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Real-world effectiveness of ombitasvir/paritaprevir/ritonavir±dasabuvir±ribavirin in patients with hepatitis C virus genotype 1 or 4 infection: A meta-analysis

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Summary

The direct-acting antiviral regimen of ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r)±dasabuvir (DSV)±ribavirin (RBV) demonstrated high rates of sustained viral response at post-treatment week 12 (SVR12) in clinical trials for treatment of hepatitis C virus (HCV) genotypes (GT) 1 and 4. To confirm the effectiveness of this regimen in the real world, we conducted meta-analyses of published literature on 30 April 2016. Freeman-Tukey transformation determined the SVR rate within GTs 1a, 1b and 4, as well as specific SVR rates by cirrhosis or prior treatment experience status. Rates of virologic relapse, hepatic decompensation, drug discontinuation and serious adverse events were also analysed. In total, 20 cohorts across 12 countries were identified, totalling 5158 patients. The overall SVR12 rates were 96.8% (95% CI 95.8-97.7) for GT1 and 98.9% (95% CI 94.2-100) for GT4. For GT1a patients, the SVR rates were 94% and 97% for those with or without cirrhosis, and 94% overall. For GT1b patients, the SVR rates were 98% and 99% for those with or without cirrhosis, and 98% overall. The virologic relapse rate of GT1 patients was 1.3%, across 3524 patients in nine studies that reported this parameter. The rate of hepatic decompensation was less than 1% across five studies, including 3440 patients, 70% of which had cirrhosis. Conclusions: Real-world SVR12 rates for OBV/PTV/r±DSV±RBV were consistently high across HCV GT1 and four irrespective of cirrhosis status or prior HCV treatment experience, confirming effectiveness within a diverse patient population across multiple cohorts and countries.

KEYWORDS
2D, 3D, HCV genotypes 1 and 4, hepatitis C, meta-analysis, real-world effectiveness

1 | INTRODUCTION

Hepatitis C virus (HCV) is a global pathogen estimated to infect between 80 and 185 million people worldwide.[1,2] Hepatitis C is a health burden because if it remains untreated, it can result in the development of cirrhosis and hepatocellular carcinoma (HCC);[3] at least a quarter of all cirrhosis and HCC is associated with chronic HCV infection.[4] Additionally, the risk of HCV-induced morbidities such as portal hypertension, hepatic decompensation and associated mortality[5,6] suggests getting HCV treatment and achieving sustained virologic response (SVR) are critical.[7]

Recently, novel direct-acting antiviral (DAA) regimens have been approved for the treatment of chronic HCV.[8] For treatment of HCV genotype (GT) 1 infection, the 3-DAA combination of ombitasvir (OBV),

Abbreviations: DAA, direct-acting antiviral; DSV, dasabuvir; ESRD, end-stage renal disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; OBV, ombitasvir; RBV, ribavirin; SAE, serious adverse event; SmPC, Summary of Product Characteristics; SVR, sustained virologic response; USPI, United States Product Insert.

paritaprevir (codosed with ritonavir [PTV/r]; identified by AbbVie and Enanta), and dasabuvir (DSV) with or without ribavirin (RBV) has resulted in high SVR rates in clinical trials.[9-12] Comprehensive analyses of patients with GT1a or GT1b infection, including those with cirrhosis, enrolled in phase 3 clinical trials and treated with the United States Product Insert (USPI) or EU Summary of Product Characteristics (SmPC) label-recommended regimen demonstrated an overall SVR12 rate of 97%.[13,14] Phase 3b clinical study demonstrated 100% SVR12 for patients with GT1b and compensated cirrhosis after treatment with OBV/PTV/r+DSV without RBV, resulting in label and treatment guidelines updates for this population.[15] Patients with GT4 infection are recommended treatment with the 2-DAA combination of OBV/PTV/r+RBV, which also resulted in high SVR rates in clinical trials.[16-18]

Although treatment of HCV with DAA therapies has increased SVR rates and decreased side effects,[3,19,20] especially within clinical trials, the real world has myriad barriers to successful HCV treatment, including comorbidities and additional risk factors. For these reasons, it is generally understood that clinical trials produce higher efficacy rates than what is truly representative of real-world effectiveness in a more diverse patient population.[21] For instance, overall SVR12 rates for 12 weeks of sofosbuvir and ledipasvir in clinical trials[22,23] and some real-world cohorts ranged between 94% and 99%;[24] however, other real-world cohorts within the same population have reported SVR rates of only 92%-93%.[25,26] Similarly, phase 3 clinical trials of patients with HCV GT2 treated with sofosbuvir plus RBV demonstrated SVR rates of 95%; however, real-world SVR rates in this group have been shown to be only 83% in some cohorts.[27] In contrast, analysis of real-world effectiveness of OBV/PTV/r±DSV-based regimens demonstrated an overall 97% SVR rate in patients with HCV GT1 or 4 infection,[28] which is equivalent to efficacy observed in phase 3 clinical trials.

