBV, use erythropoietin (EPO), and implement blood transfusions were at the investigator's discretion.

The investigators were encouraged to manage all AEs according to the guidelines issued by the French Association for the Study of the Liver (AFEF).

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS (Version 9.4; SAS Institute Inc., Cary, NC) and R software (Version 3.3.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed using means and SDs, and categorical variables were expressed by the number of patients and percentages. Comparisons between the four groups, as reflected by the duration of therapy and RBV use, were performed using one-way analysis of variance for normally distributed variables, the Kruskall-Wallis test for non-normally distributed variables, and the chi-square test or Fisher's exact test for categorical variables. Clinically relevant variables influencing failure at posttreatment week 12 were introduced into a multivariate model using logistic regression: fibrosis stage, genotype, HCV viral load at baseline, and previous treatment. The results are expressed as odds ratios with a 95% confidence interval. A P value <0.05 was considered to be statistically significant.

Results

CHARACTERISTICS OF PATIENTS

Five hundred twelve LT recipients treated with SOF plus NS5A inhibitors, with or without RBV, were selected for the present study between October 2013 and December 2015 (Fig. 1). Data were missing on 6 patients, including their HCV genotype and response to first-line treatment for HCV after LT. Six patients died before SVR12, the causes being: hyperosmolar coma (diabetes mellitus), lung carcinoma, acute myeloblastic leukemia, pancreatic cancer, metastatic hepatocellular carcinoma (HCC), and liver failure in a patient with cirrhosis with a Model

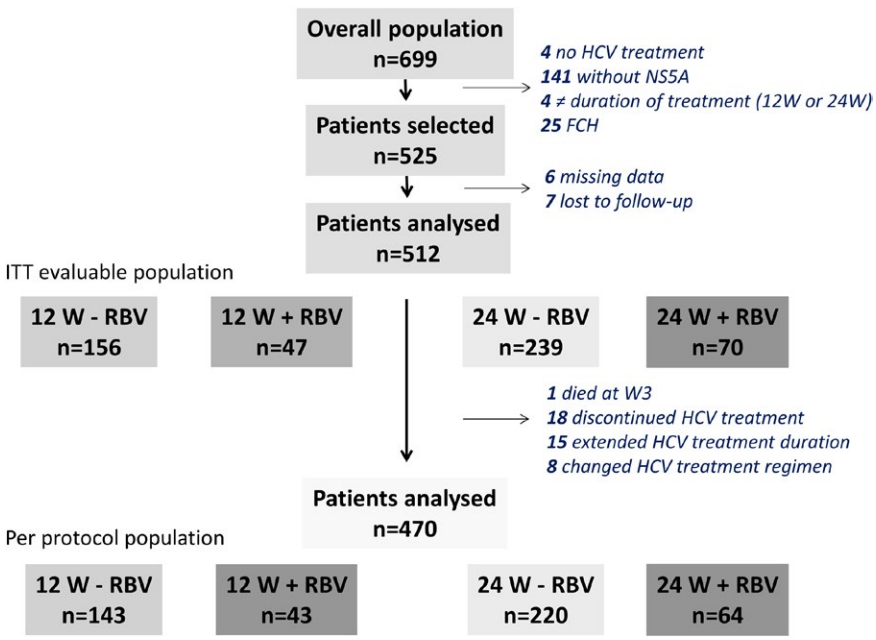

FIG. 1. Patient selection and therapeutic regimens.

for End-Stage Liver Disease (MELD) score of 22 at baseline. No relationship between treatment initiation and these events could be determined. PP data were available for 470 patients. Two hundred three patients were treated for 12 weeks (156 (30.5%) without RBV and 47 (9.2%) with RBV) and 309 patients were treated for 24 weeks (239 (46.7%) without RBV and 70 (13.7%) with RBV). According to the NS5A inhibitor regimen, 335 patients received DCV and 179 received LDV. In the RBV group, the mean baseline RBV dosage was 770 ± 247 mg/day. Baseline characteristics of these patients are presented in Table 1. There was a majority of male patients (77.1%), with a mean age of 60.3 ± 8.6 years. The principal indication

