Hepat Mon. 2018 August; 18(8):e80761. doi: 10.5812/hepatmon.80761.

Published online 2018 July 29. **Research Article**

Interferon Free Therapy with and Without Ribavirin for Genotype 1 HCV Cirrhotic Patients in the Real World Experience

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Received 2018 June 12; **Revised** 2018 July 08; **Accepted** 2018 July 24.

Abstract

Background: In the interferon era, patients with HCV-related cirrhosis were considered hard to treat due to contraindications to therapy, safety issues, and poor response.
Objectives: We investigated interferon-free regimens in cirrhotic patients in real-world practice.
Methods: We analyzed data of HCV infected patients with liver cirrhosis conducted in 22 Polish hepatology centers. They were assigned to a treatment schedule based on physician decision. Data were collected retrospectively by an online questionnaire.
Results: In total, 1113 patients infected with genotype 1 HCV were enrolled to the analysis, 96.6% presented GT1b infection. A total of 56% were treatment-experienced, mostly with PegIFN + RBV, 77.2% of group presented comorbidities with the most frequent hypertension and diabetes,73.2% patients were treated with concomitant medications, and 31% of cohort was assigned to RBV-free regimen, majority of them to OBV/PTV/r + DSV. Overall, 94.7% patients achieved the sustained virological response in intent-to-treat analysis, with comparable rate for RBV-free and RBV-containing options (94.2% vs. 94.9%). Treatment course was more often modified in RBV-containing group, whereas rate of discontinuation was the same for both cohorts. Adverse events were observed in 41% with the most common weakness/fatigue; more frequently in RBV-containing regimens (43% vs. 36.6%). Serious adverse events were reported in 4.1% patients. A total of 16 deaths not related to study drugs were documented, mostly in RBV-containing group.
Conclusions: We confirmed effectiveness of the interferon-free regimens without ribavirin in real-world cohort of cirrhotic patients with chronic HCV infection genotype 1. Therapy was well tolerated with infrequent adverse events.

Keywords: Hepatitis C Virus, Genotype 1, Liver Cirrhosis

1. Background

The hepatitis C virus (HCV) infection is a global health issue affecting approximately 71 million individuals all over the world. Untreated chronic hepatitis C is a leading cause of cirrhosis and end-stage liver disease (1). The most prevalent worldwide is genotype 1 (GT1), which accounts for 46% - 60% infections. In Europe, genotype 1 is responsible for the majority of chronic hepatitis C cases. Of the GT1 infections, subtype 1b is the most common, which accounts for about 50% of all HCV infections in Western Europe and much higher percentages in Eastern European countries, including Poland (2, 3). In the interferon era, patients with HCV-related cirrhosis infected genotype 1 were considered difficult to treat due to contraindications to therapy, safety issues, and poor response (4-7).

Introduction of interferon-free regimens containing a combination of direct acting antivirals (DAA) and possible addition of ribavirin (RBV) improved treatment efficacy in GT1 infected patients up to 100%, even in hard to treat population of cirrhotics. From 2015, four IFN-free regimens were recommended by EASL for GT 1 patients with compensated liver cirrhosis: OBV/PTV/r + DSV + RBV, SOF/LDV ± RBV, SOF + SMV ± RBV and SOF + DCV ± RBV, and two options: SOF/LDV

+ RBV and SOF + DCV + RBV for decompensated cirrhotics (8, 9).

2. Objectives

In the present analysis we have investigated interferon-free regimens in cirrhotic patients infected with GT1 in real-world practice with particular reference to efficacy and safety of ribavirin-free options.

3. Methods

The analysis is a part of EpiTer-2, real-world, investigator-initiated, manufacturer-independent, observational study, which included 22 Polish centers treating HCV infected patients.

