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ABOUT COVER

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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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INDEXING/ABSTRACTING

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EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Observational Study

Factors associated with success of telaprevir- and boceprevir-based triple therapy for hepatitis C virus infection

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Abstract

AIM

To evaluate new therapies for hepatitis C virus (HCV), data about real-world outcomes are needed.

METHODS

Outcomes of 223 patients with genotype 1 HCV who started telaprevir- or boceprevir-based triple therapy (May 2011-March 2012) at the Mount Sinai Medical Center were analyzed. Human immunodeficiency virus-positive patients and patients who received a liver transplant were excluded. Factors associated with sustained virological response (SVR24) and relapse were analyzed by univariable and multivariable logistic regression as well as classification and regression trees. Fast virological response (FVR) was defined as undetectable HCV RNA at week-4 (telaprevir) or week-8 (boceprevir).

RESULTS

The median age was 57 years, 18% were black, 44% had advanced fibrosis/cirrhosis (FIB-4 $\geq$ 3.25). Only 42% (94/223) of patients achieved SVR24 on an intention-to-treat basis. In a model that included platelets, SVR24 was associated with white race [odds ratio (OR) = 5.92, 95% confidence interval (CI): 2.34-14.96], HCV sub-genotype 1b (OR = 2.81, 95%CI: 1.45-5.44), platelet count (OR = 1.10, per x 10^4 cells/μL, 95%CI: 1.05-1.16), and *IL28B* CC genotype (OR = 3.54, 95%CI: 1.19-10.53). Platelet counts > 135 x 10^3/μL were the strongest predictor of SVR by classification and regression tree. Relapse occurred in 25% (27/104) of patients with an end-of-treatment response and was associated with non-FVR (OR = 4.77, 95%CI: 1.68-13.56), HCV sub-genotype 1a (OR = 5.20; 95%CI: 1.40-18.97), and FIB-4 $\geq$ 3.25 (OR = 2.77; 95%CI: 1.07-7.22).

CONCLUSION

The SVR rate was 42% with telaprevir- or boceprevir-based triple therapy in real-world practice. Low platelets and advanced fibrosis were associated with treatment failure and relapse.

Key words: Sustained virologic response; Hepatitis C virus; Relapse; Telaprevir; Boceprevir; Triple-therapy; Classification and regression; Adverse event; Real-world

Core tip: A cohort of 223 hepatitis C virus (HCV)-infected patients at a tertiary referral center was analyzed. All patients were treated with telaprevir and boceprevir. Using both logistic regression and a machine learning techniques we identified baseline and on-treatment factors associated with sustained virologic response and relapse. We found that both low platelet count and advanced fibrosis or cirrhosis were associated with treatment failure. Information of the effectiveness of these protease inhibitors could be used to inform clinical trials of future HCV direct-acting antivirals.

Bichoupan K, Tandon N, Martel-Laferriere V, Patel NM, Sachs D, Ng M, Schonfeld EA, Pappas A, Crismale J, Stivala A, Khaitova V, Gardenier D, Linderman M, Olson W, Perumalswami PV, Schiano TD, Odin JA, Liu LU, Dieterich DT, Branch AD. Factors associated with success of telaprevir- and boceprevir-based triple therapy for hepatitis C virus infection. *World J Hepatol* 2017; 9(11): 551-561 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i11/551.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i11.551

INTRODUCTION

The hepatitis C virus (HCV) infects about 3% of the world's population. In the United States, HCV chronically infects an estimated 2.7 to 3.9 million people and is a leading cause of liver disease, liver cancer, and liver-related death[1,2]. In 2012, the Centers for Disease Control and Prevention announced a public health initiative to identify HCV-positive individuals and transition them into care[1]. The recommendation for increased screening was affirmed by the United States Preventive Services Task Force[3]. The goal of treatment is to induce a sustained virological response (SVR) and thereby interrupt, and potentially reverse the progression of liver disease, improve the quality of life, and reduce the risk of transmission.

In the era of direct-acting antiviral (DAAs) drugs, treatment for HCV is evolving rapidly. Data about outcomes in real-world clinical practice are needed to evaluate new medications. The first generation protease inhibitors, telaprevir (TVR) and boceprevir (BOC), were approved for treatment of genotype 1 HCV in combination with pegylated-interferon (PEG) and ribavirin (RBV) in 2011. In clinical trials, overall SVR rates ranged from 64% to 75% for TVR-based triple therapy and from 59% to 66% for BOC-based triple therapy[4,5]. These trials enrolled relatively few patients $\geq$ 65 years of age and few with liver cirrhosis[6-8], although these patients are often in great need of treatment. Triple therapy with TVR or BOC is no longer the standard of care in the

United States and is no longer recommended by the American Association for the Study of Liver Disease and the Infectious Disease Society of America[9]; however, the effectiveness of these regimens in real-world practice may offer important information about currently available NS3/4A protease inhibitors. Information about their real-world effectiveness may benefit providers and patients in these regions of the globe.

