


Effect of Hepatitis C Treatment with Ombitasvir/Paritaprevir/R + Dasabuvir on Renal, Cardiovascular and Metabolic Extrahepatic Manifestations: A Post-Hoc Analysis of Phase 3 Clinical Trials

Darshan A. Mehta  · Eric Cohen · Mariem Charafeddine · Daniel E. Cohen · Yanjun Bao · Yuri Sanchez Gonzalez · Tram T. Tran

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ABSTRACT

Introduction: We analyzed phase 3 trial data of ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) ± ribavirin (RBV) in genotype 1 chronic hepatitis C patients to investigate the impact of 3D ± RBV on renal, cardiovascular and metabolic extrahepatic manifestations (EHMs), including persistency 52 weeks post treatment and differential impact by EHM disease severity.

Methods: Estimated glomerular filtration rate (eGFR), fasting triglyceride and fasting glucose

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D. A. Mehta
Schaeffer Center for Health Policy and Economics,
University of Southern California, Los Angeles, CA,
USA

D. A. Mehta (✉) · Y. Bao · Y. Sanchez Gonzalez
Health Economics and Outcomes Research, AbbVie
Inc., Mettawa, IL, USA
e-mail: darshan.mehta@abbvie.com

E. Cohen · M. Charafeddine · D. E. Cohen
Infectious Disease Development, AbbVie Inc.,
Mettawa, IL, USA

T. T. Tran
Cedars-Sinai Medical Center, Los Angeles, CA, USA

values from clinical trials were used to assess renal, cardiovascular and metabolic EHMs, respectively. Two placebo-controlled trials were used to study the effect of treatment, while the pooled sample of treated patients was used to study the persistency and differential effect of treatment by baseline EHM disease severity, as defined by baseline values of respective EHM biomarkers. Changes in EHM outcomes from baseline were assessed with mixed models adjusting for patient baseline demographic and clinical characteristics.

Results: Treatment with 3D ± RBV resulted in statistically significant declines from baseline of triglycerides and glucose and no statistical change in eGFR. By 52 weeks post treatment patients with elevated triglycerides (−35.3 mg/dl), pre-diabetes (−4.4 mg/dl), diabetes (−34.2 mg/dl) and CKD stage 3 (+1.6 ml/min/1.73 m²) at baseline experienced a statistically significant improvement in their respective EHM values. Patients with CKD stages 2, 4 and 5 experienced no statistically significant change in eGFR from baseline.

Conclusion: Treatment with 3D ± RBV resulted in improvement or no worsening of cardiovascular, metabolic and renal EHM markers, especially in patients with severe EHMs at baseline, which persisted until 52 weeks post treatment.

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Keywords: Dasabuvir; Extrahepatic manifestations; eGFR; Glucose; Hepatitis c;

Ombitasvir; Paritaprevir; Placebo; Ritonavir; Triglycerides

INTRODUCTION

Most recent estimates suggest that between 2.5 and 4.7 million people are currently living with chronic hepatitis C virus infection (HCV) in the USA [1]. Patients with HCV are at increased risk of long-term liver complications, including cirrhosis, hepatocellular carcinoma, liver failure, and liver-related mortality [2]. In addition, HCV is also associated with a number of extrahepatic manifestations (EHMs) including type 2 diabetes mellitus, insulin resistance, cardiovascular disease, mixed cryoglobulinemia, chronic kidney disease (CKD), non-Hodgkin's lymphoma and cognitive impairment [3–9]. Evidence suggests that while up to 74% of HCV-infected patients may have at least one EHM, these risks are typically not accounted or underappreciated by treaters. [4].

Several empirical studies have shown that sustained virologic response (SVR) with antiviral therapy is associated with reduced risk of hepatic complications [10–12], but few studies have evaluated the impact of SVR with HCV treatment on EHM outcomes. One study found that HIV/HCV co-infected individuals not responding to interferon (IFN)-based regimens had increased odds of non-liver and non-AIDS-related death [hazard ratio (HR): 2.85; $p = 0.036$] [13]. In a nationwide Taiwanese cohort of HCV patients, peg-IFN/RBV antiviral treatment was associated with lower odds of adverse extrahepatic outcomes (i.e., end-stage renal disease, acute coronary syndrome and ischemic stroke) [14, 15].

The standard of care for HCV patients now comprises IFN-free therapy with direct-acting antiviral agents (DAAs) that have shorter durations, higher efficacy and an improved safety profile [16]. However, the impact of DAAs on EHMs and the persistence of this effect post treatment are not well defined. Also, it is not known whether pre-treatment severity of EHMs, based on baseline biomarker values, affects the impact of DAAs. To address these evidence gaps, we leveraged clinical trial data of

ombitasvir/paritaprevir/ritonavir (paritaprevir identified by AbbVie and Enanta) and dasabuvir \pm ribavirin (3D \pm RBV) for treatment of HCV genotype 1-infected patients to study:

1. the impact of 3D \pm RBV on renal, cardiovascular and metabolic EHMs;
2. the persistency of any treatment impact on EHMs 52 weeks post treatment;
3. the differential impact of treatment by EHM disease severity.