TABLE 1. Baseline Characteristics of the Study Population (ITT Population)

	Overall Population (n = 512)	12 W – RBV (n = 156)	12 W + RBV (n = 47)	24 W – RBV (n = 239)	24 W + RBV (n = 70)	*P* Value
Sex (M), n (%)	395 (77.1)	120 (76.9)	39 (83.0)	179 (74.9)	57 (81.4)	0.5075
Age (years)	60.3 ± 8.6	60.3 ± 8.4	62.6 ± 8.5	60.3 ± 9.1	58.5 ± 7.1	0.0883
LT indication, n (%)						0.1039
Cirrhosis	221 (43.2)	77 (49.4)	16 (34.0)	106 (44.4)	22 (31.4)	
HCC	252 (49.2)	73 (46.8)	27 (57.4)	112 (46.9)	40 (57.1)	
Retransplantation	38 (7.4)	6 (3.8)	4 (8.5)	20 (8.4)	8 (11.4)	
MELD score at LT	17 ± 8 [147]	18 ± 9 [50]	15 ± 9 [10]	17 ± 8 [79]	16 ± 7 [8]	0.0427
Time post-LT (months)	85.0 ± 72.1	92.7 ± 72.3	85.3 ± 74.2	86.1 ± 73.6	63.7 ± 61.5	0.0121
Response to previous HCV treatment, n (%)						0.1563
No treatment	336 (65.6)	117 (75.0)	33 (70.2)	148 (61.9)	38 (54.3)	
Nonresponders	77 (15.0)	17 (10.9)	5 (10.6)	40 (16.7)	15 (21.4)	
Breakthrough/relapse	64 (12.5)	13 (8.3)	6 (12.8)	34 (14.2)	11 (15.7)	
Intolerance	35 (6.8)	9 (5.8)	3 (6.4)	17 (7.1)	6 (8.6)	
HCV genotype, n (%)						0.0668
1	359 (70.1)	116 (74.4)	32 (68.1)	164 (68.6)	47 (67.1)	
2	7 (1.4)	2 (1.3)	1 (2.1)	4 (1.7)	0 (0.0)	
3	93 (18.2)	18 (11.5)	11 (23.4)	44 (18.4)	20 (28.6)	
4	50 (9.8)	19 (12.2)	2 (4.3)	26 (10.9)	3 (4.3)	
5	3 (0.6)	1 (0.6)	1 (2.1)	1 (0.4)	0 (0.0)	
HCV viral load (logIU/mL)	6.28 ± 0.74	6.27 ± 0.81	6.13 ± 0.76	6.26 ± 0.70	6.46 ± 0.62	0.0924
Fibrosis stage, n (%)						< 0.0001
F0-F2	326 (63.7)	123 (78.8)	35 (74.5)	131 (54.8)	37 (52.9)	
F3	78 (15.2)	11 (7.1)	3 (6.4)	51 (21.3)	13 (18.6)	
F4	108 (21.1)[16]	22 (14.1)[1]	9 (19.1)[3]	57 (23.8)[7]	20 (28.6)[5]	
Baseline Child class, n (%)						0.0046
Class A (5-6 points)	66 (71.7)	21 (100.0)	4 (66.7)	31 (62.0)	10 (66.7)	
Class B (7-9 points)	23 (25.0)	0 (0.0)	1 (16.7)	17 (34.0)	5 (33.3)	
Class C (10-15 points)	3 (3.3)[61]	0 (0.0)[21]	1 (16.7)[7]	2 (4.0)[29]	0 (0.0)[4]	
Baseline MELD class, n (%)						0.5183
6-10	241 (53.4)	73 (54.1)	26 (65.0)	108 (51.4)	34 (51.5)	
10-15	149 (33.0)	49 (36.3)	11 (27.5)	68 (32.4)	21 (31.8)	
15-20	36 (8.0)	5 (3.7)	2 (5.0)	21 (10.0)	8 (12.1)	
20-25	19 (4.2)	4 (3.0)	1 (2.5)	11 (5.2)	3 (4.5)	
25-30	4 (0.9)	3 (2.2)	0 (0.0)	1 (0.5)	0 (0.0)	
≥30	2 (0.4)	1 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)	
Creatinine clearance MDRD (mL/min)	69.5 ± 29.4 [2]	67.8 ± 31.4	72.7 ± 27.3 [1]	69.2 ± 29.4	71.8 ± 26.1 [1]	0.6749
Hemoglobin (g/dL)	13.4 ± 1.9	13.5 ± 1.8	13.8 ± 1.9	13.2 ± 2.0	13.7 ± 1.7	0.1061

