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Research Article

Predictors of Sustained Virologic Response and Failure of First DAA Therapy in Chronic Hepatitis C Patients

Omar Y. Mousa[1*], Chang H. Kim[2], Ly-Elaine Pham[3], Chukwuma [1]. Egwim[1], Scott A. Zela[1], Victor Ankoma-Sey[1]

[1]Department of Hepatology, Liver Associates of Texas, USA

[2]Department of Internal Medicine, University Hospitals Cleveland (Case) Medical Center, USA

[3]Department of Internal Medicine, Louisiana State University Health Sciences Center, USA

[*]**Corresponding author:** Omar Y. Mousa, MD, Hepatology, Liver Associates of Texas, P.A, 6410 Fannin Street No. 225, Houston, TX 77030, USA. Tel: +19049536970; Email: omar.mousa@hotmail.com

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Abstract

Telaprevir and Boceprevir were the first FDA approved NS3/4A protease inhibitors of Chronic Hepatitis C infection in 2011. Despite being discontinued in the US market after 3 years of FDA approval, both protease inhibitors left a great impact in the treatment approach of Chronic Hepatitis C with a dramatic improvement in SVR rates from the old dual regimen of Pegylated interferon and ribavirin. However, there were associated significant adverse outcomes. Randomized clinical trials may have limited generalizability in terms of efficacy, safety, and tolerability of these drugs in everyday outpatient setting. Our prospective cohort study of 113 Chronic Hepatitis C patients, who were treated outside of a controlled trial, showed different efficacies and safety profiles compared to what was described in controlled trials of Telaprevir and Boceprevir. In addition, our analysis identified no significant predictors of end of treatment response or sustained virologic responses at weeks 12 and 24 following treatment completion. This does not correspond with data from recent studies. Studying data outside of a controlled trial from outpatient hepatology practices about new hepatitis C therapies that have obtained FDA approval is important as newer antiviral agents are being reviewed by the FDA.

Keywords: Chronic Hepatitis C; Telaprevir; Boceprevir; Sustained virologic response

Abbreviations:

SVR	:	Sustained virologic response
CHC	:	Chronic Hepatitis C
TVR	:	Telaprevir
BVR	:	Boceprevir
DAA	:	Direct Acting Anti-Viral therapy
eRVR	:	Extended Rapid Virologic Response
EOT VR	:	End of treatment virologic response
DMID	:	Division of Microbiology and Infectious Diseases

Introduction

Chronic Hepatitis C (CHC) infection is a major cause of chronic liver disease, hepatocellular carcinoma and is a common indication for liver transplantation [1]. Telaprevir (TVR) and Boceprevir (BVR), the first FDA approved NS3/4A protease inhibitors changed the landscape of CHC therapy in 2011. Despite being discontinued in the US market after 3 years of FDA approval, both protease inhibitors left a great impact in the treatment approach of CHC: ushering in a new era of Direct Acting Anti-Viral (DAA) therapy for CHC. These agents achieved higher sustained virologic responses (SVR) in clinical trials of CHC genotype 1 patients (up to 70%-80%). This is a dramatic improvement from the old dual regimen of Pegylated interferon and ribavirin which had lower SVR rates (14%-29%) [2]. A higher SVR predicts long-term response to Treatment [3] and reduces liver-specific as well as all-cause mortality [4]. Despite the enhanced efficacy of TVR/

BVR based triple therapy, there were associated significant adverse outcomes and toxicities.

Randomized clinical trials have important characteristics but may have limited generalizability in terms of efficacy, safety, and tolerability of these drugs in everyday outpatient setting outside of a controlled trial. We report our experience of 113 CHC patients, with emphasis in our analysis on the predictors of SVR and treatment failure in everyday life outside of a controlled trial setting.