METHODS

For this analysis, EHMs were defined as non-liver-related conditions that have been associated with HCV infection [17]. The current study incorporated fasting triglycerides, fasting glucose and estimated glomerular filtration rate (eGFR) as surrogate measures of cardiovascular, metabolic and renal EHMs, respectively. These biomarker levels have been associated with varying risk of clinical outcomes [18–22]. The data were extracted from two pivotal placebo-controlled phase 3 trials (SAPPHIRE I [23] and II [24]) and two long-term phase 3b trials (TOPAZ I [25] and II [26]). Furthermore, two phase 3b trials (RUBY I [27] and II [28]) were used to study the impact of treatment on renal EHMs in patients with advanced renal impairment at baseline (i.e., CKD stages 4 and 5). Appendix Table S1 provides a brief overview of the clinical trials. This analysis was conducted based on biomarker data collected in previously conducted studies and did not involve any new studies of human or animal subjects performed by any of the authors.

For cardiovascular and metabolic manifestations, only those patients whose baseline triglyceride and glucose samples were collected in a fasting state were included in the analysis. Subsequent values not collected in a fasting state were treated as missing. No such restrictions were applied to the collection of eGFR values since they are independent of fasting state, so all patients with available eGFR values at baseline were included in the analysis.

Table 1 provides a summary of the patient populations and clinical trials used for each study objective. The effect of 3D \pm RBV on EHM

Table 1 Study populations and data sources

Study population	Description	Study period	Study objective
SP1	<p>Patients from two placebo-controlled phase 3a trials (SAPPHIRE I and II) who received 12 weeks of 3D + RBV</p> <p>Patients from two placebo controlled phase 3a trials (SAPPHIRE I and II) who received 12 weeks of placebo during the DB period followed by 12 weeks of 3D + RBV during the OL period</p>	12-week DB period	Effect of HCV treatment on EHM outcomes (see Figs. 1a, 2a, 3a)
SP2	Patients who received 12 or 24 weeks of 3D ± RBV across 2 long-term phase 3b trials (TOPAZ I and II)	12/24-week treatment period followed for 52 weeks PT	Differential effect of HCV treatment by EHM severity and persistency PT (see Figs. 1b, 2b, 3b)
SP3	Patients with CKD stage 4 or 5 who received 12 or 24 weeks of 3D ± RBV across 2 phase 3b trials (RUBY I and II)	12/24 week treatment period followed for 12 weeks PT	Differential effect of HCV treatment by EHM severity and persistency PT (see Fig. 3c)

All patients in trials were GT1 patients

SP study population, *PT* post treatment, *DB* double blind, *OL* open label, *EHM* extra-hepatic manifestation, *CKD* chronic kidney disease, *RBV* ribavirin, *3D* ombitasvir/paritaprevir/ritonavir + dasabuvir

outcome was assessed by comparing the treatment and placebo arm of SAPPHIRE trials using the 12-week double-blind treatment period. For both treatment and placebo arms, mean change from baseline to end of treatment (EOT) was assessed. Statistical significance for these mean changes was evaluated using the *t* test. Longitudinal mixed model (MM) regressions [29] were used to assess the treatment effect on each EHM biomarker. The MM regression controlled for patient baseline biomarker values, demographics and clinical characteristics (i.e., fibrosis stage, genotype, age, gender, BMI, presence of diabetes, HCV treatment history, viral load). In addition, since we pooled data from two trials, the model also controlled for clinical trial enrollment of patients. Due to serial measurements, the model assumed a first order autoregressive covariance structure. The change from baseline to subsequent time points was estimated and plotted based on the regression coefficients from the MM.

Data on the treated population in TOPAZ trials were used to study the effect of HCV treatment by baseline EHM severity and persistency of this effect 52 weeks post treatment. For cardiovascular EHMs, patients with fasting baseline triglycerides greater than or equal to 150 mg/dl were defined as elevated [30]. For metabolic EHMs, patients with fasting baseline glucose values between 100 and 126 mg/dl were defined as having pre-diabetes and those with fasting baseline glucose higher than 126 mg/dl were defined as having diabetes [31], irrespective of any reported history of diabetes. For renal EHMs, CKD stages were defined based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines as stage 1 (eGFR ≥ 90 ml/min/1.73 m²), stage 2 (eGFR 60–89 ml/min/1.73 m²), stage 3 (30–59 ml/min/1.73 m²), stage 4 (eGFR 15–29 ml/min/1.73 m²) or stage 5 (eGFR <15 ml/min/1.73 m² or dialysis dependent) [32]. Mean change from baseline was assessed at EOT, post-treatment week 12 and 52. In

addition, we assessed the proportion of patients with biomarker value improvements less than, equal to or greater than 20% for each EHM severity group at EOT, post-treatment week 12 and 52. Improvement in cardiovascular and metabolic EHMs was defined as a decrease in the triglycerides and glucose values, respectively, and improvement in renal EHM was defined as an increase in eGFR. As before, MM regressions were used to estimate the persistency and differential impact of 3D ± RBV on EHM outcomes by disease severity, controlling for patient baseline values, demographics, clinical characteristics and clinical trial enrollment.