Continuous variables are expressed as a mean ± SD. n: number of missing data.
Abbreviations: M, male; n, number; MDRD, Modification of the Diet in Renal Disease.

for LT was HCC (49.2%). Most patients were infected with HCV genotype 1 (n = 359; 70.1%), mainly of the 1b type (n = 203; 39.6%), and 18.2% were genotype 3. Three hundred thirty-six patients (65.6%) were treatment-naïve, and when treated most of these patients were nonresponders (15.0%). The mean time elapsing post-LT was 85.0 ± 72.1 months. One hundred eight patients (21.1%) suffered from cirrhosis on the graft. In this population, the mean MELD score was 10 ± 4 and 61 patients had a MELD score >15 at initiation of the DAA regimen. Twenty-six patients (28.3%) had a Child-Turcotte-Pugh (CTP) score higher than B7 cirrhosis. Twenty-three patients presented with ascites at the start of DAA treatment, and 1 patient had encephalopathy. Fifty-six patients with cirrhosis (51.9%) had already been treated post-LT, and 25 of them (23.1%) were nonresponders. The majority of patients with cirrhosis (71.3%) received 24 weeks of the DAA regimen, and 29 (26.9%) were treated with RBV (20 patients for 24W and 9 for 12W). However, the 6 patients with a MELD score >25 received an RBV-free regimen for 12 weeks (4 patients) or 24 weeks (2 patients).

TREATMENT EFFICACY

Regarding the primary endpoint, 492 of 512 patients (96.1%) achieved an SVR at posttreatment W12. According to the four groups of patients, SVR12 levels were 94.9% (12W without RBV), 97.9% (24W without RBV), 95.7% (12W + RBV), and 92.9% (24W + RBV), respectively (P = 0.14). SVR12 reached 95.7% in the severe fibrosis group (98.7% in F3 and 93.5% in F4). In the group with cirrhosis, 63 of 66 patients (95.5%) with CTP A cirrhosis, 21 of 23 (91.3%) with CTP B, and 1 of 3 (33.3%) with CTP C achieved an SVR12. Response rates for SVR12 reached 95.7% in HCV genotype 3 patients and 94.8% in the nonresponder group of patients (Fig. 2). Characteristics of the 20 patients who did not achieve an SVR12 are presented in Table 2. Of them, the majority had no severe fibrosis at baseline (12 patients with F0-F2 fibrosis stage). Four patients were suffering from genotype 3 HCV infection. Eleven patients had not previously been treated post-LT. Six patients died before SVR12, and no relationship between treatment initiation and these events could be determined. Most of these 20 patients received the treatment for the planned duration from baseline. Retrospectively, we investigated their resistance mutations at both baseline and after the failure. Four patients had NS3 and/or NS5A resistance at baseline. At the time of failure, resistance mutations were determined in 7 patients. Eight patients were retreated after the failure, 1 patient died (HCC), and 5 are awaiting a new treatment. In the retreated group, 4