Past investigations of factors associated with treatment outcome have yielded varied results[4,10]. Among patients receiving TVR-based therapy, the absence of fibrosis or cirrhosis has been associated with SVR[4,10-12]. Younger age was associated with SVR in one study[4], but not in others[12,13]. Among patients receiving BOC-based triple therapy, younger age and lower fibrosis stage were associated with SVR among treatment-naïve patients, but not among treatment-experienced patients[4,7]. A study of veterans receiving either TVR- or BOC-based triple therapy found that failure to achieve SVR was associated with cirrhosis, prior null or partial response, *IL-28B* CT or TT genotype, high baseline viral load, black race, diabetes, high aspartate transaminase (AST) to platelet ratio index (APRI) and FIB-4 scores, low platelet counts, and low LDL cholesterol[14].

TVR- and BOC-based triple therapies cause side effects and adverse events, including anemia, neutropenia, thrombocytopenia, rash, and liver decompensation[4,13-16], which can lead to dose reductions and treatment discontinuations[4,14]. Several deaths have been reported[17]. A key clinical question is which patients should be treated now, and which should be advised to wait for less toxic and more effective therapies. A major concern is that the rate of liver damage may accelerate with age[18]. Modeling studies predict that HCV-related morbidity and mortality will increase sharply in the years ahead[19,20]. The aging of the HCV-positive population and the age-dependent increase in the risk of HCV-related morbidity and mortality create a need to develop and deploy HCV therapies as safely and effectively as possible.

In real-world clinical practice little is known about the factors associated with SVR rates and relapse with DAA's. This project investigates these factors and provides a benchmark for comparing newer therapeutic agents to the first generation protease inhibitors. We were especially interested in factors that may worsen over time, such liver fibrosis stage and platelet counts.

MATERIALS AND METHODS

Study subjects and methods of data collection
The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the IRB of Mount Sinai (GCO #: 10-0032). The need for informed consent was waived as the work did not alter standard clinical practice. The study group was composed of 223 adults who initiated triple therapy with PEG-IFN/RBV and TVR or BOC (HCV NS3/4A protease inhibitors) at the Mount Sinai Medical Center between May 2011 and March 2012. Providers submitted names of patients and

Mount Sinai's electronic database was queried to capture the complete cohort of patients. The electronic database query identified patients with an ICD-9 code for HCV and a prescription for either TVR or BOC. Medical records were reviewed to verify patients identified through electronic phenotyping. All patients included in the analysis received at least one dose of TVR or BOC. Human immunodeficiency virus-positive patients and patients who previously received a liver transplant were excluded.

Data about the HCV treatment regimen, age, gender, race, body mass index (BMI), *IL28B* genotype, baseline clinical laboratory values [albumin, hemoglobin, AST, alanine transaminase (ALT), platelets, creatinine, ferritin, information to calculate the estimated glomerular filtration rate (eGFR), and alpha-fetoprotein (AFP)], indicators of liver fibrosis, past medical history, including diabetes (indicated by at least one of the following-prescription for metformin, pioglitazone, insulin, a recorded diagnosis of diabetes, fasting glucose above 125 mg/dL, or hemoglobin A1c above 6.5%), depression (indicated by use of at least one of the following medications-wellbutrin, aripiprazole, bupropion, citalopram, venlafaxine, escitalopram, paroxetine, or sertraline), outcome of prior HCV treatment, HCV sub-genotype and viral load were extracted from medical records. On-treatment changes in HCV viral load, ferritin, estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration formula[21] were calculated and incident anemia (hemoglobin below 9 g/dL) was recorded.

If available, biopsy or transient elastography data were used to classify liver disease as cirrhosis (yes/no). Cirrhosis was defined as a liver biopsy score of 4 using the Batts-Ludwig system or a transient elastography value > 13.5 kPa. In addition, liver fibrosis stage was estimated from the APRI and the FIB-4 score. APRI scores > 1.5 and FIB-4 scores > 3.25 were coded as advanced fibrosis/cirrhosis. APRI and FIB-4 scores were calculated as follows: APRI = AST (U/L)/(upper limit of normal)/[platelet count (10^9/L) × 100][22-24]; FIB-4 = age (years) × AST (U/L)/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$][25,26]. The FIB-4 score is reliable and has been tested and validated in large HCV mono-infected cohorts[27].

