Time to viral suppression is not related to achievement of SVR12 in HCV GT1-infected patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin

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1 | INTRODUCTION

In the era of interferon (IFN)-based therapies for hepatitis C virus (HCV) infection, several factors have been associated with failure to achieve sustained virologic response (SVR), including but not limited to slower viral suppression kinetics, interleukin 28B (IL28B) CT or TT polymorphisms, African-American race, male gender, insulin resistance, older age and, most importantly, advanced fibrosis1,2.

Summary
High rates of sustained virologic response at post-treatment week 12 (SVR12) were achieved in six phase 3 trials of ombitasvir (OBV, an NS5A inhibitor), paritaprevir (an NS3/4A protease inhibitor) co-dosed with ritonavir (PTV/r) + dasabuvir (DSV, an NS5B RNA polymerase inhibitor) (ie, 3D regimen) with or without ribavirin (RBV) in adults with chronic genotype (GT) 1 hepatitis C virus (HCV) infection. We assessed whether time to first HCV RNA value below the lower limit of quantification in patients with and without cirrhosis was associated with achievement of SVR12. Data were analysed from GT1-infected patients enrolled in six phase 3 studies of 3D ± RBV. Patients who experienced non-virologic failure were excluded from analysis. HCV RNA was determined using the Roche COBAS TaqMan RT-PCR assay (lower limit of quantification, LLOQ =25 IU/mL). SVR12 was analysed by week of first HCV RNA suppression, defined as HCV RNA <LLOQ. The analysis included a total of 2027 patients. Cumulative proportions of subjects with initial HCV RNA suppression <LLOQ at weeks 1, 2, 4 and 6 were 31%, 81%, 99% and 100%, respectively. SVR12 was achieved by 98%, 97%, 98% and 92% of patients with initial suppression at Weeks 1, 2, 4 and 6, respectively (P=.42, trend test). Across six phase 3 trials of 3D ± RBV, most patients achieved viral suppression by week 2. Time to viral suppression was not associated with subsequent achievement of SVR12, suggesting that on-treatment virologic monitoring may not be necessary with this regimen.

KEYWORDS
direct-acting antiviral, interferon-free therapy, sustained virologic response

Abbreviations: 3D, 3 direct-acting antiviral; DSV, dasabuvir; LLOD, lower limit of detection; LLOQ, lower limit of quantification; OBV, ombitasvir; PTV/r, paritaprevir co-dosed with ritonavir; SVR, sustained virologic response.

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While the development of first-generation protease inhibitors such as boceprevir and telaprevir in combination with pegylated IFN (pegIFN) and ribavirin (RBV) increased SVR rates relative to standalone treatment with pegIFN/RBV, negative predictors of SVR including cirrhosis and prior treatment experience with pegIFN/RBV remained relevant.

Historically, an integral goal of patient management and an important on-treatment predictor of SVR has been the achievement of a rapid virologic response (RVR; defined as undetectable HCV RNA at treatment week 4)\(^5\). While the addition of boceprevir to pegIFN/RBV increased overall SVR rates, early viral kinetics remained a predictor of response\(^6\). Indeed, a Response Guided Therapy (RGT) study of pegIFN/RBV plus telaprevir demonstrated that, based on the regimen’s ability to induce RVR, treatment of 24 weeks was non-inferior to 48 weeks of treatment, which resulted in shorter treatment durations for two-thirds of patients\(^7\). Newer antiviral agents such as sofosbuvir (SOF) and simeprevir combined with pegIFN/RBV increased the proportion of patients achieving RVR and improved overall outcomes; however, an unfavourable IL28B genotype and advanced fibrosis remained predictors of lower SVR rates\(^8,9\). Little is known about the utility of viral kinetics as a predictor of response in patients receiving IFN-free combination regimens of direct-acting antivirals (DAAs), and the time to viral suppression may differ depending on viral factors such as genotype, baseline viral load and presence of resistance-associated variants (RAVs), and host and disease factors such as immune function, co-morbidities and liver fibrosis stage\(^1\).