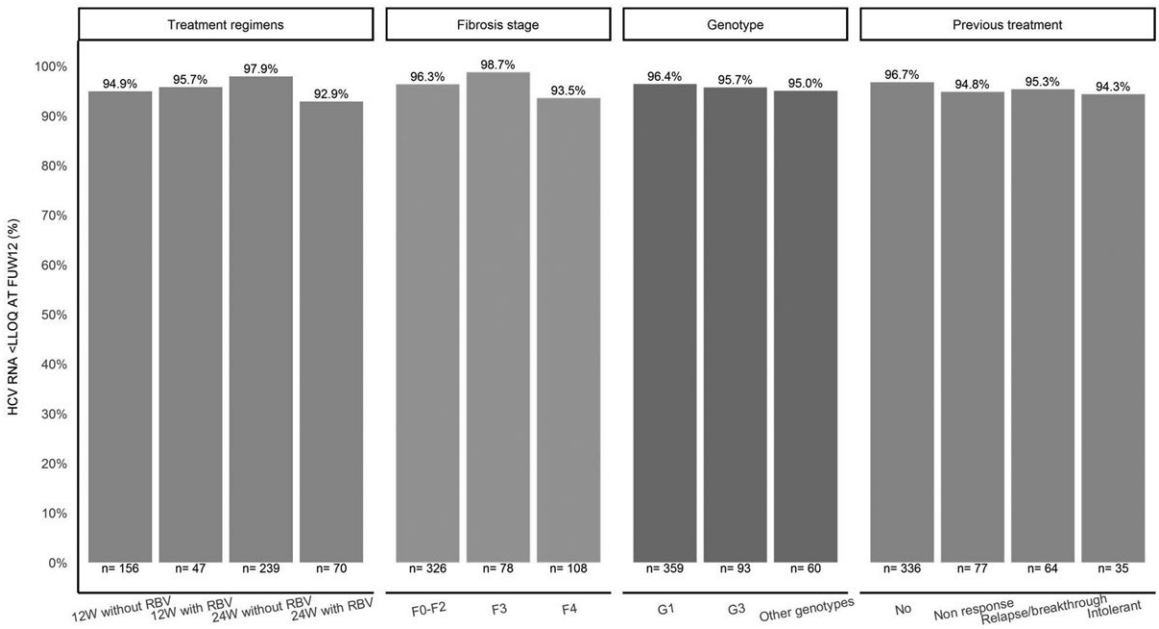

FIG. 2. SVR12 rates as a function of treatment regimen, fibrosis stage, genotype, and previous treatment (ITT population). Abbreviation: FUW12, follow-up week 12.

TABLE 2. Characteristics of patients experiencing a treatment failure and resistance profiles (ITT population)

