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Research Article

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

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Abbreviations BVR: Boceprevir; CHC: Chronic Hepatitis C; DAA: Direct Acting Anti-Viral therapy; DMID: Division of Microbiology and Infectious Diseases; eRVR: Extended Rapid Virologic Response; ETR: End of Treatment virologic Response; FDA: Food and Drug Administration; TVR: Telaprevir; SPSS: The Statistical Package for the Social Sciences; SVR: Sustained Virologic Response

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Abstract

Telaprevir and Boceprevir were the first US Food and Drug Administration (FDA) approved NS3/4A protease inhibitors of Chronic Hepatitis C infection in 2011. Despite their discontinuation from the US market 3 years after their approval by the US FDA, both protease inhibitors left a great impact in the treatment approach of Chronic Hepatitis C. Both antiviral agents allowed a dramatic improvement in SVR rates compared to 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. Research studies conducted outside of a controlled trial about new chronic hepatitis C therapies that have obtained FDA approval is important as newer antiviral agents are being reviewed by the FDA.

Introduction

Chronic Hepatitis C (CHC) infection is a major cause of chronic liver disease and hepatocellular carcinoma. It is a common indication for liver transplantation [1]. Telaprevir (TVR) and Boceprevir (BVR) were the first US Food and Drug Administration (FDA) approved NS3/4A protease inhibitors for the treatment of CHC infection in 2011. They left a great impact in the treatment approach of CHC, ushering in a new era of Direct Acting Anti-Viral (DAA) therapy. Both agents achieved higher Sustained Virologic Response (SVR) rates among CHC genotype 1 patients that reached up to70%-80%. This is a dramatic improvement in treatment response compared to the old dual regimen of Pegylated interferon and ribavirin that showed lower SVR rates (14%-29%) [2]. A higher SVR predicts long-term response to Treatment and reduces liver-specific and all-cause mortality [3,4]. Even though they changed the landscape of CHC therapy, they were discontinued from the US market 3 years after being approved by the US FDA. That was despite the enhanced efficacy of TVR and BVR-based triple therapy and mainly related to associated serious adverse events and toxicities [5].

Randomized clinical trials have important characteristics but may have limited generalizability in terms of efficacy, safety and tolerability of these antiviral agents in real life. We report our experience of 113 CHC patients who received TVR or BVR-based triple therapy, with emphasis on analyzing the predictors of SVR and treatment failure in a real life clinical experience [6,7].

Methods

Patients and study design

This was a single center prospective cohort study including CHC patients who were treated at the Liver Associates of Texas Hepatology Clinics between July 2011 and Jan 2014. Patients infected with CHC were assigned to two treatment groups in a non-random fashion and based on patient and/or physician preference for suitability of the drug regimen. Either TVR or BVR based triple regimen with Pegylated interferon and ribavirin was used. Patients were further assigned to different treatment groups depending on their prior CHC treatment status; treatment naïve group, null responders or relapsers to prior treatment. Response guided therapy was adopted and the futility rules as recommended by the treatment guidelines were applied. Endpoints of the study included comparison of Extended Rapid Virologic Response (eRVR), end of treatment virologic response (ETR), SVR at week 12 (SVR12) and 24 (SVR24) following treatment completion. Outcomes and

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

Predictors	Telaprevir N = 85	Boceprevir N = 28	*P* value
Age, mean years (SD[α])	54.65 (7.83)	53.89 (8.71)	>0.05
[#]**BMI** kg/m^2 (SD[α])	30.21 (6.73)	30.13 (6.03)	>0.05
Gender: n (%) Male Female	40 (47) 45 (53)	14 (50) 14 (50)	>0.05
Genotype: n (%) 1a 1b	67 (79) 18 (21)	21 (75) 7 (25)	>0.05
Ethnicity: n(%) Caucasian African American Hispanic Asian Other	46 (54) 25 (29) 10 (12) 3 (4) 1 (1)	19 (68) 3 (11) 5 (18) 1 (3) 0	>0.05
Category/Prior treatment experience:n(%) Treatment-Naïve Null responder Relapser	20 (24) 46 (54) 19 (22)	11 (39) 10 (36) 7 (25)	>0.05
[*]**eRVR**: n (%) Yes No	63 (74) 22 (26)	18 (64) 10 (36)	>0.05
Pre-treatment [β]HCV RNA: n(%) ≥800,000 IU/mL <800,000 IU/mL	67 (79) 18 (21)	16 (57) 12 (43)	>0.05

*eRVR: Extended Rapid Virologic Response, [β]HCV: Hepatitis C Virus, [#] BMI: Body Mass Index, [α]SD: Standard Deviation.

treatment discontinuations were analyzed, with emphasis on eight potential predictors of SVR: age, gender, body mass index (BMI), ethnicity, genotype, prior treatment experience and pre-treatment HCV RNA levels. Analysis of eRVR and cirrhosis status as potential predictors was not possible due to small sample size as a limiting factor.