Six phase 3 clinical trials of an all-oral, IFN-free treatment regimen composed of three direct-acting antiviral agents (DAAs) have demonstrated SVR rates ranging from 92% to 99% among HCV genotype 1 (GT1)-infected treatment-naïve and pegIFN/RBV treatment-experienced patients with or without cirrhosis\(^10-14\). The 3-DAA (3D) regimen included ombitasvir (OBV; an NSSA inhibitor), paritaprevir (an HCV NS3/4A protease inhibitor identified by AbbVie and Enanta that is co-administered with 100 mg ritonavir [PTV/r]), which increases peak, trough and overall drug exposure [denoted as OBV/PTV/r]) and dasabuvir (DSV; an NS5B RNA polymerase inhibitor). This post hoc analysis examined whether time to initial virologic suppression was associated with subsequent SVR rates in HCV GT1-infected patients who received the 3D regimen with or without RBV.

2 MATERIALS AND METHODS

2.1 Overall study design

The objectives of this analysis were to 1) determine the association between time to viral suppression and achievement of SVR12 (HCV RNA < LLOQ, 12 weeks after the last dose of treatment) and 2) explore the association between baseline characteristics and time to viral suppression in HCV GT1-infected patients. We conducted a pooled analysis of all patients with HCV GT1 infection with or without cirrhosis who had received 3D ± RBV during six phase 3 clinical trials: SAPPHIRE-1\(^11\), SAPPHIRE-2\(^14\), PEARL-II\(^10\), PEARL-III\(^12\) PEARL-IV\(^12\) and TURQUOISE-II\(^13\). Detailed study design information has been described previously\(^5-10\). Briefly, all six trials were randomized; PEARL-II and TURQUOISE-II were open-label studies; the PEARL-III and PEARL-IV studies were double-blinded, and the SAPPHIRE studies were double-blinded and placebo-controlled. The 3D regimen in all trials was co-formulated OBV/PTV/r 250 mg taken once daily combined with DSV 250 mg taken twice daily; when administered, weight-based RBV (1000 or 1200 mg) was taken twice daily. Patients with compensated cirrhosis (TURQUOISE-II) received treatment with 3D ± RBV for 12 or 24 weeks; patients without cirrhosis were treated for 12 weeks. All patients provided written informed consent, and all studies were conducted in accordance with International Conference on Harmonization guidelines, other guidelines governing clinical study conduct, applicable regulations and ethical principles outlined in the Declaration of Helsinki.

2.2 Patients

Patients 18-70 years of age were eligible to enroll in one of the six phase 3 studies if they had chronic HCV GT1 infection with plasma HCV RNA levels > 10,000 IU/mL. Patients with prior treatment experience (enrolled in SAPPHIRE-II, PEARL-II and TURQUOISE-II) were eligible if their previous response to pegIFN/RBV treatment was documented as a null response (<2 log\(_{10}\) IU/mL decrease in HCV RNA by week 12) or <1 log\(_{10}\) IU/mL decrease in HCV RNA by week 4), partial response (HCV RNA decrease of ≥2 log\(_{10}\) IU/mL at week 12, but detectable HCV RNA at the end of treatment) or relapse (undetectable HCV RNA at the end of treatment, but detectable HCV RNA within 52 weeks after treatment) response. Patients were categorized as treatment-naïve if they had never received any antiviral treatment for HCV infection.

Patients with cirrhosis (TURQUOISE-II) 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 FibroScan result ≥14.6 kPa. Patients were excluded if they had a positive test result for hepatitis B surface antigen or anti-HIV antibodies during screening. In the TURQUOISE-II study, patients were excluded if serum albumin levels were <2.8 g/dL or if platelet count was <60 × 10\(^9\)/L; for all other trials, patients were excluded if albumin was below the lower limit of normal (LLN) or if platelet count was <120 × 10\(^9\)/L.