Patient	Failure	Planned treatment	Real treatment	Planned duration of treatment	Real duration of treatment	Previous response to HCV treatment	Fibrosis	Genotype	HCV VL at baseline (log)	Child at baseline	Resistance profile at baseline	Resistance profile at failure	Re-treatment after failure
#1	Non responder	SOF+DCV	SOF+DCV	12 W	6 W	No treatment	F0-F2	3A	6.11	-	ND	ND	SOF/DCV 12W, relapse
#2	Non responder	SOF+LDV	SOF+LDV	12 W	12 W	No treatment	F0-F2	4D	6.97	5	ND	NS5A (L28V)	SOF/SIM/RBV 12W, SVR12
#3	Non responder	SOF+DCV	SOF+DCV	24 W	1 W	Intolerant (PEG/RBV)	F3	1B	6.69	5	ND	ND	-
#4	Non responder	SOF+DCV	SOF+DCV	24 W	12W	Partial responder (RBV/PEG/TVR)	F4	1A	5.50	7	ND	ND	Re-LT then SOF/DCV 24W, SVR12
#5	Breakthrough at W8	SOF+DCV+ RBV	SOF+DCV+ RBV	24 W	12 W	No treatment	F0-F2	1A	6.02	5	NS3 (Q80K)	NS3 (Q80K) NS5A (M28V, Q30R)	-
#6	Relapse at FUW4	SOF+LDV	SOF+LDV	12 W	12 W	Relapse (PEG/RBV)	F0-F2	4D	6.40	5	ND	ND	SOF/DCV/SIM, 12W, SVR12
#7	Relapse at FUW4	SOF+LDV+ RBV	SOF+LDV+ RBV	24 W	12W	No treatment	F4	1B	5.73	7	NS3 (Q80K)	NS3 (Q80K)	SOF/LDV/RBV 24W, SVR4
#8	Relapse at FUW4	SOF+DCVz	SOF+DCV	24 W	24 W	Nul responder (PEG/RBV)	F4	4	6.26	11	-	NS5A (Y93H)	SOF/LDV/RBV 1W interrupted for decompensation 3rd LT
#9	Relapse at FUW4	SOF+DCV	SOF+DCV	24 W	24 W	No treatment	F0-F2	3A	6.50	5	ND	ND	Died at FUW32 (HCC)
#10	Relapse at FUW4	SOF+LDV	SOF+LDV	24 W	24 W	No treatment	F4	1A	6.13	6	ND	ND	-
#11	Relapse at FUW12	SOF+DCV	SOF+DCV	12 W	12 W	No treatment	F0-F2	3A	7.28	6	-	NS5A (Y93H)	-
#12	Relapse at FUW12	SOF+LDV	SOF+LDV	12W	12 W	No treatment	F4	1B	6.83	5	NS3 (Q80K) NS5A (R30Q, Y93H)	NS3 (Q80K) NS5A (R30Q, L31M, Y93H)	SOF/DCV 24W, SVR12
#13	Relapse at FUW12	SOF+DCV	SOF+DCV	12 W	12 W	No treatment	F0-F2	1A	6.48	-	ND	ND	SOF/GZR/EBR 24W, SVR4
#14	Relapse at FUW12	SOF+DCV+ RBV	SOF+DCV+ RBV	24 W	24 W	Relapse (PEG/RBV)	F0-F2	3A	6.36	6	-	NS5A (Y93H)	-
#15	Died at FUW10 (metastatic lung cancer)	SOF+LDV+ RBV	SOF+LDV+ RBV	12 W	12 W	Relapse (PEG/RBV)	F0-F2	1A	6.55	-	ND	ND	-
#16	Died at FUW9 (acute myeloid leukemia)	SOF+LDV	SOF+LDV	12 W	12 W	No treatment	F0-F2	1B	6.38	6	ND	ND	-
#17	Died at FUW2 (corporeo-caudal pancreatic tumor mass)	SOF+LDV	SOF+LDV	12 W	12 W	Non responder (PEG/RBV)	F0-F2	1A	5.87	-	ND	ND	-
#18	Died at FUW1 (liver failure)	SOF+LDV+ RBV	SOF+LDV+ RBV	12 W	12 W	Non responder (PEG/RBV)	F4	1B	3.40	11	ND	ND	-
#19	Died at W3 (hyperosmolar coma then multi-organ failure)	SOF+DCV+ RBV	SOF+DCV+ RBV	24 W	1 W	Intolerant (PEG/RBV)	F4	1B	6.18	6	NS3 (S122T) NS5A (A92T)	ND	-
#20	Died at FUW8 (metastatic carcinoma)	SOF+DCV+ RBV	SOF+DCV+ RBV	24 W	20 W	No treatment	F0-F2	1B	6.90	6	ND	ND	-

ND: not determined

patients experienced an SVR12, 2 achieved a sustained virological response at W4 after the end of treatment, and 1 relapsed after receiving SOF + DCV for 12 weeks. One patient required a third LT. In the PP population (n = 470), 456 patients (97.0%) achieved SVR12.

FACTORS ASSOCIATED WITH FAILURE

The clinically relevant variables that influenced failure at posttreatment week 12 were analyzed: fibrosis stage, HCV genotype, HCV viral load at baseline, and previous treatment post-LT.