The standard treatment regimens are outlined in supporting Figures 1 (TVR) and 2 (BOC). Patients on TVR received 12 wk of TVR in combination with PEG/RBV. After week 12, TVR was discontinued. PEG/RBV dual therapy was continued for an additional 12 or 36 wk depending on prior treatment response, the presence of cirrhosis, and viral kinetics. With the exceptions noted below, patients on BOC-containing regimens began treatment with 4 wk of PEG-IFN/RBV dual therapy. Then BOC was added and patients received triple therapy for 24 to 44 wk depending on prior treatment response, the presence of cirrhosis and viral kinetics. Eight patients did not receive the standard PEG-IFN/RBV lead-in prior to starting BOC: Six did not have a lead-in phase, one received 19 wk of lead-in, and one received 24 wk of lead-in. Seventy-two patients, 63 on TVR and 9 on BOC, met the eligibility criteria for consideration of response
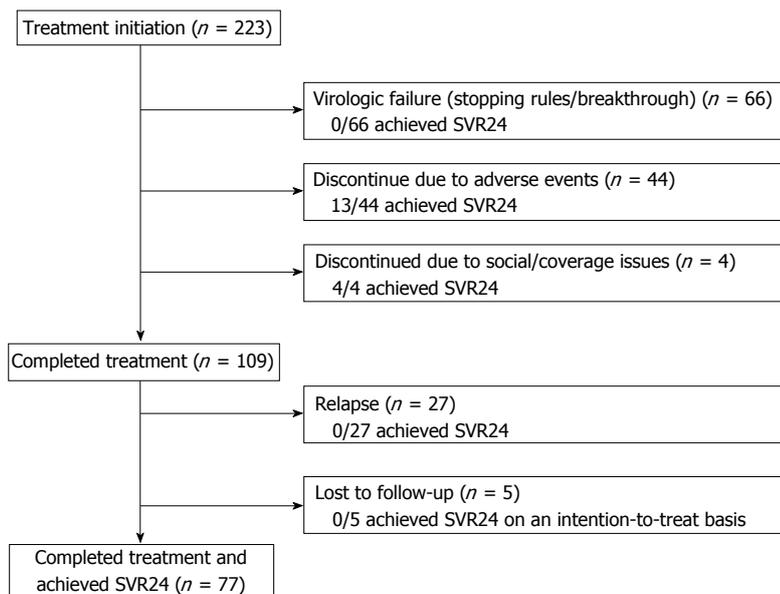
Figure 1 Outcomes of 223 patients initiating telaprevir- or boceprevir-based triple therapy. SVR: Sustained virological response.

guided therapy. Virologic stopping rules were followed.

During treatment, follow-up visits were scheduled for weeks 4, 8, 12, 24, 48, 60 and 72. Anemia was managed at the discretion of the provider. Generally, RBV dose was reduced at hemoglobin levels ≤ 10 g/dL. If hemoglobin levels remained low, erythropoietin was administered. Blood transfusions were used to treat intractable anemia[9]. Eltrombopag was not used.

SVR was defined as the absence of HCV RNA six months after the end-of-treatment (EOT), as measured by a real-time-polymerase chain reaction assay (Roche Cobas/Ampliprep Cobas Taqman version 2.0, Roche Molecular Systems Inc., Branchburg, NJ, United States). An HCV viral load below the lower limit of detection (18 IU/mL) was recorded as undetectable. Relapse was defined as the detection of HCV RNA after the absence of HCV RNA at EOT. A fast virologic response (FVR) was defined as undetectable HCV RNA 4 wk after the initiation of TVR or 8 wk after the initiation of BOC-based treatment.

Statistical analysis

Subgroups were compared using *t*-tests or Mann-Whitney tests for continuous variables and χ^2 or Fisher-exact tests for categorical variables. Pearson correlation tests were used to assess associations between continuous variables. Univariable and multivariable logistic regression were used to analyze the association between the baseline factors listed above and SVR calculated on an intention-to-treat basis. Models for relapse were built using data from patients who completed the planned treatment regimen, had undetectable HCV RNA at the EOT, and who were not lost to follow-up. Factors with a *P*-value below 0.15 in univariable models were included in multivariable analyses; variables with a *P*-value below 0.05 were retained in final models and were considered to be

independently associated with the outcome.

When variables were highly correlated with each other, a series of models was built, each with only one member of the pair. In the case of variables that contained common components (*e.g.,* APRI scores and FIB-4 scores) and variables that represent similar disease characteristics (FIB-4 ≥ 3.25 and histologically/elastography-defined cirrhosis) only one was entered into a model at a time. Missing data for HCV sub-genotype and *IL28B* polymorphism were imputed as 1a or CT/TT, respectively. A sensitivity analysis was conducted to determine whether variables associated with SVR were specific to one of the two protease inhibitors. Regression analyses were conducted on a dataset containing patients on TVR alone.

Classification and regression trees (CARTs) were built to identify baseline factors associated with SVR. Factors in the tree included race, cirrhosis (FIB-4 score), diabetes, HCV sub-genotype, *IL28B* genotype, history and previous response to HCV treatment (naïve/relapse *vs* null/intolerant), and platelet count.

The significance level was set to 0.05. Statistical analyses were conducted with SPSS and SAS.

