Time to Viral Suppression Is Not Related to Achievement of SVR12 in HCV GT1-infected Patients Treated With ABT-450/Ritonavir/Ombitasvir and Dasabuvir With or Without Ribavirin

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INTRODUCTION

- Among patients who were treated in the past with interferon (IFN)-based therapies, virologic monitoring at week 4 was a standard part of clinical care
- In the era of IFN and ribavirin (RBV) therapies, unfavorable interleukin (IL) 28 genotype,† slower viral kinetics, African-American race, male sex, insulin resistance, older age and, most importantly, advanced fibrosis have been associated with failure to achieve sustained virologic response (SVR)[2]
  - Some of these negative predictors remained relevant after the introduction of the first-generation protease inhibitors, including cirrhosis and history of prior treatment failure[3,4]
- Newer agents such as sofosbuvir and simeprevir combined with pegylated (peg)IFN/RBV increased the proportion of patients achieving rapid suppression and improved overall outcomes[5]; however, an unfavorable IL28B background and advanced fibrosis remained predictors of lower SVR rates
- Six phase 3 clinical trials of an all-oral IFN-free treatment regimen composed of 3 direct-acting antiviral agents ("3D" regimen) with or without RBV have demonstrated SVR rates ranging from 92%–99% among Hepatitis C virus (HCV) genotype 1 (GT1)–infected treatment-naïve and pegIFN/RBV treatment-experienced patients with or without cirrhosis[6–10]
  - The 3D regimen includes:
    - ABT-450 (an HCV NS3/4A protease inhibitor [identified by AbbVie and Enanta])
      - Co-administered with ritonavir 100 mg, which increases peak, trough, and overall ABT-450 drug exposure (ABT-450/r)
    - Ombitasvir (an NS5A inhibitor)
    - Dasabuvir (an NS5B RNA non-nucleoside polymerase inhibitor)
- Little is known about early viral kinetics as a predictor of response in patients receiving IFN-free regimens, and the rates of viral suppression may differ depending on viral, host, and disease factors such as stage of liver fibrosis[2]
- This pooled analysis examined whether the time of initial virologic suppression was associated with subsequent SVR rates in cirrhotic and non-cirrhotic patients with HCV GT1 infection who had received the 3D regimen with or without RBV

OBJECTIVES

- To determine the association between the time of first occurrence of HCV RNA below the lower limit of quantification (<25 IU/mL) and achievement of SVR12 (SVR [HCV RNA level <25 IU/mL] 12 weeks after the last dose of study medication) in cirrhotic and non-cirrhotic patients with HCV GT1 infection
- To explore the association between the time of first occurrence of HCV RNA below the limits of detection (<15 IU/mL) and SVR12

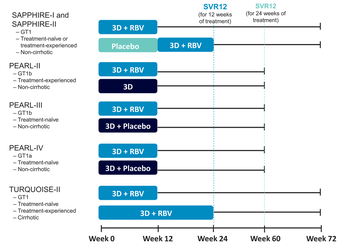
METHODS

OVERALL STUDY DESIGN

- This was a pooled analysis of all non-cirrhotic and cirrhotic patients with HCV GT1 infection who had received the 3D regimen with or without RBV during 6 phase 3 clinical trials: SAPPHIRE-I,[7] SAPPHIRE-II,[10] PEARL-II,[6] PEARL-III,[8] PEARL-IV,[8] and TURQUOISE-II[9] **(Figure 1)**
  - The SAPPHIRE studies were randomized, double-blind, placebo-controlled studies
  - PEARL-III and PEARL-IV were randomized double-blind studies; PEARL-II and TURQUOISE-II were randomized open-label studies
  - The 3D regimen in all trials included co-formulated ABT-450/r/ombitasvir (150/100/25 mg) once daily combined with dasabuvir 250 mg twice daily
  - When administered, weight-based RBV (1000–1200 mg total daily dose) was taken twice daily

METHODS (CONTINUED)

Figure 1. Schematic of Study Designs*



GT, genotype; RBV, ribavirin; SVR12, sustained virologic response at post-treatment week 12.
*3D therapy was comprised of co-formulated ABT-450/ritonavir/ombitasvir 150/100/25 mg given once daily combined with dasabuvir 250 mg twice daily. When administered, weight-based RBV (1000–1200 mg total daily dose) was taken twice daily.

