The Era of First Direct-Acting Antiviral Agents: What Did We Learn?

Omar Y. Mousa, M.D.,* Surakit Pungpapong, M.D.,*,† and Victor Ankoma-Sey, M.D.‡

BACKGROUND

The introduction of oral direct-acting antiviral agents (DAAs) revolutionized the treatment of patients infected with hepatitis C virus (HCV). The first class of DAAs to be approved by the US Food and Drug Administration were the protease inhibitors (PIs), telaprevir (TVR) and boceprevir (BOC). Because of their low potency and low genetic barrier to develop resistance-associated variants (RAVs), these drugs were approved to be used in combination with pegylated interferon- α and ribavirin (PR). Even though both PIs had significant issues related to safety and efficacy, they heralded a new era in therapy for chronic HCV infection.^{1,2} Like shooting stars in the night sky, they shone brightly yet briefly, illuminating the path for future advances in the treatment of HCV. Within 3 years of their approval to be available in the United States, both TVR and BOC were discontinued from that market. They are no longer recommended by the European Association for the Study of the Liver and the American Association for the Study of Liver

Diseases for the treatment of HCV because they have been superseded by more effective and safer second-generation PIs and/or other classes of DAAs. So what did we learn from those shooting stars, TVR and BOC?

EFFICACY OF TVR AND BOC

A previous *Clinical Liver Disease* review by Strader and Seeff³ described how TVR and BOC combined with PR set a new standard of care for HCV treatment, achieving higher rates of sustained virological response (SVR) compared with PR alone, using response-guided therapy to determine treatment duration in various patient populations (Table 1). We learned that the PIs could not be used as monotherapy because of their reduced efficacy and the risk for emerging RAVs. Futility rules that mandated treatment discontinuation were implemented because they predicted treatment failure. Although the efficacy rates presented in Table 1 were reported in

Abbreviations: BOC, boceprevir; DAA, direct-acting antiviral agent; DDI, drug–drug interactions; HCV, hepatitis C virus; PI, protease inhibitor; PR, pegylated interferon- α and ribavirin; RAV, resistance-associated variant; SAE, serious adverse event; SVR, sustained virological response; TVR, telaprevir.

From the *Division of Gastroenterology and Hepatology; †Department of Transplant, Mayo Clinic, Jacksonville, FL, and

‡Gastroenterology and Hepatology, Liver Associates of Texas, P.A., Houston, TX.

Potential conflict of interest: Nothing to report.

Received 27 August 2015; accepted 14 July 2016

View this article online at wileyonlinelibrary.com

© 2016 by the American Association for the Study of Liver Diseases

TABLE 1. EFFICACY OF TVR- AND BOC-BASED TRIPLE THERAPY (WITH PEGINTERFERON- α /RIBAVIRIN) IN PHASE 3 CLINICAL TRIALS

	TVR: SVR Rates (%)		BOC: SVR Rates (%)	
	TVR-Based Triple Therapy	Peginterferon- α /Ribavirin	BOC-Based Triple Therapy	Peginterferon- α /Ribavirin
ADVANCE ¹⁰ : treatment naive	75	44		
REALIZE ¹¹ : treatment experienced				
Relapsers	83	24		
Partial responders	59	15		
Prior nonresponders	29	5		
SPRINT-2 ¹²				
Black cohort			42	23
Non-Black cohort			67	40
RESPOND-2 ¹³				
Relapsers			69	29
Prior nonresponders			40	7

SVR rates included in this table are from randomized, double-blind placebo controlled clinical trials. The selected regimens most closely reflect US Food and Drug Administration–approved TVR- and BOC-based triple therapy regimens.

clinical trials, real-life data also revealed a greater efficacy for TVR compared with BOC-based regimens.⁴

PATIENTS WITH CHRONIC HCV WITH CIRRHOSIS

The introduction of the PIs once again highlighted the importance of achieving an SVR because survival rates were higher in the cirrhotic patients who experienced this treatment milestone. Successfully treated cirrhotic patients also experienced less frequent liver failure or hepatocellular carcinoma.⁴ However, treatment response was to a variable extent dependent on previous PR treatment outcome. In treatment-experienced patients, SVR rates at 12 weeks after treatment completion were higher among patients receiving TVR (relapsers 74.2%, partial responders 40.0%, null responders 19.4%) compared with BOC-based triple therapy (relapsers 53.9%, partial responders 38.3%, none in null responders).⁴

SAFETY OUTCOMES

The real-life experience outside of clinical trials using TVR and BOC was sobering, emphasizing the toxicity and safety concerns associated with PR as the backbone of HCV therapy. There were significant rates of serious adverse events (SAEs) that led to high rates of treatment discontinuation in those who received a triple regimen containing either PI.

It is possible that SAEs were less reported in clinical trials because of close monitoring or early detection. In addition, this regimen was unaffordable to the majority of patients infected with chronic HCV, and the burden of SAEs added to the total cost of therapy.⁵ Although subsequent non-interferon-based regimens were proven to be much better tolerated, the cost of these medications was and remains a matter of controversy.