RESULTS

Characteristics of the study group and treatment outcomes

Two complementary approaches were used to identify cases and ensure that the entire cohort of patients meeting the entry criteria were included. The traditional approach (patients identified by their providers) yielded 209 patients. A query of the Mount Sinai data warehouse identified an additional 14 patients, yielding a total of 223 patients whose baseline characteristics are presented in Table 1. One hundred and seventy-two (77%) were treated with TVR and 51 (23%) were

Figure 2 Classification and regression trees analysis of baseline factors associated with sustained virologic response. SVR: Sustained virologic response; HCV: Hepatitis C virus.

Figure 3 Treatment outcome stratified by low and high baseline platelet count. Treatment outcomes of patients with platelets $\leqslant 13.5 \times 10^4/\mu L$ and $> 13.5 \times 10^4/\mu L$ are shown in a stacked column graph. The SVR rate in the low platelet group was 28% *vs* 53% in the high platelet group. SVR: Sustained virologic response.

treated with BOC. The patients were predominantly male (65%) with a median age of 57 years (range: 22-74) and a BMI of 27.1 kg/m^3 (range: 16.3-49.3). Eighteen percent were black. Liver biopsy and/or transient elastography data were available for 202/223 (91%) patients of whom 96/202 (48%) had cirrhosis.
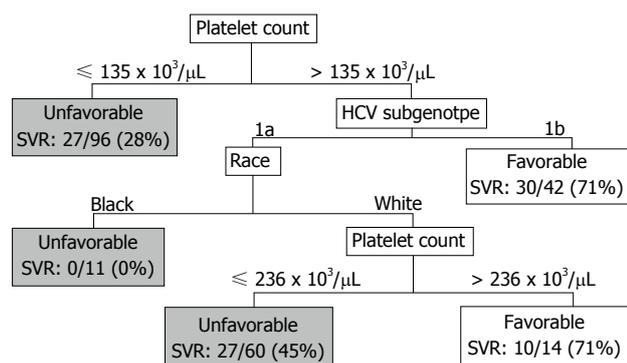
Figure 1 diagrams treatment outcomes. Of the 223 patients who initiate treatment, 66 patients had virologic failure during treatment; 44 discontinued treatment early due to adverse events (13 achieved SVR); four discontinued due to social/coverage issues (four achieved SVR); 109 (49%) completed the intended treatment regimen and were viral load negative at the EOT, but 27 relapsed and five did not return for testing at week-24 post EOT and could not be reached after repeated attempts by providers to contact them. On an intention-to-treat basis, the overall SVR rate was 42%. The overall SVR rate was 45% (77/172) for patients on TVR and 33% (17/51) for patients on BOC (*P* = 0.15) in an unadjusted analysis that did not correct for baseline differences. The SVR rates for treatment-naïve, prior non-responders, prior-interferon intolerant patients, and prior relapsers were 41%, 35%, 33% and 62%, respectively (*P* = 0.04).

Baseline factors associated with SVR

The baseline characteristics of the SVR and non-SVR groups are presented in Supporting Table 1. The SVR group had a significantly higher proportion of patients with the favorable *IL28B* CC genotype, with HCV sub-genotype 1b and higher levels of albumin and platelets, and this group had a significantly lower proportion of blacks, patients with diabetes, liver cirrhosis, a history of non-response to PEG/RBV treatment, lower levels of AFP and AST, and lower APRI and FIB-4 scores. Univariable logistic regression analysis of baseline variables showed *IL28B* CC genotype, higher platelets, higher albumin, HCV sub-genotype 1b, an HCV treatment history that included no prior treatment or relapse were positively associated with SVR and that black race, diabetes, high AST, high AFP, diagnosis of cirrhosis, or and advanced fibrosis/cirrhosis with APRI >1.5 or FIB-4 $\geqslant$ 3.25 were negatively associated with SVR (Table 2).

Before building multivariable models, the Pearson's
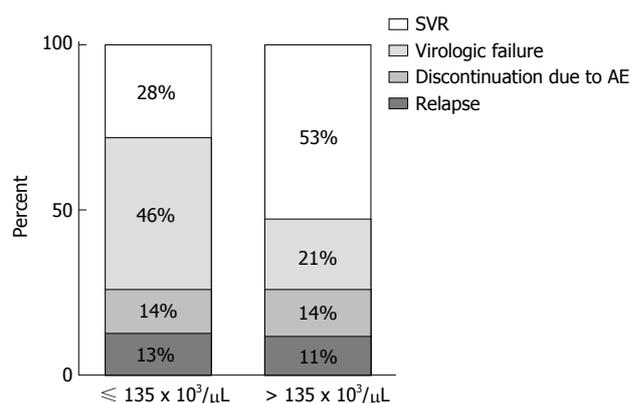
correlation coefficient for pairs of variables was determined to ensure that two highly correlated variables were not included in the same model. The multivariable logistic regression model shown in Table 2 includes the platelet count and excludes variables highly correlated with the platelet count. SVR was positively associated with *IL28B* CC genotype [odds ratio (OR) = 3.54, 95% confidence interval (CI): 1.19-10.53], higher platelet counts (OR = 1.10, per x 10^4 cells/μL, 95%CI: 1.05-1.16), white race (OR = 5.92, 95%CI: 2.34-14.96) and sub-genotype 1b HCV (OR = 2.81, 95%CI: 1.45-5.44). Four additional logistic regression models were built in which the platelet count was excluded and variables that are highly correlated with platelet count were examined individually (Table 2). In all four models white race, sub-genotype 1b, and CC *IL28B* genotype were positively associated with SVR. Variables indicative of more advanced liver disease - lower albumin, higher FIB-4 score, cirrhosis on biopsy/fibroscan - were significantly associated with treatment failure in individual models. A forest plot showing the interaction between treatment history and various baseline characteristics on outcome is presented in Supporting Figure 3.