A total of 2879 adults with chronic hepatitis C who started antiviral therapy after July 1, 2015 and completed it before December 31, 2016, with the efficacy evaluation available before June 30, 2017, were enrolled in the study. In the study cohort, 1254 patients were diagnosed as cirrhotic, of which 1113 were infected with genotype 1. The selection of the current therapy was made by treating physicians. Patients were treated according to the reimbursed therapeutic program of the National Health Fund and in line with recommendations of the Polish Group of Experts for HCV. The efficacy end point was the sustained virological response (SVR) described as undetectable HCV RNA at least 12 weeks after the end of treatment. Data concerning baseline characteristics and treatment course, including efficacy and safety, were collected retrospectively and submitted using the online questionnaire administered by Tiba sp. z o.o. The study was supported by the Polish Association of Epidemiologists and Infectiologists. In the beginning of the analyzed period, GT 1b cirrhotic patients were treated with ribavirin. However after an update of the Summary of Product Characteristics in April 2016 following TURQUOISE-III study results publication, cirrhotics became allowed to be treated without RBV (16). In Poland, the combination of SOF and DCV was not reimbursed, thus, this option was available for very few patients and was therefore not included in the current analysis.

Statistical analyses. The results are expressed as mean $\pm$ standard deviation (SD) or No. (%). P values of < 0.05 were considered to be statistically significant. The significance of difference was calculated by use of Chi-square or Fischer's exact test and where appropriate by use of GraphPad Prism 5.1 (GraphPad Software, Inc., La Jolla, CA).

4. Results

In total 1113 cirrhotic patients infected with genotype 1 HCV were included in the analysis. Males were accounted for 48% with a mean age of 58.9 $\pm$ 11.7 years; females were older than males. Over 70% of patients suffered from comorbidities, of which hypertension and diabetes were the most common. Almost three-fourths were treated with concomitant medications and 31% of the entire cohort was assigned to the RBV-free regimens, whereas remaining 69% received RBV-containing treatment. Details of baseline characteristics of the study cohort are presented in Table 1.

The vast majority of the analyzed population was infected with genotype 1b with 98% in the RBV-free and 96% in RBV-containing groups, respectively. The most frequent method of the liver fibrosis assessment supporting diagnosis of cirrhosis was transient elastography (TE) performed in almost two thirds of the cohort, followed by liver biopsy and shear-wave elastography (SWE); only single patients were diagnosed based on acoustic radiation force impulse (ARFI) (10).

Hepatic decompensation at baseline manifested as an ascites and encephalopathy was observed in 4.1% and 2.5% of patients, respectively, more often in RBV-containing (4.9% and 3.1%) than RBV-free group (2.3% and 1.2%). The majority of patients (86.7%) at baseline were classified as compensated (class A in Child-Pugh score) with comparable rate for both subpopulations, however, a history of hepatic decompensation in form of ascites and encephalopathy was more often reported in RBV-containing group (P = 0.003) as shown in Table 2. A total of 56% of the study cohort was treatment-experienced with null response as the most frequent type of non-response. Most of them (58%) were treated previously with pegylated interferon alfa (PegIFN) and RBV, and 31.5% received triple therapy with telaprevir, boceprevir, simeprevir, or sofosbuvir combined with PegIFN and RBV. The most frequent option without RBV was 12 weeks of ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV) accounting for 63% of therapies in this population. The frequency of application of other treatment options are presented in Table 3. Overall, 94.7% of patients achieved the sustained virological response in intent-to-treat analysis, with comparable rate for RBV-free and RBV-containing options (94.2% vs. 94.9%, P = 0.61). Treatment efficacy for the most common therapeutic options with OBV/PTV/r + DSV for 12 weeks was 96% regardless RBV administration. In RBV-free regimens, SVR rate for 12-week options was higher than 24-week ones (96% vs. 89%, P = 0.01), whereas in RBV-containing schedules SVR rate was 95% irrespective of the treatment duration (Table 4). Treatment course was more often modified in the RBV-

Table 1. Baseline Characteristics of 1113 Cirrhotic Patients Infected with Genotype 1 HCV Included in the Analysis[a]