Statistical analysis

Statistical analysis was performed using statistical software package R (version 3.1.0, R Foundation for Statistical Computing) and the Statistical Package for the Social Sciences 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

113 CHC patients were treated with a DAA based triple regimen. Eighty five patients received TVR and twenty eight received BVR. The majority of patients in both groups were Caucasians and had CHC G1a infection. The two treatment groups were not statistically different in terms of baseline characteristics, as summarized in table 1. Potential predictors of treatment response are shown in the same table. Compensated cirrhosis was present in 41CHC patients based on liver biopsy (35 received TVR and 6 received BVR).

Virologic responses

SVR12 and SVR24 data were available for 107 and 105 patients, respectively. In the TVR based triple therapy group, CHC patients who were relapsers to previous treatment experienced the highest SVR12 (83%) and SVR24 rates (78%). Treatment naïve patients experienced lower SVR12 (59%) and SVR24 rates (56%), and previous non-responders had the lowest SVR12 (40%) and SVR24 rates (40%). Similar trends in SVR12 and SVR24 rates was observed among patients who received BVR-based triple therapy, as shown in the Table 2. Patients who had cirrhosis experienced lower SVR12 and SVR24 rates compared to non-cirrhotic patients (Table 2). Table 3 compares SVR24 rates in both cohorts who were treated at our center with virologic responses as published in clinical trials.

DAAs treatment regimen failure

Treatment regimen failure rates using both TVR and BVR are presented in table 4. CHC therapy was discontinued in 44.7% (38/85) of patients in the TVR cohort and 32.1% (9/28) of patients in the BVR cohort. Causes of treatment discontinuation included: viral breakthrough during therapy, non-response to DAAs or serious adverse events. 5% (4/85) relapsed to TVR-based therapy and9.4% (8/85) did not respond to treatment. 11% (3/28) relapsed to BVR-based therapy and 21.4% (6/28) did not respond to treatment.

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

Telaprevir n/N (%)					*p* value	Boceprevir[*] n/N (%)				*p* value
Treatment category	eRVR	ETR	SVR12	SVR24		cEVR16	ETR	SVR12	SVR24	
Naïve	16/20 (80)	15/20 (75)	10/17[#] (59)	9/16[#] (56)	>0.05	11/11 (100)	10/11 (91)	10/11 (91)	9/10[#] (90)	>0.05
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 ETR, 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, due to lack of liver biopsy results for some patients.

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Table 3: Comparison of SVR24 rates in our study to those in clinical trials.

	Telaprevir		Boceprevir	
Treatment category	**Study cohort**	**Clinical Trials**	**Study cohort**	**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[5] trial (Telaprevir) and SPRINT-2[6] trial (Boceprevir).

[b,c]SVR rates were compared to the REALIZE[7] trial (Telaprevir), and RESPOND-2[8] trial (Boceprevir).

Table 4: Treatment regimen failure rates with DAA therapy.

	Telaprevir			Boceprevir		
	Treatment Naive	Previous Non-Responders	Previous Relapsers	Treatment Naive	Previous Non-Responders	Previous Relapsers
Discontinuation reason:n(%) - Viral Breakthrough - Non-Response to DAAs - Serious adverse event - Other (e.g lost insurance)	 2 (10) 1 (5) 6 (30) 0	 8 (17.4) 7 (15.2) 10 (21.7) 1 (2.2)	 1 (5.3) 0 2 (10.5) 0	 0 0 1 (9) 0	 0 6 (60) 2 (20) 0	 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

Serious adverse events included hematological changes (Thrombocytopenia, anemia or neutropenia - DMID toxicity grades 3-4), hepatic decompensation, DRESS syndrome, GI bleeding, myocardial Infarction, acute kidney injury, depression with suicidal ideation or fever and retroperitoneal inflammation.

In CHC patients with cirrhosis, rates of non-response to treatment were 8.6% and 33% in TVR and BVR-based therapy, respectively. Among cirrhotics who relapsed, 6% received TVR and 17% received BVR. Treatment was discontinued secondary to viral breakthrough in 14% of TVR patients with cirrhosis. None of the patients who received BVR experienced viral breakthrough. Serious adverse events were seen in 21% of patients who received TVR and 11% of those who received BVR.

Maintenance of Virologic Response

Analysis of correlation matrices was performed to evaluate maintenance of treatment response. There was no significant difference in maintenance of treatment response at ETR, SVR12, and SVR24 among TVR or BVR treatment groups ($p > 0.05$).