An additional multivariable logistic regression analysis was conducted on the subgroup of patients receiving TVR-based triple therapy. Results were similar to those for the entire study group. SVR was positively associated with platelets (OR = 1.07 per × 10^4 cells/μL; 95%CI: 1.01-1.14), white race (OR = 5.22; 95%CI: 1.76-15.50), and HCV sub-genotype 1b (OR = 3.27; 95%CI: 1.51-7.07).

On-treatment factors associated with SVR

Table 3 shows the association between SVR and changes that occurred during treatment. As expected, SVR was strongly associated with viral kinetics. Patients whose HCV viral load decreased rapidly after starting the protease inhibitor and who thus had a FVR were significantly more likely to achieve an SVR (*P* < 0.01). SVR was also significantly associated with a greater decrease in

Table 1 Baseline characteristics of the study group

	n	Continuous variables: Median (IQR)/categorical variables: *n* (%)	Range
Telaprevir	223	172 (77)	-
Demographics and anthropometrics			
Age, yr	223	57 (51-61)	22-74
Gender, male	223	144 (65)	-
Race, white	223	182 (82)	-
BMI, kg/m^3, 17-24: Normal; 25-30: Overweight; > 30: Obese[a]	186	27.1 (24.5-30.7)	16.3-49.3
Past medical history			
Diabetes	223	48 (22)	-
Depression	223	47 (21)	-
IL28B genotype	223		
CC		20 (9)	-
CT		50 (22)	-
TT		21 (10)	-
Unknown		132 (59)	-
Treatment history	223		
Naïve		68 (31)	-
Non-responder		95 (43)	-
Relapser		45 (20)	-
Intolerance		12 (5)	-
Unknown		3 (1)	-
HCV treatment related characteristics			
HCV viral load, log IU/mL	221	6.31 (5.89-6.66)	3.07-7.64
Sub-genotype	223		
1a		118 (53.5)	-
1b		72 (32)	-
1a/1b		1 (0.5)	-
Unknown		32 (14)	-
Laboratory tests			
Hemoglobin, g/dL, female:12-15.5 g/dL; male: 13.5-17.5 g/dL[a]	220	14.3 (13.2-15.3)	9.2-18.2
AFP, ng/mL, 1.6-4.5 ng/mL[a]	158	6.85 (3.58-13.83)	0.80-208.60
Albumin g/dL, 3.5-4.9 g/dL[a]	219	4.20 (3.90-4.50)	2.60-5.30
AST, U/L, 1-50 U/L[a]	221	62 (39-106)	19-324
ALT, U/L, 1-53 U/L[a]	221	67 (44-107)	15-403
Platelets, × 10^3/μL, 150-450 × 10^3/μL[a]	223	152 (106-195)	14-365
Creatinine, mg/dL, 0.60-1.40 mg/dL[a]	205	0.91 (0.81-1.04)	0.58-10.2
Ferritin, ng/mL, 15-150 ng/mL[a]	54	184 (113-373)	22-893
eGFR, mL/min/1.73 m^2 < 60 mL/min per 1.73 m^2[ab]	204	88 (75-99)	6-125
Indication of liver fibrosis			
APRI score	221	0.82 (0.43-1.82)	0.10-12.48
FIB-4 score	221	2.65 (1.77-5.66)	0.35-35.30
FIB-4, advanced fibrosis/cirrhosis[c]	221	98/221 (44)	-
Cirrhosis, biopsy	189	85/189 (45)	-
Transient elastography score, kPa	80	11.8 (7.2-20.3)	3.9-55.1
Cirrhosis, transient elastography[d]	80	36/80 (45)	-
Cirrhosis, transient elastography/biopsy	202	96/202 (48)	-

[a]Normal range; [b]Estimated glomerular filtration rate calculated with epidemiology formula; [c]FIB-4 score ≥ 3.25 kPa; [d]Transient elastography > 13.5 kPa. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

eGFR in the first 4 wk. Treatment discontinuation due to adverse events was less common in the group that achieved SVR than the group that failed therapy (14% *vs* 24%), however, this difference was not statistically significant, *P* = 0.06. There was a trend of patients achieving SVR to having higher median changes in ferritin levels than patients who failed to achieve SVR (146 ng/mL *vs* 62 ng/mL, *P* = 0.08).