Parameter	All, N = 1113	RBV-Free N = 344	RBV-Containing N = 769
Gender, females/males	574 (51.6)/539 (48.4)	192 (55.8)/152 (44.2)	382 (49.7)/387 (50.3)
Age (y), mean + SD (min - max)	58.9 ± 11.7 (21 - 91)	59.9 ± 12.2 (25 - 90)	58.5 ± 11.6 (21 - 91)
Females	62.3 ± 10.8 (25 - 91)	62.9 ± 11.6 (25 - 90)	62 ± 10.4 (26 - 91)
Males	55.3 ± 11.7 (21 - 86)	56.1 ± 11.9 (29 - 84)	54.9 ± 11.6 (21 - 86)
BMI, mean + SD (min - max)	27.3 ± 4.5 (13.4 - 49.4)	27.2 ± 4.1 (15.6 - 42.6)	27.4 ± 4.6 (13.4 - 49.4)
Comorbidities			
Any comorbidity	859 (77.2)	268 (77.9)	591 (76.9)
Hypertension	545 (49)	173 (50.3)	372 (48.4)
Diabetes	245 (22)	69 (20)	176 (22.9)
Renal disease	43 (3.9)	19 (5.5)	24 (3.1)
Autoimmune diseases	27 (2.4)	10 (2.9)	17 (2.2)
Non-HCC tumors	19 (1.7)	6 (1.7)	13 (1.7)
Other	584 (52.5)	167 (48.5)	417 (54.2)
Concomitant medications	815 (73.2)	247 (71.8)	568 (73.8)
ALT IU/L	95.7 ± 66.2	95.1 ± 65.5	96 ± 66.6
Bilirubin mg/dL	1.19 ± 0.96	1.14 ± 1.06	1.22 ± 0.9
Albumin g/dL	3.8 ± 0.56	3.8 ± 0.53	3.8 ± 0.58
Creatinine mg/dL	0.84 ± 0.58	0.92 ± 0.92	0.8 ± 0.32
Hemoglobin g/dL	14.1 ± 1.76	14 ± 1.8	14.1 ± 1.74
Platelets × 1000/μL	120 ± 60.9	133 ± 62.5	115 ± 59.6
HCV RNA × 10^6 IU/mL	1.54 ± 3.69	1.46 ± 1.92	1.58 ± 4.27

Abbreviations: ALT; alanine aminotransferase, BMI; body mass index, HCC; hepatocellular carcinoma, HCV RNA; hepatitis C virus-ribonucleic acid, SD; standard deviation.
[a] Values are expressed as No. (%) or mean + SD unless otherwise indicated.

containing group (7.2% vs. 0.3%, P < 0.001), mainly due to RBV dose modification or RBV discontinuation. However, rate of treatment discontinuation was the same for both cohorts (3.8% vs. 3.4%). Adverse events were more frequently observed in RBV-containing regimens (43% vs. 36.6%, P = 0.04) with the most common weakness/fatigue reported in 18.5% of patients (Table 5). Rate of adverse events leading to treatment discontinuation was comparable in both cohorts. Serious adverse events were reported in 4.1% of patients, and tended to be more frequent in RBV-free cohort (4.9% vs. 3.8%), although not statistically significant, whereas the rate of liver-related events was the same for both populations.

Liver decompensation manifested as an ascites deterioration or hepatic encephalopathy was observed in 2.3% and 1.5% vs. 2.6% and 2.7% in RBV-free and RBV-containing groups, respectively (Table 5). A total of 16 deaths not related to treatment of HCV infection were documented, mostly in RBV-containing group.

5. Discussion

Patients with chronic HCV infection and liver cirrhosis are at the highest risk for liver-related complications. Numerous clinical trials and real-life studies have proved that HCV eradication in cirrhotic patients can reduce progress to end-stage liver disease, rate of hepatic decompensation, HCC development, need of transplantation, and mortality (11-14). In the interferon era, patients with HCV genotype 1 infection and liver cirrhosis have been recognized as difficult-to-treat due to low response rates and high frequency of side effects with consequent treatment discontinuation. Approval of the all-oral direct antiviral therapy resulted in significant improvement of treatment response and tolerability, even in cirrhotic patients (15-21). For that, in the beginning of the IFN-free era, antiviral treatment was prioritized in this population according to EASL and national guidelines (8, 9, 22).