2.3 Efficacy assessments

HCV RNA was measured using the Roche COBAS TaqMan real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, with a lower limit of detection (LLOD) of 15 IU/mL and a lower limit of quantitation (LLOQ) of 25 IU/mL. The primary endpoint for this analysis was the rate of SVR12 according to the time of first viral suppression, defined as the first study visit at which a patient demonstrated HCV RNA < LLOQ. A similar analysis was conducted for the rate of SVR12 according to HCV RNA < LLOD. Plasma samples were collected at baseline (pre-dose on day 1), week 1 and week 2,
then every 2 weeks through week 12 and, for subjects assigned to receive 24 weeks of treatment in TURQUOISE-II, weeks 16, 20 and 24. Additional endpoints included analyses of time to viral suppression by baseline characteristics, including baseline HCV RNA level, HCV sub-genotype, presence of cirrhosis, gender, prior response to treatment, body mass index (BMI) and IL28B genotype.

2.4 | Statistical analyses

The association between time of first suppression <LLOQ or <LLOD and subsequent achievement of SVR was analysed using the Cochran–Armitage trend test. Time to suppression was compared between subgroups of demographic characteristics or clinical characteristics using a log-rank test in univariate analyses. Patients with non-virologic failure (eg, loss to follow-up, premature treatment discontinuation) were excluded from these analyses. Analysis of covariance was used to determine characteristics that were jointly associated with time to suppression. SAS software for the UNIX operating system (SAS Institute) was used for all analyses. All statistical tests were two-sided, with a significance level of 0.05.

3 | RESULTS

3.1 | Patients

A total of 2053 patients received at least one dose of study drug in the six phase 3 trials. Demographic and baseline characteristics are summarized in Table 1. Twenty-six patients had non-virologic failure and were excluded from the analysis; time to suppression <LLOQ and <LLOD and subsequent achievement of SVR12 were evaluated in the resulting 2027 patients.

3.2 | TIME TO SUPPRESSION AND SVR12 RATE

The cumulative proportions of subjects with initial HCV RNA suppression <LLOQ at weeks 1, 2, 4 and 6 were 31%, 81%, 99% and 100%, respectively. Achievement of SVR12 was not affected by the time to viral suppression <LLOQ (<LLOD (P=.42, Figure 1A) or time to viral suppression <LLOD (P=.64, Figure 1B). The absence of a relationship between time to suppression and SVR12 was not affected by the presence of cirrhosis (Figure 1C).

3.3 | ASSOCIATION BETWEEN TIME TO SUPPRESSION AND BASELINE CHARACTERISTICS

Univariate analyses were conducted to evaluate which, if any, baseline characteristics were associated with an increased time to viral suppression <LLOQ. 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 to <25 IU/mL (Figure 2), whereas IL28B genotype, sex, race, BMI and insulin resistance (as determined by the homoeostatic model assessment for insulin resistance, HOMA-IR) did not significantly affect achievement of time to HCV RNA to <LLOQ (Figure 3). By multivariable analysis of covariance, a higher baseline HCV RNA, older age, GT1b subtype, presence of cirrhosis and prior null response to pegIFN/RBV were independently associated with longer time to suppression (Table 2).

### TABLE 1 Baseline demographics and disease characteristics

| Characteristics                          | OBV/PTV/r + DSV ± RBV |
|------------------------------------------|-----------------------|
| OBV/PTV/r + DSV ± RBV N=2053             |                       |
| Male, n (%)                              | 1193 (58.1)           |
| Race, n (%)a                             |                       |
| White                                    | 1873 (91.3)           |
| Black/African American                   | 123 (6.0)             |
| Asian                                    | 34 (1.7)              |
| American Indian/Alaska native            | 9 (0.4)               |
| Native Hawaiian or other Pacific Islander| 2 (<0.1)              |
| Multirace                                | 9 (0.4)               |
| Other                                    | 2 (<0.1)              |
| Age (y), mean ± SD                       | 51.7 ± 10.9           |
| Age distribution, n (%)                  |                       |
| <65 years                                | 1879 (91.5)           |
| ≥65 years                                | 174 (8.5)             |
| 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 (%)b             |                       |
| 1a                                       | 1060 (51.6)           |
| 1b                                        | 992 (48.3)            |
| HOMA-IR, (mmol/L x μIU/mL), n (%)c        |                       |
| <3                                       | 1157 (71.4)           |
| ≥3                                       | 463 (28.6)            |
| Cirrhosis present, n (%)                 | 384 (18.7)            |
| Prior HCV medication history, n (%)      |                       |
| Treatment-naive                          | 1357 (66.1)           |
| pegIFN/RBV treatment-experienced         | 696 (33.9)            |
| Stable opiate substitution, n (%)        | 10 (0.5)              |