RESULTS

Patient Demographics and Descriptive Analyses

Table 2 presents the baseline characteristics of the study population. Across the different clinical trials, the mean age of the population was 51 (50.1–57.7) years, with at least 69% (69–91%) of the population being in the F0–F2 fibrosis stages. With respect to clinical profile, at least 66% (66–83%) and 58% (58–74%) of the study population had BMI <30 kg/m² and HOMA-IR <3 mU mmol/l², respectively. There was fairly even distribution across sub-genotype 1a and 1b and at least 55% (55–82%) of patients were treatment naïve. SVR rates across the study population were greater than 95% (95–97.6%). Appendix Table S2 presents baseline characteristics of the patients by baseline EHM disease severity.

Descriptive analysis of the proportion of patients experiencing improvements showed across EHMs a greater proportion of patients who had severe EHM manifestations at baseline improved by greater than 20% from baseline (Table 3). These effects were sustained at all time points.

Regression analyses on cardiovascular EHMs show a significant reduction in mean triglyceride levels 12 weeks EOT with 3D ± RBV vs. placebo. The mean adjusted change from baseline to EOT week 12 for treated patients was –33.7 mg/dl ($p < 0.0001$; 95% CI –41.1,

26.5 mg/dl), while patients in the placebo group did not have statistically significant changes (–5.6 mg/dl at week 12; $p = 0.53$; 95% CI –23.5, 12.2 mg/dl) (Fig. 1a). Patients with elevated levels of triglycerides at baseline experienced greater declines in triglycerides during treatment compared to patients with normal triglycerides. Moreover, this difference persisted 52 weeks post treatment (Fig. 1b): patients with elevated triglycerides experienced a decline of 35.3 mg/dl ($p < 0.001$; 95% CI –48.2, –22.3 mg/dl), and patients with normal triglycerides had an increase of 16.2 mg/dl ($p < 0.001$; 95% CI 11, 21.4 mg/dl), which did not result in levels over 150 mg/dl.

Treatment with 3D ± RBV also significantly improved metabolic EHMs, as the adjusted mean glucose levels 12 weeks EOT were significantly lower in patients treated with 3D ± RBV vs. placebo [mean adjusted change of –12.1 mg/dl ($p < 0.0001$) for treated patients vs. –4.6 mg/dl ($p = 0.02$) for the placebo group; Fig. 2a]. Among the EHM subgroups, patients with pre-diabetes and diabetes experienced greater reduction in glucose levels during treatment (Fig. 2b) compared to patients with normal glucose levels. This difference persisted 52 weeks post treatment. Patients with pre-diabetes and diabetes experienced a decline of 4.4 mg/dl ($p = 0.004$; 95% CI –7.3, –1.4 mg/dl) and 34.2 mg/dl ($p < 0.0001$; 95% CI –39.4, –28.9 mg/dl), respectively, and patients with normal glucose had a statistically insignificant increase of 1.9 mg/dl ($p = 0.062$; 95% CI –0.09, 3.85 mg/dl), which did not result in levels over 100 mg/dl (Fig. 2b).

Renal EHMs were not significantly affected after 12 weeks of treatment with 3D ± RBV vs. placebo as both groups had no statistically significant changes in eGFR values from baseline [mean adjusted change of +0.37 ml/min/1.73 m² ($p = 0.82$) for patients treated with 3D ± RBV vs. +3.48 ml/min/1.73 m² ($p = 0.19$) for patients in placebo arm] (Fig. 3a). However, the subgroup of patients with CKD stage 2 and 3 experienced minor to significant improvements in eGFR during treatment (Fig. 3b) compared to patients with normal eGFR values, respectively. By 52 weeks post treatment, stage 3 patients experienced an improvement of 1.6 ml/min/

Table 2 Baseline characteristics of study population

	CV and metabolic			Renal			
	Phase 3a studies (SAPPHIRE I and II)		Phase 3b: TOPAZ studies	Phase 3a studies (SAPPHIRE I and II)		Phase 3b: TOPAZ studies	Phase 3b: RUBY studies
	SP1, treatment	SP1, placebo	SP2, all treated	SP1, treatment	SP1, placebo	SP2, all treated	SP3 all treated
<i>N</i>	630	199	1845	776	255	2206	82
Age (years, mean)	50.1	52.1	51.8	50.3	52.6	52.1	57.7
Gender							
Male (%)	56.0	52.3	53.0	57.2	52.2	53.0	80.5
Female (%)	44.0	47.7	47.0	42.8	47.8	47.3	19.5
Race							
White (%)	90.6	90.5	93.4	90.7	90.6	93.6	45.1
Black (%)	6.3	6.5	4.2	6.4	7.1	6.7	54.9
Asian (%)	2.4	1.5	0.0	2.2	1.2	0.0	6.1
Others (%)	0.6	1.5	0.2	0.6	1.2	0.0	4.9
Region/countries							
North America (%)	47.0	38.7	25.8	47.6	42.0	27.9	100.0
Australia/New Zealand/other (%)	4.9	6.0	58.8	5.7	6.7	59.2	0.0
Europe (%)	48.1	55.3	15.4	46.8	51.4	13.1	0.0
Fibrosis							
F0–F1 (%)	74.9	72.9	55.9	73.1	71.0	56.6	41.5
F2 (%)	15.7	16.1	13.2	16.1	17.3	13.4	28.0
F3 (%)	9.4	11.1	15.1	10.8	11.8	14.3	12.2
F4 (%)	0.0	0.0	15.8	0.0	0.0	15.9	18.3
Sub-genotype							
1A (%)	63.2	59.3	48.5	64.4	63.5	51.8	72.0
1B (%)	36.8	40.7	51.2	35.6	36.5	48.1	22.0
Other (%)							6.1
Treatment arms							
3D 12 weeks (%)	0.0	0.0	43.3	0.0	0.0	40.8	40.2
3D + RBV 12 weeks (%)	100.0	0.0	50.0	100.0	0.0	52.4	50.0