Baseline and on-treatment factors associated with relapse

Overall, 109 patients had an undetectable HCV viral load

at the time when they completed the intended therapy. Five were lost to follow-up. Relapse was confirmed in 27/104 (25%) of the patients who had follow-up data. Among the patients who were viral load negative at the time treatment ended and who later became viral load positive, the median time to confirmed relapse was 12 wk after the EOT (IQR = 5-12 wk, range = 2-34 wk); however, in some cases, relapse may have occurred before the time it was detected because of missed visits. Multivariable logistic regression analysis revealed an association between relapse and HCV sub-genotype 1a (OR = 5.15; 95%CI: 1.40-18.97) and advanced

Table 2 Univariable and multivariable logistic regression for baseline factors associated with sustained virological response

	Univariable			Multivariable[a]		
	OR	95%CI	*P*	OR	95%CI	*P*
Protease inhibitor, telaprevir	1.62	0.84-3.12	0.15	-	-	-
Age, yr	0.98	0.96-1.01	0.23	-	-	-
Gender, male	1.11	0.64-1.94	0.71	-	-	-
Race, white	3.12	1.41-6.90	< 0.01	5.92	2.34-14.96	< 0.01
Diabetes	0.43	0.21-0.87	0.02	-	-	-
Depression	1.58	0.83-3.02	0.17	-	-	-
BMI, kg/m^2	0.98	0.93-1.04	0.52	-	-	-
IL28B, CC *vs* CT/TT	3.56	1.31-9.64	0.01	3.54	1.19-10.53	0.02
Treatment history, naïve/relapser	1.86	1.08-3.20	0.03	-	-	-
HCV viral load, log IU/mL	0.79	0.54-1.14	0.21	-	-	-
Sub-genotype, 1b (*vs* all other)	2.06	1.17-3.65	0.01	2.81	1.45-5.44	0.02
Hemoglobin, g/dL	1.03	0.86-1.23	0.78	-	-	-
AFP, ng/mL	0.95	0.92-0.98	< 0.01	-	-	-
Albumin, g/dL	2.56	1.33-4.92	< 0.01	-	-	-
AST, U/L	0.99	0.99-0.99	0.02	-	-	-
ALT, per U/L	1.00	0.99-1.01	0.61	-	-	-
Platelets, per × 10^4/μL	1.08	1.03-1.13	< 0.01	1.10	1.05-1.16	< 0.01
Creatinine, per mg/dL	0.8	0.42-1.53	0.50	-	-	-
Ferritin, per ng/mL	0.99	0.99-1.00	0.63	-	-	-
eGFR, per mL/min per 1.73 m^2	1.00	0.99-1.02	0.65	-	-	-
APRI	0.84	0.70-1.02	0.08	-	-	-
FIB-4	0.91	0.83-0.99	0.02	-	-	-
APRI > 1.5	0.44	0.24-0.82	0.01	-	-	-
FIB-4 ⩾ 3.25	0.39	0.22-0.68	< 0.01	-	-	-
Cirrhosis transient elastography/biopsy	0.5	0.29-0.87	0.01	-	-	-

[a]Model includes platelets and no variable significantly correlated with platelets. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

Table 3 Comparison of on-treatment variables in the sustained virologic response and non- sustained virologic response group

	Total cohort Categorical: *n* (%) Continous: Median (IQR)	SVR (*n* = 94)	Fail to achieve SVR (*n* = 129)	*P*
Discontinuation due to adverse events	44/223 (20%)	13/94 (14%)	31/94 (24%)	0.06[a]
Change in ferritin from baseline to week 4 of treatment, ng/mL	91 (45-212)	146 (81-331)	62 (-20-175)	0.08[b]
Development of severe anemia	94/223 (42%)	54/94 (57%)	66/129 (51%)	0.35[a]
Change in eGFR from baseline to week 4[c], mL/min per 1.73 m^2	-4.41 (-14.87-3.23)	-6.59 (-16.98-0.52)	-1.68 (-13.99-5.00)	0.04[b]
Fast viral kinetics	139/223 (62%)	83/94 (88%)	56/129 (43%)	< 0.01[a]

[a] χ^2 test; [b] Mann-Whitney test; [c] Estimated glomerular filtration rate calculated with epidemiology formula. SVR: Sustained virological response; eGFR: Estimated glomerular filtration rate.

fibrosis/cirrhosis (FIB-4 score ⩾ 3.25; OR = 2.77; 1.07-7.22) (Table 4). The absence of an FVR (OR = 4.77, 95%CI: 1.68-13.56) was the only on-treatment variable independently associated with relapse.