HCV, hepatitis C virus; HOMA-IR, homoeostasis model assessment for insulin resistance; pegIFN, pegylated interferon; IL, interleukin; r, ritonavir; RBV, ribavirin.

aData not reported for one patient.

bOne patient had a genotype other than GT1.

cData not reported for 433 patients.
In this pooled analysis of HCV GT1-infected patients with or without cirrhosis who received 3D ± RBV in six phase 3 trials, the time of initial viral suppression (HCV RNA <25 IU/mL [LLOQ] or <15 IU/mL [LLOD]) was not associated with subsequent achievement of SVR12. Although several factors including higher baseline HCV RNA level, older age, GT1b subtype, presence of cirrhosis and prior null response to pegIFN/ RBV were associated with a longer time to viral suppression, the magnitudes of the effects were small and did not impact subsequent achievement of SVR12. The observation of slower time to HCV RNA suppression among patients with HCV genotype 1b was unexpected, as high SVR rates (≥99%) have been observed in this population.10,12,13,15.

Among patients with cirrhosis, the increase in time to viral suppression may be due to the myriad effects of cirrhosis on antiviral activity. For example, drug delivery may be reduced by either portosystemic shunting or altered intrahepatic microcirculation as a consequence of increased collagen and intracellular matrix.16. Cirrhosis may also be associated with significant immune dysfunction that could impede viral suppression.17. In older patients, the delay in viral suppression may be attributable to a reduction in liver blood flow or blunted adaptive response.18.

The observed lack of a relationship between achievement of SVR12 and time to viral suppression may have several explanations. Response to DAA treatment is measured by plasma HCV RNA levels, which are a surrogate for viral decline in the liver, and compartmental differences may exist. Plasma HCV RNA levels early after treatment initiation (0-4 days) have been shown to be lower than in the liver, which is the primary site for viral replication.19. Therefore, it is possible that for the 81% of patients that achieved HCV RNA <LLOQ by week 2, the observed viral suppression may not correspond to the decline in viral replication in the liver necessary to achieve SVR12.20. Conversely, even if plasma viral decline does correlate closely with intrahepatic decline, it is still possible that durations of therapy that extend for many weeks beyond the time of initial plasma clearance result in higher SVR12 rates, as slower responders are able to reach SVR12, which they may not have achieved with shorter treatment durations. As immune function can play a role in initial viral suppression, it is likely that a comprehensive immune response also plays a significant role in achievement of SVR12. However, it is difficult to both measure and quantify the magnitude of these effects.

While time to initial viral suppression was not a predictor of sustained virologic response in our analysis, initial viral decline may predict response to shorter treatment durations. The SODAPI study showed that in 26 HCV GT1b patients without cirrhosis treated with SOF + daclatasvir (an NS5A inhibitor) + simeprevir (an HCV NS3/4A protease inhibitor), 18 patients who achieved HCV RNA <500 IU/mL by day 2 of treatment had their treatment duration reduced to 3 weeks and still went on to achieve SVR12.21. However, the impact of fibrosis stage and other baseline characteristics on SVR was not assessed in...
the SODAPI study. One limitation of our study is the lack of treatment durations shorter than 12 weeks. We cannot exclude the possibility that early viral kinetics may identify patients in whom further shortening of treatment is possible.

In conclusion, we show that early virologic suppression of HCV RNA is nearly universal by week 4 following treatment with OBV/PTV/r + DSV, with or without RBV. Unlike previous findings evaluating the viral kinetics of IFN-containing regimens\textsuperscript{21}, time to initial suppression following treatment with 3D ± RBV was not related to subsequent achievement of SVR12, suggesting that monitoring of HCV RNA levels at week 4 may not be useful for clinical decision-making regarding treatment duration and that on-treatment virologic monitoring could be eliminated. As RBV use is part of the treatment guidelines for GT1a, monitoring for safety and adherence is still recommended. The interferon-free 3D regimen of OBV/PTV/r + DSV appears sufficiently potent to achieve both rapid and sustainable viral suppression, which may permit treatment durations shorter than 12 weeks in select patient populations.