KEY INCLUSION CRITERIA

- Age: 18–70 years
- Chronic HCV GT1 infection
- Plasma HCV RNA levels >10 000 IU/mL
- Treatment-experienced patients met 1 of the following classifications:
  - Relapser: received pegIFN/RBV for ≥36 weeks and had undetectable HCV RNA levels at the end of treatment but had detectable HCV RNA within 24 or 52 weeks after treatment discontinuation
  - Partial responder: did not achieve an undetectable level of HCV RNA at the end of treatment after receiving pegIFN/RBV for ≥20 weeks and achieving a ≥2 $\log_{10}$ IU/mL HCV RNA decrease at week 12
  - Null responder: did not achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 after receiving pegIFN/RBV for ≥12 weeks OR received 4 weeks of pegIFN/RBV and did not achieve ≥1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4
- Cirrhotic patients had to have a Child-Pugh class A score <7 and documentation of cirrhosis through liver biopsy (Metavir score >3 or Ishak score >4), or a FibroScan result ≥14.6 kPa

KEY EXCLUSION CRITERIA

- Positive for hepatitis B surface antigen or anti-HIV antibodies
- Albumin <lower limit of normal (for SAPPHIRE-I and -II and PEARL-II, -III, and -IV) or <2.8 g/dL (for TURQUOISE-II)
- Platelets <120 000 cells/mm^3 (for SAPPHIRE-I and -II and PEARL-II, -III, and -IV) or <60 000 cells/mm^3 (for TURQUOISE-II)

EFFICACY ASSESSMENTS

- SVR12 rates according to the time of initial suppression of HCV RNA below the lower limit of quantification (<25 IU/mL) and initial suppression of HCV RNA below the limit of detection (<15 IU/mL) were evaluated
- In these analyses, week 1 = days 1–10, week 2 = days 11–21, and week 4 = days 22–35, week 6 = days 36–49, week 8 = days 50–63, and week 10 = days 64–77
- Time to initial suppression of HCV RNA <25 IU/mL by baseline characteristics (ie, baseline HCV RNA level, HCV subtype, presence of cirrhosis, sex, prior response to treatment, and IL28 genotype) was also analyzed
- HCV RNA was measured using the Roche COBAS TaqMan real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay, with a lower limit of quantification of 25 IU/mL and a lower limit of detection of 15 IU/mL

STATISTICAL ANALYSES

- Patients with non-virologic failure (eg, loss to follow-up, premature treatment discontinuation) were excluded from these analyses
- Time to suppression of HCV RNA below the limit of quantification (<25 IU/mL) was compared between subgroups defined by demographic or clinical characteristics using a log-rank test in univariate analyses
- Analysis of covariance was used to determine characteristics that were jointly associated with time to suppression

RESULTS

PATIENTS

- A total of 2053 patients were treated in the six phase 3 trials
  - Demographic and baseline characteristics are summarized in **Table 1**
- A total of 26 patients had non-virologic failure that prevented achievement of SVR and were excluded from the analysis; time to suppression and subsequent achievement of SVR12 were evaluated in 2027 patients

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	3D ± RBV (n = 2053)
Male, n (%)	1193 (58.1)
Race,* n (%)	
Non-black/African American	1923 (93.7)
Black/African American	129 (6.3)
Age (y), mean ± SD	51.7 ± 10.9
HCV RNA level (log$_{10}$ IU/mL), mean ± SD	6.45 ± 0.63
IL28b genotype, n (%)	
CC	446 (21.7)
CT	1233 (60.1)
TT	374 (18.2)
HCV genotype/subtype,† n (%)	
1a	1060 (51.6)
1b	992 (48.3)
HOMA-IR (mmol/L × μIU/mL),‡ n (%)	
<3	1157 (71.4)
≥3	463 (28.6)
Cirrhosis present, n (%)	384 (18.7)
Prior HCV medication history, n (%)	
Treatment-naïve	1357 (66.1)
pegIFN/RBV treatment-experienced	696 (33.9)
Type of response to prior treatment	
Relapser	203 (9.9)
Partial responder	147 (7.2)
Null responder	346 (16.9)

3D, co-formulated ABT-450/ritonavir, ombitasvir, and dasabuvir; HCV, hepatitis C virus; HOMA-IR, homeostasis model assessment for insulin resistance; IFN, interferon; IL, interleukin; RBV, ribavirin.
*Data not reported for 1 patient.
†1 patient had a genotype other than genotype 1.
‡Data not reported for 433 patients.