In the Polish real-world study we retrospectively evaluated the efficacy and safety of interferon-free regimens in this cohort. Since the beginning of the IFN-free era, the ad-

Table 2. Characteristics of Liver Disease in Patients Receiving Regimens with and Without Ribavirin[a]

Parameter	All, N = 1113	RBV-Free, N = 344	RBV-Containing N = 769	P[b]
HCV genotype				
1	17 (1.5)	3 (0.9)	14 (1.8)	0.11
1a	21 (1.9)	3 (0.9)	18 (2.4)	
1b	1075 (96.6)	338 (98.2)	737 (95.8)	
Liver fibrosis assessment				
Biopsy	155 (13.9)	30 (8.7)	125 (16.2)	< 0.001
TE	814 (73.1)	256 (74.4)	558 (72.6)	
SWE	141 (12.7)	58 (16.9)	83 (10.8)	
ARFI	3 (0.3)	0	3 (0.4)	
History of hepatic decompensation				
Ascites	120 (10.8)	17 (4.9)	103 (13.4)	0.003
Encephalopathy	32 (2.8)	6 (1.7)	26 (3.4)	
No data	68 (6.1)	24 (7)	44 (5.7)	
Documented esophageal varices	346 (31.1)	81 (23.5)	265 (34.4)	< 0.001
Hepatic decompensation at baseline				
Moderate ascites-responded to diuretics	44 (3.9)	7 (2)	37 (4.8)	0.41
Tense ascites-not responded to diuretics	2 (0.2)	1 (0.3)	1 (0.1)	
Encephalopathy	28 (2.5)	4 (1.2)	24 (3.1)	
MELD				
< 15	992 (89.1)	296 (86)	696 (90.5)	0.14
15 - 18	43 (3.9)	17 (4.9)	26 (3.4)	
19 - 20	11 (1)	6 (1.8)	5 (0.6)	
> 20	13 (1.2)	6 (1.8)	7 (0.9)	
No data	54 (4.8)	19 (5.5)	35 (4.6)	
Child-Pugh				
A	965 (86.7)	303 (88.1)	662 (86.1)	0.56
B	105 (9.4)	27 (7.8)	78 (10.1)	
C	9 (0.8)	2 (0.6)	7 (0.9)	
No data	34 (3.1)	12 (3.5)	22 (2.9)	
History of liver cancer (HCC)	46 (4.1)	14 (4.1)	32 (4.1)	0.95
Liver transplant before treatment No. (%), time from OLT (mo), mean ± SD (min - max)	21 (1.9), 66.8 ± 58.2; 5 - 168	4 (1.2), 46 ± 65; 5 - 120	17 (2.2), 71 ± 58; 8 - 168	0.23
HIV coinfection	7 (0.6)	2 (0.6)	5 (0.6)	0.89
HBV coinfection				
HBsAg (+) HBV DNA (+)	8 (0.7)	0	8 (1.05)	0.38
HBsAg (+) HBV DNA (-)	3 (0.3)	1 (0.3)	2 (0.3)	
HBsAg (-)/aHBctotal (+)	129 (11.6)	43 (12.5)	86 (11.2)	
Extrahepatic manifestation				
Cryoglobulinemia	69 (6.2)	15 (4.4)	54 (7)	0.004
Thyroid abnormalities with antithyroid antibodies	13 (1.2)	7 (2)	6 (0.8)	
Other	11 (1)	7 (2)	4 (0.52)	

Abbreviations: ARFI; acoustic radiation force impulse, aHBctotal; antibody to the hepatitis B core antigen, HBsAg; hepatitis B surface antigen, HBV; hepatitis B virus, HBV DNA; hepatitis B virus deoxyribonucleic acid, HCV; hepatitis C virus, HIV; human immunodeficiency virus, MELD; model of end-stage liver disease, OLT; orthotopic liver transplantation, SWE; shear wave elastography, TE; transient elastography.

[a] Values are expressed as No. (%) or mean + SD unless otherwise indicated.

[b] P-value between RBV-free and RBV-containing.

dition of RBV was recommended in cirrhotics for possible improvement of efficacy, special attention was given in our study to compare RBV-free and RBV-containing regimens. The majority of analyzed cohort was infected with GT 1b, which is the most common subtype in Poland, and 87% was diagnosed as compensated (3).