Classification and regression tree analysis of factors associated with SVR

A CART analysis underscored the predictive value of the platelet count and was largely consistent with the results of the logistic regression analysis (Figure 2). The strongest baseline predictor was a platelet count > 135 × 10^3 cells/μL. Among patients with platelets > 135 × 10^3 cells/μL, HCV sub-genotype 1b and white race were predictive of SVR. Among patients with platelets > 135 × 10^3 cells/μL and sub-genotype 1a HCV, platelet counts > 236 × 10^3 cells/μL were predictive of SVR among whites; however, all of the black patients in this subgroup failed

therapy. As illustrated in Figure 3, among patients with platelets > 135 × 10^3/μL the virologic failure rate was 21% *vs* 46% in the lower platelet group (*P* < 0.01), and the SVR rate was 53% *vs* 28% (*P* < 0.01).

DISCUSSION

This study analyzed treatment outcomes in a real-world cohort of patients treated with TVR- and BOC-based triple therapy by experienced hepatologists. The results are important because TVR-based triple therapy is still used in many parts of the world[28]. Our cohort closely resembles the population of HCV-infected individuals in the United States. Twenty-two percent of the United States population is black, 38% have advanced fibrosis/cirrhosis, and the average age is approximately 50 years with 5% above the age of 65 years[28-31]. In our cohort,

Table 4 Univariable and multivariable logistic regression of factors associated with relapse

	Univariable			Multivariable		
	OR	95%CI	*P*	OR	95%CI	*P*
Protease inhibitor, Telaprevir	0.41	0.15-1.10	0.08	-	-	-
Age, yr	1.00	0.96-1.05	0.95	-	-	-
Gender, female	1.36	0.53-3.48	0.52	-	-	-
Race, black	1.16	0.28-4.71	0.84	-	-	-
Diabetes	1.86	0.65-5.28	0.25	-	-	-
Depression	0.54	0.17-1.75	0.30	-	-	-
BMI, per kg/m^2	0.98	0.88-1.10	0.76	-	-	-
IL28B, CC *vs* CT/TT[a]	-	-	-	-	-	-
Treatment history, naïve/relapser	1.10	0.45-2.72	0.84	-	-	-
HCV viral load, log IU/mL	1.74	0.80-3.78	0.16	-	-	-
Sub-genotype, 1a (*vs* all other)	6.26	1.75-22.45	0.01	5.15	1.40-18.97	0.01
Hemoglobin, g/dL	1.24	0.88-1.73	0.22	-	-	-
AFP, ng/mL	1.02	0.99-1.05	0.15	-	-	-
Albumin, g/dL	1.02	0.34-3.08	0.97	-	-	-
AST, U/L	1.01	1.00-1.02	0.06	-	-	-
ALT, U/L	1.00	0.99-1.01	0.23	-	-	-
Platelets, × 10^4/μL	0.95	0.89-1.02	0.19	-	-	-
Creatinine, mg/dL	1.41	0.72-2.74	0.31	-	-	-
Ferritin, ng/mL	1.00	0.99-1.01	0.26	-	-	-
eGFR, mL/min per 1.73 m^{2b}	0.99	0.97-1.02	0.66	-	-	-
APRI score	1.16	0.94-1.43	0.17	-	-	-
FIB-4 score	1.03	0.94-1.13	0.49	-	-	-
APRI > 1.5	2.33	0.87-6.23	0.09	-	-	-
FiB-4 ≥ 3.25	2.77	1.12-6.86	0.03	2.77	1.07-7.22	0.04
Cirrhosis, transient elastography/biopsy	2.55	1.05-6.19	0.04	-	-	-

[a]Zero patients with *IL28b* CC genotype relapsed after completing treatment; [b]Estimated glomerular filtration rate calculated with epidemiology formula. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

18% were black, approximately half had cirrhosis, and 10% were above the age of 65 years. Our most significant findings were the low 42% SVR rate and the association between treatment failure and factors indicative of more advanced liver disease such as low platelets, cirrhosis, high FIB-4 score, high AFP, and low albumin. CART analysis identified platelet counts > 135 × 10^3/μL as the strongest baseline predictor of SVR. Seventy-two percent of patients with platelet counts < 135 × 10^3/μL failed therapy.

Our clinical outcomes are consistent with those of the multicenter CUPIC trial, which examined TVR and BOC in 511 patients with compensated cirrhosis[32]. In both studies, non-responders to dual therapy had low SVR rates, whereas prior relapsers had an SVR rate of 62% in our study and 74% in the CUPIC cohort, supporting the use of triple therapy in prior relapsers. Discontinuations due to adverse events and virologic failure were common in both studies. Only 49% of our cohort and 52% of the CUPIC study group completed the planned treatment. The SVR rate in CUPIC was 48%, similar to the 42% in our study (*P* = 0.15). These results highlight the need for more effective therapies.

The association we observed between high platelets and SVR is consistent with published data. The relationship between thrombocytopenia and failure to achieve SVR was demonstrated in ENABLE-1 and ENABLE-2[33], two phase III multicenter randomized controlled trials in which patients on PEG/RBV were either treated with eltrombopag (a drug that stimulates platelet production) or placebo. In both trials, the SVR rate was significantly higher in the patients receiving eltrombopag: ENABLE-1 (23% *vs* 14%, *P* < 0.01) and ENABLE-2 (19% *vs* 13%, *P* = 0.02).