Methods

A single center prospective cohort of CHC patients (treatment naïve, experienced and Cirrhotics) treated at the Liver Associates of Texas Hepatology Clinics between July 2011 and Jan 2014. Patients were non-randomly assigned to two treatment groups, either TVR or BVR based triple regimen with Pegylated interferon and ribavirin. Response guided therapy was adopted. Futility rules were applied. Endpoints of the study included comparison of Extended Rapid Virologic Response (eRVR), end of treatment virologic response (EOT VR), SVR at 12 weeks (SVR12) and 24 weeks (SVR24.Outcomes and treatment discontinuations were analyzed, with emphasis on 8 potential predictors of SVR: Gender, Age, BMI, Genotype, Ethnicity, eRVR, Prior treatment experience and Pre-treatment HCV RNA levels.

Statistical analysis was performed using statistical software package R (version 3.1.0, R Foundation for Statistical Computing) and SPSS statistics v19. Correlation matrices were built to compare maintenance of treatment response between the TVR and BVR groups at ETR, SVR12, and SVR24. Logistic regression models for treatment response at ETR, SVR12, and SVR24 were built to identify predictors of treatment response. Reduction of predictor variables for the logistic regression models was performed through a regression variable selection method (Akaike's information criterion).

Results

Patient characteristics and Virologic responses

113 CHC patients were treated with either TVR (85/113) or BVR (28/113) based triple regimen. Patient characteristics and potential predictors of treatment response are shown in Table 1. Virologic responses are summarized in Table 2, and are compared to SVR rates in clinical trials in table 3. SVR12 and SVR24 data were available for 107 and 105 patients, respectively. Compensated cirrhosis was present in 41 CHC patients based on liver biopsy (35 received TVR and 6 received BVR).

Predictors	Telaprevir N = 85	Boceprevir N = 28
Age, mean years (SD[α])	54.65 (7.83)	53.89 (8.71)
[#]**BMI** kg/m^2 (SD[α])	30.21 (6.73)	30.13 (6.03)
Gender: n (%)		
Male	40 (47)	14 (50)
Female	45 (53)	14 (50)
Genotype: n (%)		
1a	67 (79)	21 (75)
1b	18 (21)	7 (25)
Ethnicity: n (%)		
Caucasian	46 (54)	19 (68)
African American	25 (29)	3 (11)
Hispanic	10 (12)	5 (18)
Asian	3 (4)	1 (3)
Other	1 (1)	0
Category/Prior treatment experience: n (%)		
Treatment-Naïve	20 (24)	11 (39)
Null responder	46 (54)	10 (36)
Relapser	19 (22)	7 (25)
[*]**eRVR**: n (%)		
Yes	63 (74)	18 (64)
No	22 (26)	10 (36)
Pre-treatment [β]HCV RNA: n (%)		
High (≥ 800,000 IU/mL)	67 (79)	16 (57)
Low (<800,000 IU/mL)	18 (21)	12 (43)

*eRVR: extended rapid virologic response.
[β]HCV: Hepatitis C Virus.
[#] BMI: Body mass index.
[α]SD: Standard deviation.

Table 1: Characteristics of Chronic Hepatitis C patients and potential predictors of response to therapy.

	Telaprevir n/N (%)				**Boceprevir*** n/N (%)			
Treatment category	eRVR	EOT VR	SVR12	SVR24	cEVR16	EOT VR	SVR12	SVR24
Naïve	16/20 (80)	15/20 (75)	10/17# (59)	9/16# (56)	11/11 (100)	10/11 (91)	10/11 (91)	9/10# (90)
Relapsers to previous treatment.	17/19 (89)	17/19 (89)	15/18# (83)	14/18# (78)	7/7 (100)	7/7 (100)	6/6# (100)	6/6# (100)
Non-Responders to previous treatment.	30/46 (65)	19/45# (42)	18/45# (40)	18/45# (40)	1/10 (10)	2/10 (20)	1/10 (10)	1/10 (10)
Cirrhotics©	27/35 (77)	20/34 (59)	18/34 (53)	16/33 (48)	4/6 (67)	3/6 (50)	3/6 (50)	3/6 (50)
Non-Cirrhotics©	21/25 (84)	16/25 (64)	13/23 (57)	13/23 (57)	10/13 (77)	10/13 (77)	10/13 (77)	10/13 (77)

*Patients receiving BVR had a 4-week lead-in phase.
#Total N may be lower at EOT VR, SVR12 or SVR24 because of missing laboratory values for up to 8 patients by week 72, i.e. patient lost to follow up, medical insurance issue.
©Total number of Cirrhotic and non-cirrhotic patients is lower than 113, depending on availability of liver biopsy results.