**STATEMENTS OF INTEREST**

S. Alqahtani has acted as a consultant or advisory board member for AbbVie, Gilead, Janssen, Merck and has received research support (paid to Johns Hopkins University) from AbbVie, Gilead, Merck and Janssen. M. S. Sulkowski has acted as a consultant or advisory board member for AbbVie, Cocrystal, Gilead, Janssen, Merck and Trek, has received research support (paid to Johns Hopkins University) from AbbVie, BMS, Gilead, Merck and Janssen and participated on a data safety monitoring board for Gilead (funds paid to Johns Hopkins University). R. Ozaras has no conflict of interests to disclose. V. Isakov has served as a consultant for AbbVie, Merck, Janssen and Gilead, sat on the speakers bureau for AbbVie, BMS, Merck, Janssen, Gilead and Roche and received research support from BMS and Merck. D. Wyles has received grant or research support from AbbVie, BMS, Gilead, Merck and Vertex Pharmaceuticals and has acted as a consultant for AbbVie, BMS, Gilead and Janssen. P. Ferenci has served on advisory boards for Roche and Rottapharm-Madaus, has been an advisor for AbbVie, Boehringer-Ingelheim, Janssen, BMS Austria, Idenix, Achillion, GlaxoSmithKline Pharma, Gilead and MSD and received research support from Gilead Austria. J. Feld has received research support from AbbVie, Boehringer-Ingelheim, Gilead Sciences, Roche, Vertex and Santaris and has acted as a consultant for AbbVie, Achillion, Boehringer-Ingelheim, BMS, Janssen, Idenix, Merck and Vertex. F. Calinas has served on advisory boards and/or speakers bureaus for AbbVie, BMS, Gilead Sciences, Janssen, MSD and Roche and acted as a consultant for Boehringer-Ingelheim and Intercept.
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M. Gschwantler has acted as an advisor for Abbvie, Janssen, Vertex/Tibotec, MSD, BMS, Gilead, and GlaxoSmithKline, and acted as a speaker for Abbvie, Janssen, Roche Austria, Vertex/Tibotec, MSD, BMS, Gilead and GlaxoSmithKline. E. Gane has served as a member of an advisory committee for AbbVie, Gilead, Achillion, Idenix, Novartis, Roche, Merck and Janssen. Darrell Crawford has served on advisory boards for Abbvie, Gilead, Roche, BMS, Janssen. IM Jacobson has received research support from AbbVie, Bristol-Myers Squibb (BMS), Gilead, Janssen, Merck, has acted as a consultant for AbbVie, BMS, Gilead, Intercept, Janssen, Merck, Trek, Vertex and has been a speaker for BMS, Gilead, Janssen, Roche, Vertex. M. King and E. Dumas are employees of AbbVie and may hold stock or stock options.

FIGURE 3 Baseline characteristics not significantly associated with time to viral suppression. Univariate analyses using a log-rank test show that there is no association between cumulative percent of patients with HCV RNA <LLOQ and A, IL28B CC, CT or TT polymorphisms, B, race, C, gender, D, HOMA-IR (a measure of insulin resistance) and E, BMI. Data are missing for one patient.

TABLE 2 Association of baseline characteristics with time to suppression following OBV/PTV/r + DSV ± RBV treatment (multivariable analysis)

| Baseline characteristic | Mean number of additional days to suppression <LLOQ | P-value |
|-------------------------|-----------------------------------------------|---------|
| Baseline HCV RNA        | 4.8d per 1.0 log_{10} higher baseline HCV RNA | <.0001  |
| Age                     | 0.8d per 10 years older                      | <.0001  |
| Subtype (1a v 1b)       | 1.9d for GT1b                                | <.0001  |
| Cirrhosis               | 1.5d for presence of cirrhosis               | .001    |
| Prior response to P/R   | 1.2d for prior null responders               | .012    |
| Gender, race, IL28B genotype, HOMA-IR, BMI | n/a                                | ns      |

LLOQ, lower limit of quantification; d, days; GT, genotype; P/R, pegIFN/RBV; NA, not applicable; NS, not significant; BMI, body mass index.
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