Regimens prescribed for compensated patients in our study were OBV/PTV/r + DSV + RBV for 12 or 24 weeks de-

Table 3. Current Treatment Regimens

Parameter	All	12 wk	24 wk
Without ribavirin[a]	344	243	101
ASV + DCV	42 (12.2)	0	42
LDV/SOF	81 (23.5)	22	59
OBV/PTV/r + DSV	218 (63.4)	218[b]	0
SOF + SMV	3 (0.9)	3	0
With ribavirin[a]	769	728	41
SOF + SMV + RBV	2 (0.3)	2	0
LDV/SOF + RBV	269 (35)	228	41
OBV/PTV/r + DSV + RBV	498 (64.7)	498	0

Abbreviations: ASV; asunaprevir, DCV; daclatasvir, DSV; dasabuvir, LDV; ledipasvir, OBV; ombitasvir, PTV; paritaprevir, r; ritonavir, RBV; ribavirin, SMV; simeprevir, SOF; sofosbuvir.
[a] Values represented as No. (%).
[b] Including one patient treated for 8 weeks.

Table 4. Treatment Effectiveness According to Regimen - SVR ITT[a,b]

Regimen	All	RBV-Free	RBV-Containing	P-Value
OBV/PTV/r + DSV, 12 weeks	686/716 (95.8)	209/218 (95.9)	477/498 (95.8)	0.95
LDV/SOF, 12 weeks	234/250 (93.6)	22/22 (100)	212/228 (93)	0.29
LDV/SOF, 24 weeks	94/100 (94)	55/59 (93.2)	39/41 (95.1)	0.69
SOF + SMV, 12 weeks	5/5 (100)	3/3 (100)	2/2 (100)	-
ASV + DCV, 24 weeks	35/42 (83.3)	35/42 (83.3)	-	-
All regimens	1054/1113 (94.7)	324/344 (94.2)	730/769 (94.9)	0.61
12 weeks regimens	925/971 (95.3)	234/243 (96.3)	691/728 (94.9)	0.38
24 weeks regimens	129/142 (90.8)	90/101 (89.1)	41/43 (95.3)	0.23

Abbreviations: ASV; asunaprevir, DCV; daclatasvir, DSV; dasabuvir, LDV; ledipasvir, OBV; ombitasvir, PTV; paritaprevir, r; ritonavir, RBV; ribavirin, SMV; simeprevir, SOF; sofosbuvir.
[a] ITT - "intent to treat" analysis, which included all patients receiving at least 1 dose of the treatment.
[b] Statistical significance of $P < 0.05$ between IFN-free vs IFN-containing regimens.

pending on GT 1 subtype, combination of SOF/LDV + RBV for 12 weeks, simeprevir (SMV) and SOF with RBV for 12 weeks, and SOF plus daclatasvir (DCV) with RBV for 12 weeks. In Poland an additional regimen dedicated for GT 1b patients - combination of DCV and asunaprevir (ASV) for 24 weeks was available (22). The choice for patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C) included the fixed-dose combination of SOF and LDV or SOF and DCV regimen with or without RBV, for 12 or 24 weeks, respectively. The first IFN-free regimen available in our country was OBV/PTV/r + DSV and almost two thirds of the study cohort was assigned to this therapeutic option, which was highly effective and safe in the real world experience (23, 24). Finally, 30% of cirrhotics were assigned to RBV-free regimens, of whom 70% were treated for 12 weeks. Over half of the entire study cohort was treatment experienced with higher percentage in RBV-containing group (59% vs. 48%); the majority of patients were previously treated with PegIFN and RBV, however, nearly 30% of them received triple therapy with the first generation protease inhibitors. As shown by our analysis IFN-free regimens were applied to more than 1100 cirrhotic patients with GT 1 infection. SVR rate in this historically defined "hard-to-treat" population reached 95% and was similar in patients treated with both RBV-free and RBV-containing regimens. Twelve-week options without RBV were even more effective than 24 week ones (96% vs. 89%). This can be explained by fact that 42% of patients in 24-wks population was treated with DCV and ASV with SVR of 83%. A similar outcome was reported for cirrhotics in the HALLMARK-DUAL study, therefore, this regimen was finally recognized as a suboptimal therapeutic option (25). High response rates for other IFN-free regimens, with and without ribavirin, observed in the current analysis, are comparable to clinical trial results. Two phase 3 randomized studies with SOF/LDV ± RBV for 12 or 24 weeks (ION-1 and ION-2) reported SVR rate of 82%-100% in cirrhotics, according to the previous treatment history with no effect of RBV addition (26, 27). Patients infected with GT1b with compensated liver cirrhosis treated with OBV/PTV/r + DSV for 12 weeks in the TURQUOISE-III study achieved SVR of 100% (19). Excellent efficacy demonstrated in the current analysis is highly consistent with recently published real-world European studies, which evaluated IFN-free options applied to GT 1 infected cirrhotics and demonstrated no difference between RBV-free and RBV-containing cohorts (28-39). There are some indications supporting more frequent use of ribavirin in patients with more advanced liver disease, which could theoreticaly affect our efficacy analysis. According to data presented in Table 2 the only significant difference was related to historic information on possible worse hepatic conditions in the RBV group (history of decompensation and oesophageal varices). However, it was not a case for current hepatic compensation status (signs of hepatic decompensation, MELD, Chil-Pugh, HCC and liver transplantation) at the begining of the treatment.