Table 2 continued

	CV and metabolic			Renal			
	Phase 3a studies (SAPPHIRE I and II)		Phase 3b: TOPAZ studies	Phase 3a studies (SAPPHIRE I and II)		Phase 3b: TOPAZ studies	Phase 3b: RUBY studies
	SP1, treatment	SP1, placebo	SP2, all treated	SP1, treatment	SP1, placebo	SP2, all treated	SP3 all treated
3D + RBV 24 weeks (%)	0.0	0.0	6.7	0.0	0.0	7.1	9.8
Placebo (%)	0.0	100.0	0.0	0.0	100.0	0.0	0.0
Baseline HCV viral load categories (IU/ml) ^a							
≥800,000 (%)	80.8	84.4	68.8	81.2	85.5	69.8	64.6
BMI ^b							
<30 (%)	83.8	82.9	80.8	83.1	80.4	80.6	65.9
Prior diabetes history ^c							
Yes (%)	4.4	4.5	8.0	4.4	3.5	7.0	0.0
HOMA-IR							
<3 (%)	74.1	73.4	65.0	60.8	57.6	64.0	0.0
≥3 (%)	18.1	17.6	35.0	14.8	13.7	36.0	0.0
Missing (%)	7.8	9.0	0.0	24.4	28.6	0.0	0.0
HCV history ^d							
Treatment naïve (%)	61.0	61.8	54.5	61.6	62.0	55.3	81.7
SVR12							
Yes (%)	96.8	94.5	95.4	95.6	93.3	95.3	97.6
No (%)	2.1	4.5	1.4	2.1	5.1	1.5	2.4
Missing (%)	1.1	1.0	3.3	2.3	1.6	3.4	0.0

BMI body mass index

^a Rest of the proportion represents patients with baseline viral load less than 800,000 IU/ml

^b Rest of the proportion represents patients with BMI ≥30

^c Rest of the proportion represent patients with no diabetes

^d Rest of the proportion represents patients who are experienced with an interferon-based regimen. All patients in trials were GT1 patients. HOMA-IR: Homeostatic model assessment: insulin resistance

1.73 m² ($p = 0.7$; 95% CI $-6.6, 9.9$ ml/min/1.73 m²). Stage 2 patients experienced a statistically insignificant decline of 2.2 ml/min/1.73 m² ($p = 0.13$; 95% CI $-4.9, 0.6$). Stage 1 patients experienced a decrement of 9.3 ml/min/1.73 m² ($p < 0.001$; 95% CI $-10.8,$

-7.8 ml/min/1.73 m²) (Fig. 3b). The CKD stage 4 and 5 patients experienced no statistically significant decrements during treatment and returned to baseline values by week 12 post treatment (Fig. 3c). Stage 4: -0.81 ml/min/1.73 m²; $p = 0.53$; 95% CI $-3.4, 1.7$ ml/min/

Table 3 Proportion of treated population improving from baseline value at specific time points

	≤20% Improvement			>20% Improvement		
	EOT (%)	PTW12 (%)	PTW52 (%)	EOT (%)	PTW12 (%)	PTW52 (%)
Triglycerides						
Normal	21	22.7	22.1	13.8	13.5	15.4
Elevated	17.8	17.7	13.5	54	48.3	50.4
Glucose						
Normal	32.5	24.7	32.1	16.8	32.4	18.2
Pre-diabetic	49	43	46.3	21.4	37.1	21.7
Diabetic	34.3	30.6	42.9	46.2	51.9	45.5
eGFR ^a						
Stage 1	32.2	29.4	19.7	2.4	2.3	2.2
Stage 2	38.1	35.3	20.4	6.2	6.4	4.8
Stage 3	33.3	31.5	16	10.4	7.4	8
Stage 4 [^]	40.4	30.8	–	6.7	15.4	–
Stage 5 [^]	41.4	33.3	–	24.1	11.9	–

Results based on patients enrolled in long-term TOPAZ trials. [^] Results for stage 4, 5 CKD patients based on patients enrolled in RUBY trials

Fasting baseline TGL greater than or equal to 150 mg/dl was defined as elevated. Patients with a fasting baseline glucose value between 100 and 126 mg/dl were defined as pre-diabetic and with glucose higher than 126 mg/dl were defined as diabetic. Chronic kidney disease stages were defined based on guidelines as stage 1 [signs of kidney damage but normal or elevated (eGFR ≥90)], stage 2 (eGFR 60–89), stage 3 (30–59), stage 4 (eGFR 15–29) or stage 5 (eGFR <15 or dialysis dependent)

EOT end of treatment, *PTW12* post-treatment week 12, *PTW52* post-treatment week 52, *TGL* triglycerides, *GLC* glucose, *eGFR* estimated glomerular filtration rate

^a For eGFR improvement was defined as an increase in eGFR from baseline to a defined time point. For TGL and glucose, improvement was defined as a reduction in biomarker from baseline to a defined time point. All patients in trials were GT1 patients

1.73 m². Stage 5: 0.09 ml/min/1.73 m²; *p* = 0.9; 95% CI –1.25, 1.43 ml/min/1.73 m².