Under multivariate analysis, these factors did not influence SVR12 rates in the four study groups in the ITT (P = 0.21) and PP (P = 0.15) populations. There was no significant effect of RBV/12W or 24W on the probability of failure in this population. These results are presented in Table 3 and Supporting Table S1.

SAFETY

AEs were common, occurring in 354 patients (69.1%), although the majority were mild to moderate, as presented in Table 4. SAEs were reported in 127 patients (24.8%), which notably included infections in 11 patients and cardiac disorders in 14. There were no treatment-related SAEs and no deaths during treatment in this population. The most common AE was anemia (21.9%), which increased significantly with the use of RBV (P < 0.0001). RBV dose was reduced during treatment in 41 patients (35.0%) and discontinued in 19 because of anaemia. Fifty-six patients (10.9%) required EPO injections and 21 (4.1%) needed blood transfusions. Two patients experienced acute graft rejection and were treated effectively by increasing their immunosuppressive therapy. Nine patients developed grade 3-4 renal insufficiency, and 63.9% of patients had an estimated glomerular filtration rate ≤60 mL/min during treatment. Ten patients developed cancer during the study period: skin carcinoma (basocellular, squamous cell), metastatic lung adenocarcinoma, thyroid nodule, urothelial carcinoma, and acute myeloid leukaemia. Only 1 patient experienced an HCC recurrence (1 month after starting the treatment), and a resection was performed.

Discussion

Liver recipients with HCV recurrence have always been considered as a difficult-to-treat population. Previous HCV treatment post-LT, progression of fibrosis on the graft, a high HCV viral load, and the immunosuppressive therapy implemented had originally prompted clinicians to choose treatment for 24 weeks with RBV in order to improve SVR12 rates.

TABLE 3. Factors associated with failure (multivariate analysis) in ITT population

	Population	Failure (n)	OR (95% CI)	*P*
Groups RBV/12 or 24 W	512	20		0.2058
12W+RBV	47	2	1	
12W- RBV	156	8	1.26 (0.26-6.23)	
24W- RBV	239	5	0.44 (0.08-2.41)	
24 W + RBV	70	5	1.59 (0.28-9.01)	
Fibrosis stage	512	20		0.7658
F0-F2	326	12	1	
F3-F4	186	8	1.17 (0.42-3.24)	
HCV genotype	512	20		0.7231
G1	359	13	1	
G3	93	4	1.34 (0.40-4.52)	
Other genotype	60	3	1.63 (0.44-6.10)	
Previous treatment	512	20		0.7737
No	336	11	1	
Non response	77	4	1.70 (0.48-5.97)	
Relapse/breakthrough	64	3	1.53 (0.40-5.88)	
Intolerant	35	2	1.87 (0.38-9.35)	
HCV viral load at baseline (Log IU/mL)	512	20	0.88 (0.48-1.62)	0.6836

TABLE 4. Adverse events (ITT population)