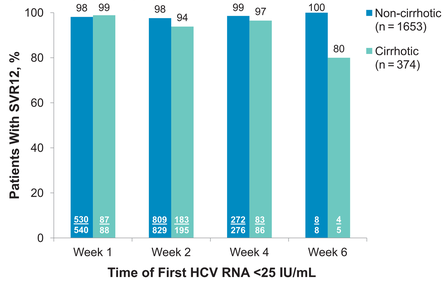
TIME TO SUPPRESSION AND SVR12 RATE

- By week 2, most patients (76% of cirrhotic patients [283/374] and 83% of non-cirrhotic patients [1369/1653]) achieved HCV RNA levels <25 IU/mL
- Of the remaining 375 patients, 362 (97%) demonstrated HCV RNA levels <25 IU/mL by week 4
- SVR12 rates were high for patients with or without cirrhosis regardless of time of initial suppression of HCV RNA <25 IU/mL **(Figure 2)**
- Time to suppression of HCV RNA levels <25 IU/mL was not associated with SVR12 rates in cirrhotic or non-cirrhotic patients **(Figure 2)**

TIME TO SUPPRESSION AND BASELINE CHARACTERISTICS

- In univariate analyses, higher baseline HCV RNA level, the presence of cirrhosis, prior treatment with pegIFN/RBV, GT1b subtype, and age ≥60 years were significantly associated with an increased time to suppression of HCV RNA levels <25 IU/mL **(Figure 4)**
- IL28B genotype, sex, race, and HOMA-IR did not significantly affect achievement of HCV RNA level <25 IU/mL **(Figure 5)**
- By analysis of covariance, baseline HCV RNA, age, GT1 subtype, and cirrhosis were jointly associated with time to suppression **(Table 2)**

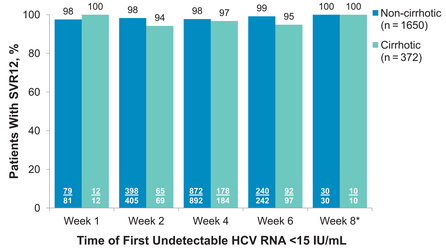
Figure 2. SVR12 by Time of HCV RNA Suppression <25 IU/mL (n = 2027 Patients)*



HCV, hepatitis C virus; SVR12, sustained virologic response at post-treatment week 12.
*Among 375 patients not demonstrating HCV RNA less than the lower limit of quantification (25 IU/mL) by week 2, most (n = 362) achieved suppression at week 4, while 13 patients (8 non-cirrhotic and 5 cirrhotic) achieved suppression for the first time at week 6. All except 1 of these cirrhotic patients ultimately achieved SVR12.

- Similarly, time to undetectable HCV RNA levels was not associated with SVR12 rates in cirrhotic or non-cirrhotic patients **(Figure 3)**
- The SVR12 rate was similar in patients who achieved undetectable HCV RNA (RNA levels lower than the limit of detection [<15 IU/mL]) by week 4 and those who had HCV RNA detectable but unquantifiable (HCV levels <25 IU/mL) at week 4 (98.0% vs 98.5%, respectively, for non-cirrhotic patients and 96.2% vs 95.1%, respectively, for cirrhotic patients; *P*-values not significant for either comparison)

Figure 3. SVR12 by Time of First Undetectable HCV RNA (<15 IU/mL; n = 2022 Patients)



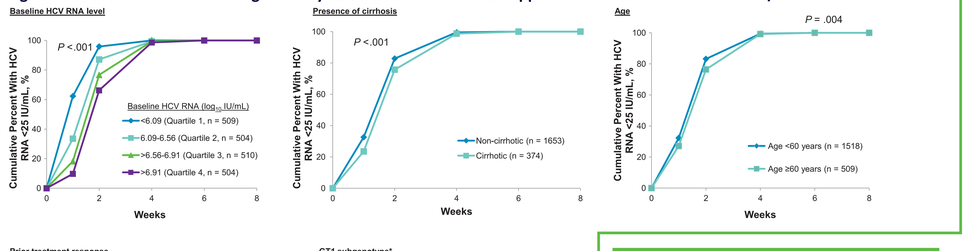
HCV, hepatitis C virus; SVR12, sustained virologic response at post-treatment week 12.
*Includes 1 non-cirrhotic patient who achieved undetectable HCV RNA at week 10.
Note: 5 patients (3 non-cirrhotic, 2 cirrhotic; 0.2%) did not achieve undetectable HCV RNA.