Unadjusted analysis is presented in appendix Table S3 for the three EHMs and is consistent with the adjusted results presented.

DISCUSSION

The results from this analysis suggest that treatment with 3D ± RBV was associated with improvements in EHM biomarkers for cardiovascular, metabolic and renal EHMs. These results are consistent with the beneficial effect

observed in patients treated with interferon-based regimens [14, 15, 33]. Furthermore, the beneficial effect of treatment was most pronounced in individuals with more severe markers of EHMs, and EHM improvements were sustained at least 1 year post treatment.

Cardiovascular EHMs

The mean decrement of triglycerides in treated patients at 52 weeks post treatment was 9.5 mg/dl overall and 35.2 mg/dl for patients with elevated triglycerides at baseline. The magnitude

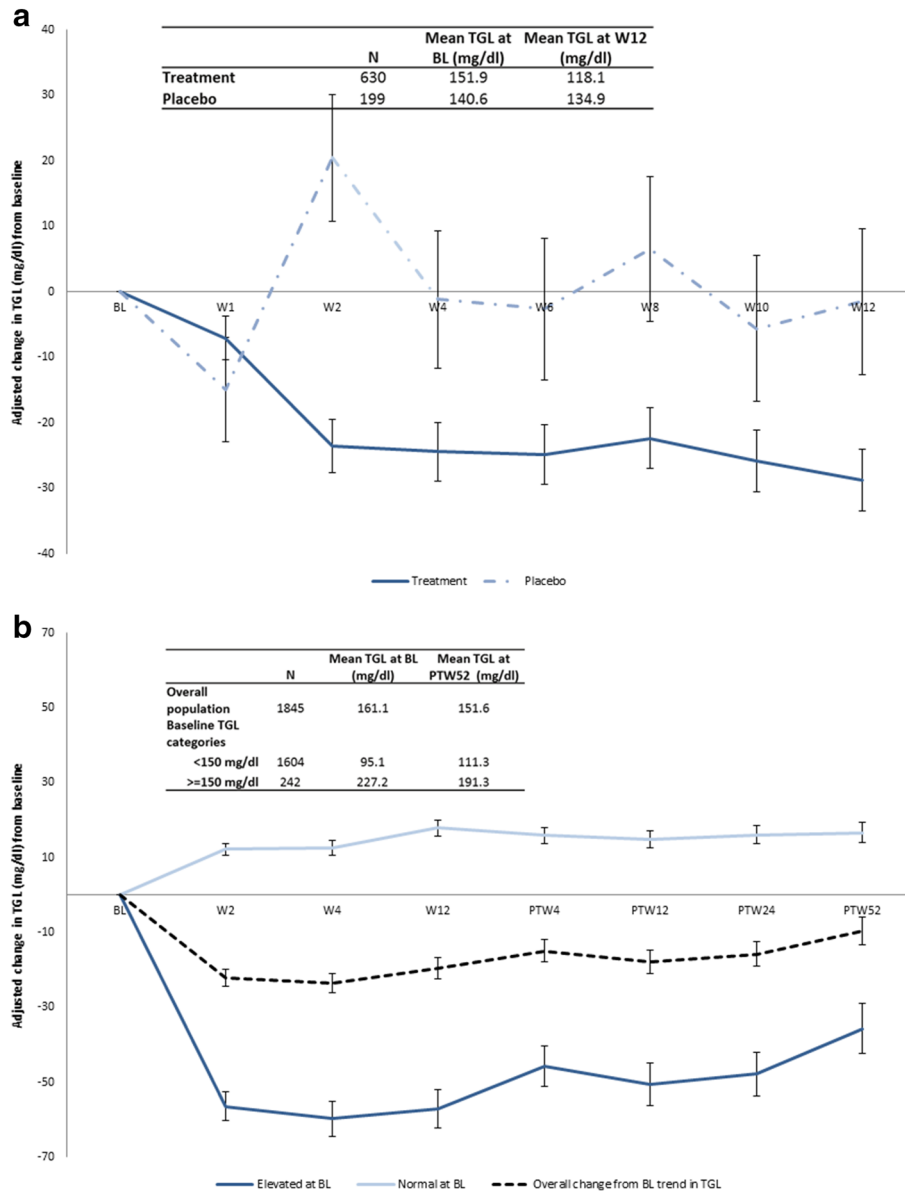


Fig. 1 a Predicted change in triglycerides from baseline: comparison of HCV-treated and placebo arms. Study conducted on treatment and placebo arms of SP1 [i.e., patients from placebo controlled phase 3a trials (SAPPHIRE I and II)]. All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed value of triglycerides at each time point on whether patients were in HCV-treated or placebo group and adjusted for baseline triglyceride level, fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *TGL* triglycerides, *BL* baseline, *W* week. **b** Predicted triglyceride change from

baseline until post-treatment week 52 among treated patients by baseline triglyceride levels. Fasting baseline TGLs greater than or equal to 150 mg/dl were defined as elevated TGLs. Study conducted on SP3. SP3 comprises of all the HCV-treated population from long-term phase 3b trials (TOPAZ I and II). All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed longitudinal triglyceride value on baseline triglyceride level categories and adjusted for fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *TGL* triglycerides, *BL* baseline, *W* week, *PTW* post-treatment week