Parameters	Overall population (n = 512)	12 W –RBV (n = 156)	12 W +RBV (n = 47)	24 W –RBV (n = 239)	24 W +RBV (n = 70)	*P*
Grade 3/4 AE, n(%)	127 (24.8)	23 (14 7)	13 (27.7)	65 (27.2)	26 (37.1)	0.0017
Acute Rejection, n(%)	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.4)	0.4976
Anaemia, n(%)						
Grade 0	17 (3.3)	0 (0 0)	4 (8.5)	1 (0.4)	12 (17.1)	< 0.0001
Grade 1/2	70 (13.7)	13 (8.3)	10 (21.3)	27 (11.3)	20 (28.6)	
Grade 3/4	25 (4.9)	3 (1.9)	7 (14.9)	7 (2.9)	8 (11.4)	
EPO use, n(%)	56 (10.9)	8 (5.1)	6 (12.8)	21 (8.8)	21 (30.0)	< 0.0001
Blood transfusion, n(%)	21 (4.1)	1 (0.6)	7 (14.9)	7 (2.9)	6 (8.6)	0.0001
RBV reduction for anemia, n(%)	41 (35.0)	0 (0.0)	13 (27.7)	0 (0.0)	28 (40.0)	0.2356
RBV discontinuation for anemia, n(%)	19 (16.2)	0 (0.0)	6 (12.8)	0 (0.0)	13 (18.6)	0.4540
Creatinine clearance (MDRD), n(%)						
>60 ml/min	185 (36.1)	53 (34.0)	23 (48.9)	84 (35.1)	25 (35.7)	0.3740
]30;60]ml/min	258 (50.4)	81 (51.9)	19 (40.4)	117 (49.0)	41 (58.6)	
]10;30|ml/min	52 (10.2)	16 (10.3)	5 (10.6)	28 (11.7)	3 (4.3)	
< 10 ml/min	17 (3.3)	6 (3.8)	0 (0.0)	10 (4.2)	1 (1.4)	
Cardiac disorders, n(%)						
Grade 1/2	2 (0.4)	0 (0 0)	1 (2.1)	1 (0.4)	0 (0.0)	0.0645
Grade 3/4	14 (2.7)	1 (0.6)	0 (0.0)	10 (4.2)	3 (4.3)	
Infection, n(%)						
Grade 1/2	72 (14.1)	14 (9.0)	5 (10.6)	33 (13.8)	20 (28.6)	0.0044
Grade 3/4	11 (2.1)	1 (0.6)	1 (2.1)	7 (2.9)	2 (2.9)	

However, the availability of DAAs should change these dogmas. An effective treatment for HCV recurrence remains the primary objective post-LT in order to improve patient and graft survival, but issues concerning both the duration of treatment and use of RBV have remained unresolved.[14,15]

Previous studies had focused on either the impact of RBV-free treatment for 12 or 24 weeks or that of the duration of treatment post-LT.[3-10] We attempted to answer both questions: the need for RBV and the necessary duration of treatment for HCV recurrence in LT patients, by reporting on our real-life experience of treating HCV recurrence with SOF and an NS5A inhibitor regimen in a large number of patients. We were able to identify four groups of patients as a function of their treatment and its duration: SOF + NS5A without RBV for 12 (156 patients) or 24 (239 patients) weeks; SOF + NS5A + RBV for 12 (47 patients) or 24 (70 patients) weeks. We concluded that SOF + NS5A inhibitors without RBV for 12 weeks constituted reliable therapy for recurrent HCV post-LT and achieved an excellent SVR 12 whatever the fibrosis stage, HCV genotype, and previous HCV treatment.

In the post-LT context, several studies have focused on a reduced duration of treatment for HCV.[8,16] Charlton et al. reported the efficacy of a 12-week SOF/LDV regimen with RBV post-LT in patients with cirrhosis and confirmed that extending the treatment to 24 weeks did not improve SVR12 rates.[3] During the ALLY I study, 39 of 41 patients (95%) with HCV genotype 1 and 10 of 11 (91%) with genotype 3 achieved an SVR12 in a post-LT population treated with SOF/DCV plus RBV for 12 weeks.[17] Of these patients, 55% had severe fibrosis at baseline and 58% had been previously treated. The efficacy of SOF + NS5A inhibitors with RBV for 12 weeks was therefore confirmed. However, RBV is poorly tolerated and anemia is the principal adverse effect experienced during its use. Post-LT, some treatment, such as mycophenolate mofetil, valgancyclovir, or cotrimoxazole, may be used, but they are also responsible for anemia. EPO and blood transfusions are therefore frequently required, and it may be necessary to reduce or discontinue RBV. Moreover, patients may experience renal dysfunction post-LT, which requires an adaptation of the RBV dose and close monitoring. Finally, analysis of the phase III ION trials suggested that an RBV-free regimen might increase patient adherence to treatment by reducing the incidence of AEs.[12] Furthermore, kidney injury post-LT necessitates close management of the RBV regimen. A worsening of disease status and duration of treatment are often linked to the discontinuation