We did not find an association between younger age and SVR. This association was previously reported in a study by Frei and colleagues in which patients < 60 years of age or ≥ 60 years of age were matched on gender, cirrhosis, HCV genotype, and prior treatment response[34]. Further studies are needed to clarify the relationship between age and SVR among patients receiving triple therapy.

In our study, relapse occurred in about one-quarter of the patients who completed treatment and had an EOT. Relapse is emerging as the most common cause of non-SVR with newer DAAs. Sofosbuvir is an NS5B inhibitor that recently received FDA approval. In clinical trials, 9% of patients treated with sofosbuvir and PEG/RBV relapsed and 22% of patients treated with sofosbuvir and RBV relapsed[35,36]. Simeprevir is an NS3/4A protease inhibitor that recently received FDA approval. In clinical trials of simeprevir, relapse occurred in 11% of treatment-naïve and 18.5% of treatment-experienced patients[37]. In our study, relapse was related to both viral and host factors. HCV sub-genotype 1a and advanced fibrosis/cirrhosis (FIB-4 ≥ 3.25) were independently associated with relapse. Additionally, the absence of FVR was also associated with relapse, consistent with

results of dual therapy[37]. Recent data suggest that viral double-stranded RNA may play a role in relapse[38]. Understanding the molecular basis of relapse may allow the development of drugs that specifically target the processes underlying this type of treatment failure.

The strengths of our study include the complementary methods used to ensure that the entire cohort of patients was included, use of a study group with a high percentage of blacks, older patients and patients with advanced liver disease who were treated in real-world clinical practice, and use of two methods - multivariable logistic regression and CART analysis - to identify factors associated with treatment outcome. The limitations include the relatively small number of patients on BOC, and the observational study design, which limits the ability to compare the two protease inhibitors to each other.

Unless and until treatments are available that greatly reduce the risk of hepatocellular carcinoma in patients who have advanced liver disease, it will be essential to treat patients before extensive liver damage has occurred, as noted by others[36]. Several newly approved DAAs are available for HCV-infected patients including: Simeprevir, sofosbuvir, and the combination of ombitasvir, paritaprevir with ritonavir, and dasabuvir. In clinical trials, these compounds achieved high SVR rates; however, their effectiveness in the real-world is unknown and needs to be determined. This study provides a standard against which new therapies can be objectively evaluated.

COMMENTS

Background

Hepatitis C virus (HCV) infects 3% of the world's population. In the United States, HCV chronically infects an estimated 2.7 to 3.9 million people and is a leading cause of liver disease. Prior to 2011, treatments for HCV involved pegylated-interferon and ribavirin and had low rates of success. New drugs for HCV-infection, called direct-acting antivirals (DAAs), were first approved in 2011 and provided higher rates of success with lower adverse event rates. Understanding the effectiveness of these DAAs bears relevance for future clinical trials and simulation studies. This paper successfully analyzed a real-world cohort of patients treated with telaprevir- and boceprevir-based therapies to provide better information on cohorts using this class of therapies in the future.

Research frontiers

NS3/4A protease inhibitors are a relatively new class of therapies available to treat HCV-infection. This paper investigates the effectiveness of the first two FDA-approved protease inhibitors for HCV. Understanding the characteristics associated with successful treatment in HCV-infected patients is critical for the ongoing treatment of the HCV-infected population.

Innovations and breakthroughs

The authors used traditional and machine learning methods to identify factors associated with achieving a sustained virologic response in HCV-treatment. The authors found that factors indicative of more advanced fibrosis or cirrhosis were associated with lower rates of sustained virological response. They also found that specific cut-off points in platelet count that could be used to risk-stratify patients. The results imply that treating patients before they develop more advanced disease is an important message that should be relayed to care-providers.

Applications

The results could help improve design of future clinical trials for NS3/4A protease inhibitors for HCV. The population contained individuals with characteristics that were lacking in clinical trials, offering unique information on the effectiveness of NS3/4A protease inhibitors in this population. Currently, numerous protease inhibitors are on the market for HCV. Understanding the risk profile of this class of therapies and the factors associated with their risks and benefits could lead to improvements. Additionally, this real-world study could provide some additional information for future simulation studies to use.

Terminology

Sustained virologic response - the absence of HCV RNA 12-24 wk after the end-of-treatment. Considered a cure in HCV-treatment. Direct-acting antivirals (DAAs) - a class of therapies that directly target HCV and prevent replication. DAAs are composed of NS3/4A protease inhibitors, nucleos(t)ide and non-nucleos(t)ide NS5B Polymerase Inhibitors, and NS5A inhibitors.

Peer-review

This study will give some useful information to clinicians and provided a successful ways to evaluate the new medications. The manuscript read and organized well, and the data treated were also reasonable.

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