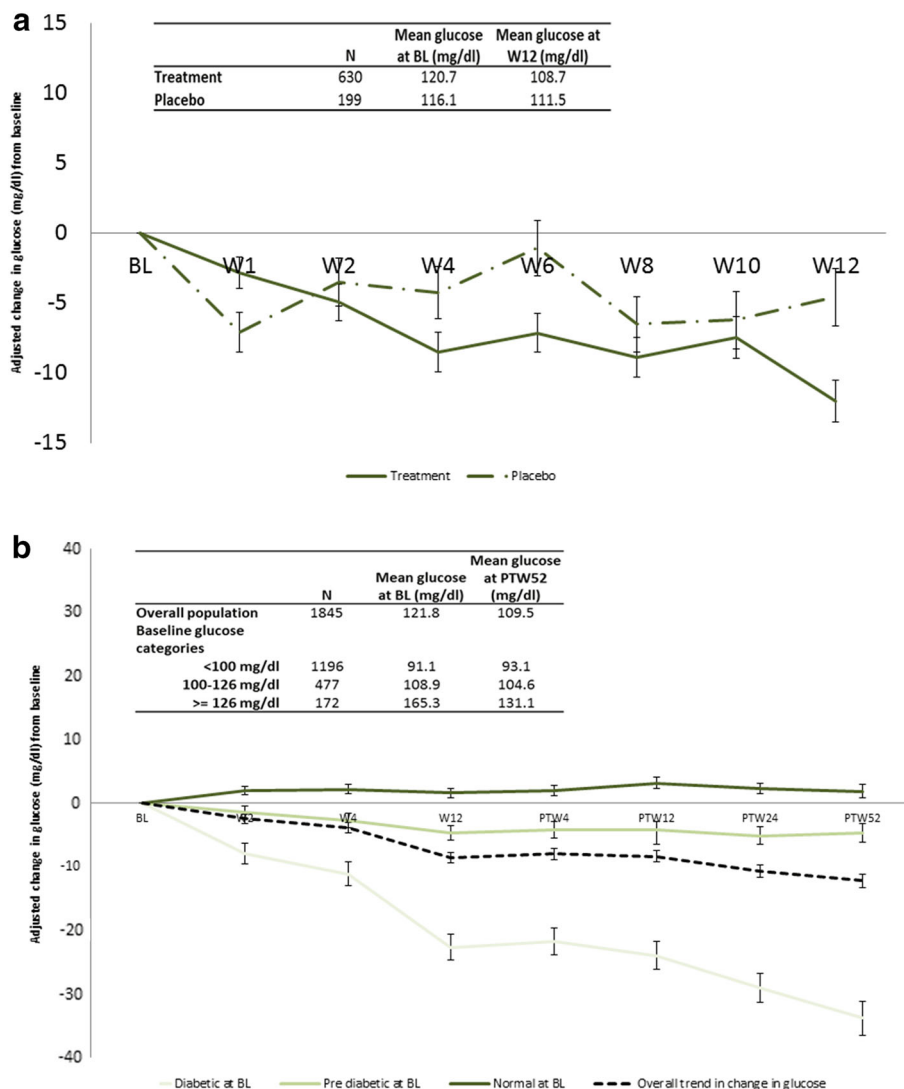
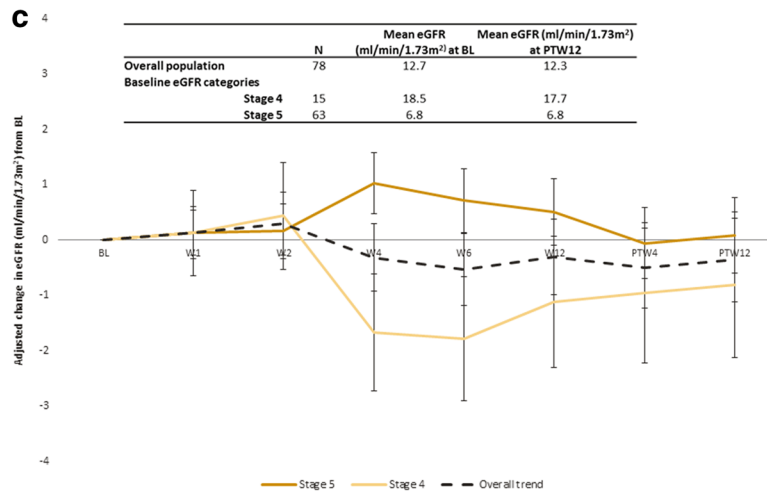
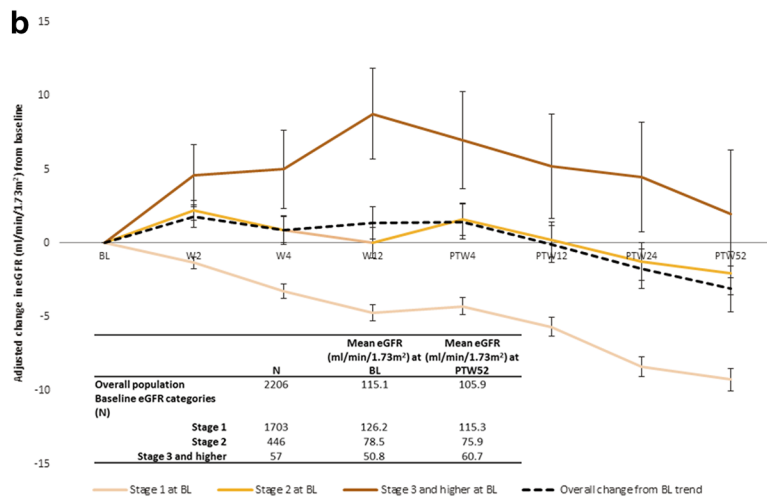
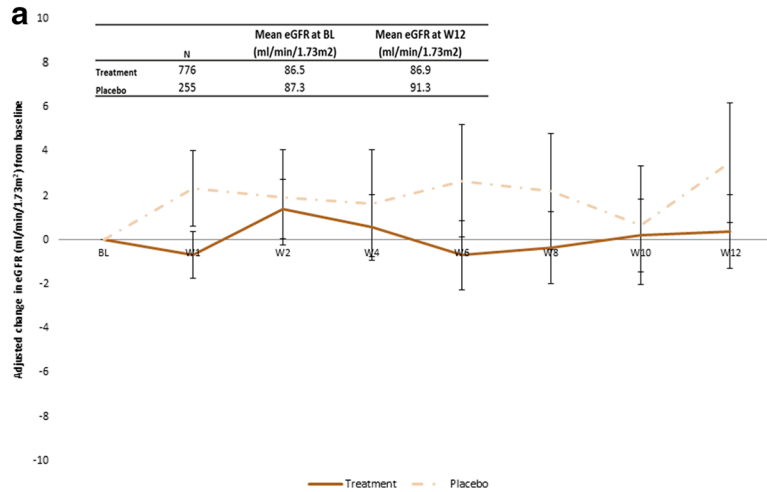