Deaths were reported in patients with cirrhosis who received TVR- or BOC-containing therapy, and Hézode et al.⁴ described 11 deaths (of 511 patients, or 2.2% of patients) during therapy. Severe complications related to this therapy included hepatic decompensation, renal failure, severe infections, asthenia, and a variety of hematological abnormalities, including anemia (requiring erythropoietin and/or blood transfusion), neutropenia (requiring granulocyte-stimulating agent), and thrombocytopenia (requiring thrombopoietin).⁴ Furthermore, patients receiving TVR were at higher risk for experiencing severe cutaneous adverse reactions including drug rash with eosinophilia and systemic symptoms⁶ and toxic epidermal necrolysis, as well as anorectal discomfort and pruritus. Patients who underwent TVR-based triple therapy were at higher risk for SAEs than patients who received a BOC regimen.

Prescribers of PIs had to recognize the potential for significant drug–drug interactions (DDI) that were reported

TABLE 2. REPORTED RAVS IN PATIENTS RECEIVING TVR OR BOC

PI-Based Triple Regimen	RAVs
BOC or TVR	V36A/M/L
	T54A/S
	V55A/I
	Q80R/K
	Q86
	R155K/T/Q
	AL155
	A156S/T/V
	I71V
	T72I

in patients receiving either TVR or BOC. This was related to interactions at the level of the cytochrome P450 enzyme 3A4 and the drug transporter P-glycoprotein.⁷ The focus on DDI would continue as other therapies were approved to treat HCV.

TREATMENT FAILURE AND RAVs

In using the first-generation PIs, we began to appreciate the impact of RAVs on treatment success or failure. Phase 2 and 3 clinical trials reported failure rates of 20% to 30% and 50% to 60% in treatment-naïve and treatment-experienced patients, respectively. PIs led to selection of RAVs, which expanded if the HCV did not respond adequately to PR, a key insight into treatment failure.⁸ Furthermore, patients with HCV genotype 1a experienced higher treatment failure rates because of RAVs (Table 2).⁹

PREDICTORS OF VIRAL RESPONSE AND SPECIAL POPULATIONS

Because the SVR rate was less than 90%, the minimal standard in patients treated with the newer DDA combinations, the TVR/BOC era required trying to predict which patients would achieve a treatment response. Similarly, we continued to see that there were patient groups (so-called special populations) who were resistant to antiviral therapy. The impressive efficacy and safety record of the newer agents for practically all patients has rendered the term *special populations* and the need to predict response almost obsolete.

In summary, combining the PIs (TVR or BOC) with PR showed better efficacy resulting in higher SVR rates compared with the previous standard of care using PR alone. Furthermore, the new regimens avoided the unwanted effects and length of treatment of interferon-based therapy. However, the regimens containing the first-generation PIs were costly to prescribe and monitor, had high rates of treatment discontinuation secondary to SAEs, and were limited by extensive DDIs. Their use introduced the importance of emerging RAVs, issues that have continued as safer and more effective all-oral regimens have been approved for HCV treatment. As a result, TVR and BOC have become footnotes in the history of treatment for HCV.

CORRESPONDENCE

Omar Y. Mousa, M.D., Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Rd S, Davis 6th floor, GI, Jacksonville, FL. E-mail: omar.mousa@hotmail.com

REFERENCES

- 1) Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. *Nat Med* 2013;19:837-849.
- 2) Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med* 2013;368:1859-1861.
- 3) Strader DB, Seeff LB. A brief history of the treatment of viral hepatitis C. *Clin Liver Dis* 2012;16:1-11.
- 4) Hézode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014;147:132-142.e4.
- 5) Giménez-Manzorro Á, García-González X, Rodríguez-González CG, Ochoa-Palomino A, Sanjurjo-Sáez M, Clemente-Ricote G. Cost-effectiveness and safety of telaprevir and boceprevir for chronic hepatitis C in real-world clinical practice. *Gastroenterol Hepatol* 2015;38:575-582.
- 6) Mousa OYS, Khalaf R, Shannon RL, Egwim CI, Zela SA, Ankoma-Sey V. Chronic hepatitis C therapy in liver cirrhosis complicated by telaprevir-induced DRESS. *Case Rep Med* 2014;380424. doi: 10.1155/2014/380424.
- 7) Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. *Hepatology* 2012;55:1620.
- 8) Pawlotsky J-M. Treatment failure and resistance with direct-acting antiviral drugs against hepatitis C virus. *Hepatology* 2011;53:1742-1751.
- 9) Paolucci S, Fiorina L, Mariani B, Landini V, Gulminetti R, Novati S, et al. Development and persistence of DAA resistance associated mutations in patients failing HCV treatment. *J Clin Virol* 2015;72:114-118.

- 10) Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al.; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-2416.
- 11) 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.
- 12) Poordad F, McCone J Jr, 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.
- 13) 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.