Table 2. Association of Demographic and Baseline Characteristics at Baseline With Time to Suppression With 3D Therapy (Multivariate Analysis)*

Baseline Characteristics	Direction of Effect	Magnitude of Effect (Mean Additional Days to Suppression)	*P* Value
Baseline HCV RNA	Longer time to suppression for higher baseline values	4.8 d per 1 $\log_{10}$ IU/mL	<.0001
Age	Longer time to suppression for older age	0.7 d per 10 y	<.0001
GT1 subtype (1a vs 1b)	Longer time to suppression for GT1b	1.8 d	<.0001
Cirrhosis	Longer time to suppression for patients with cirrhosis	1.7 d	.0003

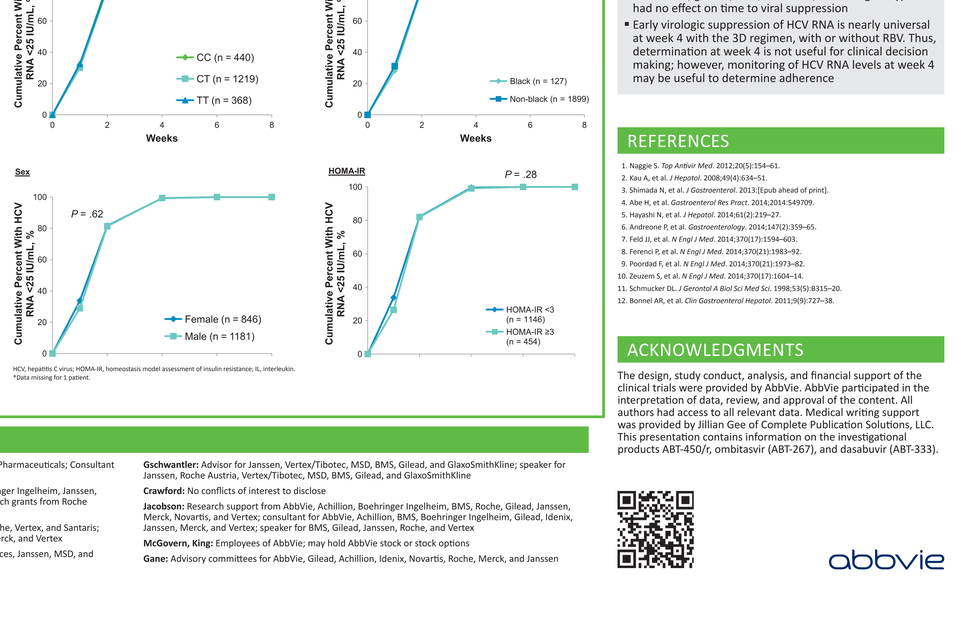
3D, co-formulated ABT-450/ritonavir, ombitasvir, and dasabuvir; GT, genotype; HCV, hepatitis C virus.
*Sex, race, prior treatment response, interleukin 28 genotype, and HOMA-IR were tested in the multivariate analysis, but no significant effect on time to suppression was observed.

Figure 4. Baseline Characteristics Significantly Associated With Time to Suppression of HCV RNA Levels <25 IU/mL



*Data missing for 1 patient.
GT, genotype; HCV, hepatitis C virus.

Figure 5. Baseline Characteristics Not Significantly Associated With Time to Suppression of HCV RNA Levels <25 IU/mL



HCV, hepatitis C virus; HOMA-IR, homeostasis model assessment of insulin resistance; IL, interleukin.
*Data missing for 1 patient.

CONCLUSIONS

- In this pooled analysis of 6 clinical trials in cirrhotic and non-cirrhotic treatment-naïve and treatment-experienced patients with HCV GT1 infection who received the 3D regimen with or without RBV, achievement of SVR12 was not associated with time to viral suppression as assessed by assays examining HCV RNA <25 IU/mL or <15 IU/mL
- SVR12 rates were high for patients with or without cirrhosis regardless of time to initial suppression of HCV RNA
- Higher baseline HCV RNA level, older age, GT1b subtype, and presence of cirrhosis were associated with a longer time to initial viral suppression <25 IU/mL, but the magnitude of the effect was small and time to suppression did not affect achievement of SVR12
  - The increased time to viral suppression among older patients may be attributable to a reduction in liver blood flow or blunted adaptive responses[11]
  - Slower viral suppression among patients with cirrhosis may reflect different effects of cirrhosis on antiviral activity. Drug delivery may be reduced by either portosystemic shunting or altered intrahepatic microcirculation as a consequence of increased collagen and intracellular matrix. Cirrhosis itself, may also be associated with significant immune dysfunction[12]
- In contrast, gender, race, HOMA-IR, or IL28B genotype had no effect on time to viral suppression
- Early virologic suppression of HCV RNA is nearly universal at week 4 with the 3D regimen, with or without RBV. Thus, determination at week 4 is not useful for clinical decision making; however, monitoring of HCV RNA levels at week 4 may be useful to determine adherence

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