Fig. 2 a Predicted change in glucose from baseline: comparison of HCV-treated and placebo arms. Study conducted on treatment and placebo arms of SP1 [i.e., patients from placebo controlled phase 3a trials (SAPPHIRE I and II)]. All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed value of glucose at each time point on whether patients were in the HCV-treated or placebo group and adjusted for baseline glucose level, fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *BL* baseline, *W* week. **b** Predicted glucose change from baseline until post-treatment week 52 among treated patients by baseline glucose

levels. Patients with fasting baseline glucose value between 100 and 126 mg/dl were defined as pre-diabetic and glucose higher than 126 mg/dl were defined as diabetic. Study conducted on SP3. SP3 comprises all of the HCV-treated population from long-term phase 3b trials (TOPAZ I and II). All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed longitudinal glucose value on baseline glucose level categories and adjusted for fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *BL* baseline, *W* week, *PTW* post-treatment week



◀**Fig. 3** **a** Predicted change in eGFR from baseline: comparison of HCV-treated and placebo arms. Study conducted on treatment and placebo arms of SP1 [i.e., patients from placebo controlled phase 3a trials (SAPPHIRE I and II)]. All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed values of eGFR at each time point on whether patients were in the HCV-treated or placebo group and adjusted for baseline eGFR level, fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *eGFR* estimated glomerular filtration rate, *BL* baseline, *W* week. **b** Predicted eGFR change from baseline until post-treatment week 52 among treated patients by baseline eGFR levels. Chronic kidney disease stages were defined based on guidelines as stage 1 (signs of kidney damage but normal or elevated (eGFR ≥ 90), stage 2 (eGFR 60–89), stage 3 (eGFR 30–59), stage 4 (eGFR 15–29) and stage 5 (eGFR <15 or dialysis dependent). Study conducted on SP2. SP2 comprises all of the HCV-treated population from long-term phase 3b trials (TOPAZ I and II). All patients in trials were GT1 patients. The graphs depict predicted change from baseline at individual time points based on longitudinal mixed model regression. The model regressed longitudinal eGFR value on baseline eGFR level categories and adjusted for fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *eGFR* estimated glomerular filtration rate, *BL* baseline, *W* week, *PTW* post-treatment week. **c** Predicted eGFR change from baseline until post-treatment week 12 among treated patients with CKD stage 4 or 5 at baseline. Chronic kidney disease stages were defined based on guidelines as stage 1 [signs of kidney damage but normal or elevated (eGFR ≥ 90)], stage 2 (eGFR 60–89), stage 3 (eGFR 30–59), stage 4 (eGFR 15–29) or stage 5 (eGFR <15 or dialysis dependent). Study conducted on SP3. SP3 comprises all of the HCV-treated population from renal-specific phase 3b trials. All patients in trials were GT1 patients. The graphs depict predicted changes from baseline at individual time points based on longitudinal mixed model regression. The model regressed longitudinal eGFR value on baseline eGFR level categories and adjusted for fibrosis stages, genotype, age, BMI, presence of diabetes, treatment history, viral load and study enrollment. *Error bars* represent standard errors. *eGFR* estimated glomerular filtration rate, *BL* baseline, *W* week, *PTW* post-treatment week

of these declines is comparable to the improvements observed in clinical trials of triglyceride-lowering drugs, which ranged from 8 to 50% [34]. Elevated serum triglycerides are a known risk factor for coronary heart disease (CHD) and long-term all-cause mortality [18, 19], suggesting that treatment with $3D \pm RBV$ may lead to potential long-term beneficial cardiovascular outcomes.