Predictors of ETR, SVR12 and SVR24

We evaluated for predictors of ETR, SVR12 and SVR24 as shown 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 ETR: Logistic regression models for ETR with all 8 predictors revealed no significant predictors of response at end of

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

Predictors of ETR, SVR12 and SVR24		
	Odds Ratio	***P*-value**
ETR		
Age	1.03	0.367
BMI	0.98	0.658
Gender Male	0.79	0.681
Ethnicity Caucasian	0.35	0.186
Treatment experienced: **Non-Responder** **Relapser**	 0.36 2.41	 0.099 0.327
Genotype1b	2.13	0.369
Pre-treatment HCV RNA <800,000 IU/mL	1.24	0.792
SVR12		
Age	1.03	0.317
BMI	0.97	0.500
Gender Male	0.76	0.612
Ethnicity Caucasian	0.68	0.591
Treatment experienced: **Non-Responder** **Relapser**	 0.44 2.70	 0.200 0.273
Genotype1b	2.26	0.333
Pre-treatment HCV RNA <800,000 IU/mL	1.15	0.862
SVR24		
Age	1.04	0.281
Gender Male	0.87	0.808
Ethnicity Caucasian	0.61	0.486
Treatment experienced: **Non-Responder** **Relapser**	 0.49 3.23	 0.299 0.201
Genotype1b	2.52	0.275
Pre-treatment HCV RNA = Low (<800,000 IU/mL)	0.94	0.934

Odds ratios for eRVR and cirrhosis are not presented in this table due to small sample size ($p = 0.989$).

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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.

Discussion

The efficacy and safety of DAA sin studies conducted outside of a controlled trial differed from previously reported data in clinical trials, with major differences in SVR rates.CHC patients who received TVR-based regimen achieved lower SVR24 rates than patients treated in clinical trials, except for prior non-responders. Those who received BVR-based regimen achieved higher SVR24 rates compared to patients treated in clinical trials, except for prior non-responders [8].

DAA treatment outcomes and causes of discontinuations varied significantly among both treatment groups. The TVR-based regimen was associated with higher rates of serious adverse events that lead to treatment discontinuation. The BVR-based regimen was associated with treatment failure secondary to non-response or relapse to DAA therapy. The higher rates of viral breakthrough in the TVR group could be explained by earlier treatment discontinuation secondary to serious adverse event occurrence. Similar treatment outcomes were noticed among patients with liver cirrhosis. This reflects an example why such agents were discontinued from the US market 3 years after being approved by the US FDA [9].

Three logistic regression models were built for predictor variables at ETR, 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. Therefore 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 presented in other studies [10-14].

Our study provides important evidence that reassessment of US FDA approved pharmaceutical agents in real life is crucial and data from clinical trials may have limited generalizability.

References

1. GT soulfas, I Goulis, D Giakoustidis, EA kriviadis, P Agorastou, G Imvrios, et al. Hepatitis C and liver transplantation. Hippokratia. 2009; 13: 211-215.
2. Falck-Ytter Y, Kale H, Mullen KD. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med. 2002; 136: 288-292.
3. Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49: 1335-1374.
4. Backus LI, Boothroyd DB, Phillips BR. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011; 9: 509-516.
5. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, et al. ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011; 364: 2405-2416.
6. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364: 1195-1206.
7. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. REALIZE Study Team. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011; 364: 2417-2428.
8. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364: 1207-1217.
9. Mousa OY, Pungpapong S, Ankoma-Sey V. The era of first direct-acting antiviral agents: What did we learn? Clinical Liver Disease. 2016; 8: 72-75.
10. Christoph R Werner, Carolin Franz, Daniel P Egetemeyr, Robert Beck, Nisar P Malek, Ulrich M Lauer, et al. First-generation protease inhibitor-triple therapy: SVR 24, safety, and predictors of response in a large single center cohort. Virol J. 2015; 12: 37.
11. Manzano-RobledaMdel C, Ornelas-Arroyo V, Barrientos-Gutiérrez T, Méndez-Sánchez N, Uribe M, Chávez-Tapia NC. Boceprevir and telaprevir for chronic genotype 1 hepatitis C virus infection. A systematic review and meta-analysis. Ann Hepatol. 2015; 14: 46-57.
12. AA Butt, P Yan, OS Shaikh, MS Freiberg, V Lo Re, AC Justice, et al. Virologic response and haematologic toxicity of boceprevir- and telaprevir-containing regimens in actual clinical settings. J Viral Hepat. 2015; 22: 691-700.
13. Sterling RK, Kuo A, Rustgi VK, Sulkowski MS, Stewart TG, Fenkel JM, et al. Virological outcomes and treatment algorithms utilisation in observational study of patients with chronic hepatitis C treated with boceprevir or telaprevir. Aliment Pharmacol Ther. 2015; 41: 671-685.
14. Neukam K, Munteanu DI, Rivero-Juárez A, Lutz T, Fehr J, Mandorfer M, et al. Boceprevir or Telaprevir Based Triple Therapy against Chronic Hepatitis C in HIV Coinfection: Real-Life Safety and Efficacy. PLoS One. 2015; 10.

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