The tolerability profile of IFN-free regimens in the current analysis was in accordance with clinical trials and real-world studies (40-45). A total of 41% of the entire cohort reported at least one AE, more often in RBV-containing group.

Table 5. Treatment Safety

Parameter	All N = 1113	RBV- N = 344	RBV + N = 769	P-Value
Patients with at least one AE	457 (41.1)	126 (36.6)	331 (43)	0.04
Serious adverse events	46 (4.1)	17 (4.9)	29 (3.8)	0.36
SAEs liver-related[a]	18 (1.6)	6 (1.7)	12 (1.6)	0.82
AEs leading to treatment discontinuation	34 (3.1)	12 (3.5)	22 (2.9)	0.45
Most common AEs (> 5%)				
Weakness/fatigue	206 (18.5)	57 (16.6)	149 (19.4)	0.26
Anemia	56 (5.1)	5 (1.5)	55 (7.2)	< 0.001
Pruritus	62 (5.6)	20 (5.8)	42 (5.5)	0.81
AEs of particular interest				
Deterioration of ascites	28 (2.5)	8 (2.3)	20 (2.6)	0.78
Hepatic encephalopathy	26 (2.4)	5 (1.5)	21 (2.7)	0.20
Gastrointestinal bleeding	9 (0.8)	2 (0.6)	7 (0.9)	0.32
Death[b]	16 (1.4)	2 (0.6)	14 (1.8)	0.11

Abbreviations: AE; adverse event, CCC; cholangiocarcinoma, HCC; hepatocellular carcinoma, SAE; serious adverse event.
[a] RBV-free group: HCC 3 patients, hepatic decompensation, increase of bilirubin level, increase of ALT activity; RBV-containing group: HCC 5 patients, hepatic decompensation 3 patients, portal vein thrombosis 2 patients, dysplastic nodules, CCC.
[b] HCC 4 patients, decompensation 3 patients, pancreatic cancer 2 patients, sudden cardiac death 2 patients, cholangiocarcinoma, acute pancreatitis, subarachnoid hemorrhage, intra-peritoneal bleeding, unknown reason (death in follow-up).

The most common AEs were weakness/fatigue, pruritus, and in individuals treated with RBV, anemia. The majority of patients completed the treatment course as scheduled with a low rate of discontinuations. Therapy modification concerned only RBV-containing options and included RBV dose reduction or discontinuation due to anemia.

The overall rate of serious adverse events was low (4%), and there were no significant differences between groups. Detailed analysis revealed that liver-related events rate was the same for both cohorts. No adverse events related to drug-drug interactions were observed. Deaths reported in the study, mostly in RBV-containing arm, were considered by investigators as not related to treatment.

Limitations of this study included it's retrospective observational nature resulting in underreporting of minor adverse events, electronic data collection connected with potential physician bias, choice of the regimen and treatment duration based on investigator discretion meaning no randomization, as well as possible data entry errors. Duration of follow up period seems to be insufficient to assess the benefits of successful treatment in terms of reducing disease progression.

Strengths of our study are large number of patients from numerous hepatologic centers, resulting with diversity of patient population managed in routine practice, and low rate of patients lost to follow-up (2%).

5.1. Conclusions

In summary, we confirmed high effectiveness and safety of the interferon and ribavirin-free regimens in real-world setting of cirrhotics with chronic genotype 1 HCV infection.

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