Metabolic EHM

Fasting blood glucose levels over 110 mg/dl have been associated with vascular complications [20]. Similarly, recurrence of cardiovascular events have been observed to increase as fasting plasma glucose levels rise above 90 mg/dl and double with fasting plasma glucose levels of 110–115 mg/dl [21]. The American College of Endocrinology guidelines thus recommend a glycemic control target of <110 mg/dl [35]. Results from our analysis showed that the overall mean decrease in serum glucose levels at 52 weeks post treatment with $3D \pm RBV$ was 12.3 mg/dl overall, 4.3 mg/dl in patients with pre-diabetes and 34.2 mg/dl in patient with diabetes. Moreover, these patients were more likely to experience a decrease in serum glucose levels of $>20\%$, which increases the likelihood of reducing glucose levels below 110 mg/dl.

Renal EHM

The results of this analysis showed no significant impairment of renal function with $3D \pm RBV$ treatment, consistent with previous studies of $3D$ clinical trial data [36]. Our study did identify a decrease in mean eGFR at week 52 for patients with CKD stage 1, which does not appear to be clinically meaningful and was not seen in patients with more advanced CKD at baseline. This finding might be attributed to differences in baseline characteristics between CKD groups, since a higher proportion of stage 1 patients had BMI >30 and HOMA-IR score >3 at baseline as compared to patients with lower eGFR levels as baseline. These factors have previously been associated with a decline in eGFR [37–39]. The overall decline in eGFR observed in

treated patients during the post-treatment period is also consistent with the effect of aging as reported previously [40, 41]. A meta-analysis of 35 cohorts of patients enrolled in a CKD prognosis consortium concluded that the adjusted HR of all-cause mortality and end-stage renal disease (ESRD) was largely unchanged in patients with an increase or decrease in eGFR of 10% or less relative to patients with stable eGFR, but was increased with eGFR declines greater than 10%. Furthermore, patients with an increase in eGFR >10% had a lower risk of progression to ESRD [20]. In the current analysis more than 40% of the HCV-treated population who had a baseline eGFR <60 ml/min/1.73 m² experienced an eGFR improvement of up to 20%, suggesting that treatment with 3D ± RBV may reduce the risk of ESRD development and all-cause mortality in the long run.

Our findings should be interpreted within certain limitations. First, the parameters selected as surrogates for extrahepatic disease were chosen in a post hoc manner since they were routinely measured in clinical trials. If de novo trials were being conducted, different tests and biomarkers could improve the measurement of EHMs. For example, a fasting lipid panel would provide a more robust indication of cardiovascular risk than fasting triglycerides alone; serial HOMA-IR calculations would more precisely measure changes in glucose metabolism; serial urine collection would have allowed a more detailed description of the impact of treatment on renal disease. In addition, since the analysis was conducted on patients enrolled in clinical trials, it may have limited generalizability to the overall population. However, results seem consistent with prior literature assessing different patient populations. Furthermore, our analyses by baseline EHM severity did not distinguish between patients who did or did not achieve SVR. Nonetheless, it is likely that antiviral efficacy drives improvement in EHM biomarkers as the overall SVR rate in these trials exceeded 95% and our regression models found a statistically significant association between viral load reduction and EHM biomarker improvements. This study might also suffer from unobservable bias where clinical variables (e.g., other comorbidities or concomitant medications) not

collected in the database might influence the study results. To mitigate this issue, we leveraged double-blind trial data on patients randomly assigned to HCV treatment or placebo to assess the effect of treatment on EHM outcomes. Additionally, a real-world study did not find concomitant medications to be a significant predictor of EHM clinical outcomes in the presence of antiviral treatment [15]. In addition, we extrapolated the improvement observed in EHM biomarkers to clinical outcomes based on prior published literature. This may not be accurate and may warrant further research using real-world data with confirmed diagnosis of clinical outcomes. Finally, it should be noted that some of the patients included in the analysis did not receive an approved regimen as indicated in the current product label.

Nevertheless, this analysis contributes to the understanding of HCV treatment outcomes. It is one of the first to assess the impact of an oral IFN-free DAA regimen on EHM outcomes. It leverages a broad base of clinical trial data and included a comparison between treatment and placebo arms to evaluate the effect of DAA therapy on EHM outcomes.

CONCLUSION

In this post hoc analysis including large study populations, treatment with 3D ± RBV improved cardiovascular, metabolic and renal EHMs, especially in patients with elevated triglycerides, pre-diabetes/diabetes and CKD stage 2 and 3. CKD stage 4 and 5 patients had a stable eGFR during and post-treatment period. These positive effects of treatment on EHMs persisted at least 1 year post completion of treatment.

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Compliance with Ethics Guidelines. This analysis was conducted based on biomarker data collected in previously conducted studies and did not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The underlying data during and/or analyzed during the current study are not publicly available as they are clinical trial data. However, we can release a summary of results (i.e., DOF packet) upon request.

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