Table 2: Virologic responses to DAA therapy; TVR vs BVR-based triple regimen.

	Telaprevir		**Boceprevir**	
Treatment category	**Our experience in everyday outpatient practice**	**Clinical Trials**	**Our experience in everyday outpatient practice**	**Clinical Trials**
[a]Naïve	56%	75%	90%	42% to 68% depending on Ethnicity
[b]Prior relapsers to Peg-IFN and RBV	78%	83%	100%	69-75%
[c]Prior non-responders	40%	29%	10%	40-52%

[a] SVR rates were compared to the ADVANCE trial (TVR) and SPRINT-2 trial (BVR).
[b, c]SVR rates were compared to the REALIZE trial for TVR, and RESPOND-2 trial for BVR.

Table 3: Comparison of SVR rates in everyday outpatient practice vs clinical trials.

DAAs treatment Failure

Rates of treatment failure with DAAs are presented in table 4. Overall, CHC therapy was discontinued in 38/85 (44.7%) patients in the TVR cohort and 9/28 (32.1%) patients in the BVR cohort. This is due to either viral breakthrough during therapy, non-response to DAAs or secondary to serious adverse events. 4/85 (5%) relapsed to TVR-based therapy and 8/85 (9.4%) experienced a non-response. 3/28 (11%) relapsed to BVR-based therapy and 21.4% (6/28) experienced a non-response.

Serious adverse events included hematological changes (Thrombocytopenia, anemia or neutropenia - DMID toxicity grades 3-4), hepatic decompensation, DRESS syndrome, GI bleeding, myocardial Infarction, acute renal failure, depression with suicidal ideation or fever and retroperitoneal inflammation. In CHC patients with cirrhosis, non-response to TVR was observed in 8.6% of cirrhotic patients and with BVR in 33%. 6% of cirrhotic TVR patients and 17% of the cirrhotic BVR patients relapsed. 14% of TVR patients with cirrhosis experienced treatment discontinuation secondary to viral breakthrough. Serious adverse events were seen in 20% of TVR patients.

	Telaprevir			Boceprevir		
	Treatment Naive	Previous Non-Responders	Previous Relapsers	Treatment Naive	Previous Non-Responders	Previous Relapsers
Discontinuation reason: n (%)						
- Viral Breakthrough	2 (10)	8 (17.4)	1 (5.3)	0	0	0
- Non-Response to DAAs	1 (5)	7 (15.2)	0	0	6 (60)	0
- Serious adverse event	6 (30)	10 (21.7)	2 (10.5)	1 (9%)	2 (20)	0
- Other (e.g lost insurance)	0	1 (2.2)	0	0	0	0
Relapse to direct acting agents: n (%)	1 (5)	2 (4.3)	1 (5.3)	2 (18.2)	1 (10)	0
Total	10/20	28/46	4/19	3/11	9/10	0/7

Table 4: Treatment failure rates with DAA therapy.

Maintenance of Virologic Response

Analysis of correlation matrices revealed no significant difference in maintenance of treatment response at ETR, SVR12, and SVR24 between TVR or BVR treatment groups ($p > 0.05$).