of RBV. During the SOLAR 1 and 2 studies, a high incidence of AEs (especially hematological disorders) was observed (86.4%), particularly among patients in the posttransplant population with cirrhosis receiving RBV.[3,4] Elfeki et al. recently reported no failures with an SOF/LDV regimen without RBV for 12W or 24W following LT.[9] Thirty-two of 46 patients (70%) received a 12-week course of treatment with SOF/LDV, but had minimal fibrosis at baseline. Globke et al. reported no failures in a cohort of 51 patients treated with SOF/LDV without RBV for 12W (minimal fibrosis stage) and 24W (severe fibrosis at baseline) post-LT.[18] A reduced-duration RBV-free regimen had therefore only been tested previously in a population with minimal fibrosis post-LT. Abaalkhail et al. confirmed these results in 50 LT recipients infected with HCV genotype 4 receiving SOF/LDV without RBV, but no patients were suffering from cirrhosis.[10] The recent data of the Magellan 2 study demonstrated a high SVR 12 rate (99%) with an RBV-free glecaprevir/pibrentasvir regimen for 12W in 100 liver and kidney transplant patients suffering from HCV 1-6 genotype infection. However, 78 of these patients had minimal fibrosis (F0-F1) and no patients had cirrhosis.[19] Agarwal et al. reported the efficacy of SOF + velpatasvir for 12 weeks after LT in 79 patients, 44% of whom had HCV genotype 3, 27% were with cirrhosis, and 54% had previously been treated.[20] The SVR12 rate reached 96%, and NS5A RAS mutations were reported in the context of two VFs. The cost of DAAs has also been highlighted, but the cost-effectiveness of RBV versus that of managing an anemia event also needs to be studied.[21]

Our study highlighted the efficacy of an SOF + NS5A inhibitor regimen without RBV for 12 weeks, even in patients with several negative predictors of response. One hundred fifty-six patients (30.5%) received an RBV free regimen for 12 weeks, and 22 of them (14.1%) had cirrhosis. In our cohort, 108 of the 512 patients (21.1%) were with cirrhosis and more than one third of them had previously been treated. Overall, 18.2% of the patients were infected by genotype 3, including 15 with cirrhosis, 6 of whom had previously been treated with pegylated IFN and RBV. Only 20 patients experienced a treatment failure and most of them had not previously been treated, displaying minimal fibrosis at baseline. Six patients died before SVR12; these included 1 case of liver failure in a patient with cirrhosis with a MELD score of 22 at baseline. The other causes of death underlined the fact that liver recipients remain a frail population. The majority of patients experiencing a VF had NS5A (particularly Y93H) or NS3 (Q80K) resistance mutations. In this population with negative predictors of response, it appears that the study of resistance mutations will be an important factor when choosing the best second-generation DAA.[22,23]

This study had certain limitations. It concerned an observational cohort. The treatment, doses of medications, and durations of treatment were at the discretion of each investigator. We are well aware that the investigators tended to opt for long-term treatment for the most seriously ill patients, especially given that inclusions in the CUPILT cohort started in 2013. The RBV-free 24W regimen was chosen for 239 patients (46.7%): 57 (23.8%) with cirrhosis, 44 with HCV genotype 3 (18.4%), and a majority of previously treated patients (38.1%). However, a significant difference between the four groups was only found regarding fibrosis stage at baseline ($P < 0.0001$). This study was not designed to determine the impact of fibrosis stage and genotype on SVR12; however, the large size of our study population (512 patients in ITT) enabled us to evaluate prognostic factors of interest in the setting of LT.

In conclusion, our results showed that a regimen of SOF and NS5A inhibitors without RBV for 12 weeks could be sufficient to ensure the effective treatment of more than 93% of liver recipients. The response rates to DAA combination therapy in LT patients were similar to those observed in the nontransplanted population.[24] According to these findings, LT recipients should not be considered as a "difficult-to-treat" population.

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Author names in bold designate shared co-first authorship.

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