Predictors of EOT VR, SVR12 and SVR24 (presented in Table 5)

Due to low subject to variable ratio in our single center study, we implemented regression variable selection using Akaike's Information Criterion (AIC). Applied to our model, regression variable selection revealed age, genotype, BMI, eRVR, and prior treatment experience as the most relevant predictor variables for treatment response at end of treatment and SVR12 (Pre-treatment HCV RNA viral load, Gender, and Ethnicity were dropped). For SVR24, the AIC-selected predictors were age, genotype, eRVR, prior treatment experience and low pretreatment HCV RNA (BMI, Gender, and Ethnicity were dropped).

Predictors of EOT: Logistic regression models for EOT VR with all 8 predictors revealed no significant predictors of response at end of treatment. In addition, based on AIC-selected predictors, regression variable selection showed that none of these variables were significant predictors of response.

Predictors of SVR12: Logistic regression models with 8 predictors of SVR12, showed that age was a positive predictor, although the odds ratio was very small (OR: 1.07, p=0.0476).

However, regression variable selection showed that none of the variables were significant predictors of SVR12.

Predictors of SVR24: Logistic regression models with 8 predictors of SVR24 showed that age was a positive predictor of treatment response, although the odds ratio is very small (OR: 1.08, p=0.0444). However, based on AIC-selected predictors, none of the variables were significant predictors of SVR24.

	Odds Ratio	P-value
EOT VR		
Age	1.03	0.367
BMI	0.98	0.658
Treatment experienced: Non-Responder Relapser	 0.358 2.41	 0.099 0.327
Genotype 1b	 2.13	0.369
SVR12		
Age	1.03	0.317
BMI	0.967	0.500
Treatment experienced: Non-Responder Relapser	 0.443 2.70	 0.200 0.273
Genotype 1b	2.26	0.333
SVR24		
Age	1.04	0.281
Pre-treatment HCV RNA = Low (<800,000 IU/mL)	0.938	0.934
Treatment experienced: Non-Responder Relapser	 0.487 3.23	 0.299 0.201
Genotype 1b	2.52	0.275
Odds ratio for eRVR is not presented in this table due to small sample size (p = 0.989).		

Table 5: Predictors of EOT VR, SVR12 and SVR24 based on regression variable selection.

Discussion

The efficacy of DAAs in our experience in everyday outpatient setting outside of a controlled trial differed from that of previously reported to the clinical trials, with major differences in SVR rates. This supports the importance of studying FDA approved pharmaceutical agents in real life as clinical trials data can have limited generalizability. In everyday outpatient hepatology practice, outcomes and causes of discontinuations varied significantly among both treatment groups. The TVR group experienced higher rates of serious adverse events leading to treatment discontinuation, while the BVR group failed therapy mainly secondary to non-response or relapse to DAA. The higher rates of viral breakthrough in the TVR group could be explained by earlier treatment discontinuation secondary to serious adverse event occurrence. The same outcomes apply to patients with liver cirrhosis.

Of the three logistic regression models built for predictor variables at EOT VR, SVR12 and SVR24, only the SVR12 and SVR24 models had a significant predictor of response. Age was a positive predictor of response at SVR12 and SVR24. However, given that the odds ratio was very small, and that advanced age rarely leads to better clinical outcomes, this is likely statistical noise due to small power rather than a real effect of the predictor. This was confirmed when regression variable selection was performed to improve model stability and subject-to-variable ratio, where the small positive effect of age on treatment outcome did not exist for both SVR12 and SVR24 models. As a result, based on AIC-selected predictors, regression variable selection showed that none of the variables significantly predicted end of treatment response, SVR12 and SVR24. This does not correspond with data from recent studies [5-8].

In summary, our study demonstrates the importance of everyday outpatient hepatology practice data for new drugs that have obtained FDA approval.

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Potential competing interests:

The authors declare that there is no conflict of interest regarding the publication of this paper, except for the following author:

Victor Ankoma-Sey, MD:

- Speaking: Abbvie, Intercept, Gilead, Merck, Salix.
- Research: Gilead, Hologic, Conatus, Intercept, Novo Nordisk, Genfit, Octeta, Inovio, Abbvie, Mayo, Exalenz, EiSAI.

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