Here, we explored the real-world effectiveness of OBV/PTV/r±DSV±RBV for the treatment of HCV GT1 and 4 within 20 unique patient cohorts across 25 studies, encompassing a total of 5158 patients. Meta-analyses determined real-world rates of virologic relapse, hepatic decompensation, drug discontinuation, serious adverse event rates (SAEs) and SVR rates for patient sub-groups, including those with cirrhosis and prior treatment experience.

2 | METHODS

2.1 | Literature search

A literature search that combined terms and subject headings for "hepatitis C" with terms and subject headings related to the 2-DAA and 3-DAA regimens (OBV/PTV/r±DSV±RBV) was performed on 31 March 2016 across PubMed and Embase. Study data available only via oral or poster presentations or other conference/congress materials were also included. Conferences were searched on 30 April 2016 using the same search terms as above, via Embase when possible, or via conference-specific websites. If relevant data were not readily accessible, authors were contacted to obtain the original presented materials and other relevant information. Selection criteria for conference inclusion are outlined below. Conferences meeting those criteria are shown in Table S1.

2.2 | Literature screening

Titles and abstracts were screened against predefined selection criteria (Table S2) using the Doctor Evidence Library Management System (Doctor Evidence: *Library Management System.* Santa Monica, CA: Doctor Evidence, LLC), a software platform with term recognition within titles or abstracts, as well as keyword search and ranking functionality to allow quality control validation. Quality control was performed by validating a random sample of included and excluded abstracts. All included abstracts and a random sample of excluded abstracts were screened by full-text review, and studies of uncertain eligibility were included or excluded at the discretion of Doctor Evidence. PRISMA flow charts detailing the studies included and excluded (Fig. S1), and the number of patients available for each subgroup analysis (Fig. S2), are shown in the Supporting Information. Primary publications that reported SVR in this study and corresponding Wilson score confidence intervals at significant level 0.05 are shown in Table S3. Table S4 lists studies included in the meta-analysis only for safety parameters, as they did not report SVR or the cohort overlapped with another, larger cohort that reported SVR. Complete reference information for all 25 primary publications used in the meta-analysis is in the Supporting Information.

2.3 | Data extraction

Data extraction was performed with the DOC Data 2.0 (Doctor Evidence: *DOC Data*, *Version 2.0* Santa Monica, CA: Doctor Evidence, LLC) software platform using a universal electronic extraction form. Data points and metadata (variables that characterize numerical data points) were manually inputted into the electronic form by Doc Evidence, LLC, and data extraction was supported by quality control features (eg prevention of incorrect data-type entry into incompatible fields). Data discrepancies were resolved by contacting primary publication authors regarding potential author-reported errors and missing information. Using an ontology management tool within the platform, consistency of naming across outcomes of similar type based on the author-reported outcome name, as well as author-reported definitions (eg reported definition of SVR and intent-to-treat analysis in primary publications), was verified. Subsequent database-level quality control was performed using platform tools to evaluate data points *en masse* to identify outliers and ensure consistency of data and metadata across the entire set of primary publications.

2.4 | Meta-analysis and Freeman-Tukey transformation

Random-effects meta-analyses of proportions were performed using the DOC Data 2.0 software platform with the integrated R Project for Statistical Computing package *metafor*. All proportions were transformed using the Freeman-Tukey double arcsine transformation[29,30]

because many of the proportions being analysed were near the extremes of 0 and 1 (ie 100%). The double arcsine transformation prevents the confidence interval of a summary estimate of proportion from falling outside of the range of 0-1 (0%-100%). It also prevents individual estimates at the extremes of 0 or 1 from receiving undue weighting in meta-analysis. To determine the statistical heterogeneity between studies, the I^2 statistic was used.[31] Heterogeneity was considered substantial if $I^2 \geq 50\%$. The calculation was carried out as follows: $I^2=([Q-df]/Q)\times 100\%$, where Q is the chi-squared statistic and df is its degrees of freedom. The I^2 statistic estimates how much variability between studies is due to study and data heterogeneity rather than random chance.

For meta-analyses of patients with HCV GT1, seven studies (Tables S3 and S4; studies 7, 8, 14, 15, 16, 20 and 23) included a small number of participants with GT4; however, the proportion was no more than 26%, and thus, these populations were considered primarily GT1. For analysis of SVR12 for GT1a, two studies (studies 3 and 11) reported SVR12 proportions but did not report the population denominator (ie the total number of persons with GT1a who had SVR12 measured). These denominators were imputed based on the overall population denominator (ie the overall number of persons in the study who were GT1a, irrespective of whether they had SVR12 measured), and the proportion of those who achieved SVR was measured among the imputed total. For the analysis of SVR12, four studies did not report SVR at exactly 12 weeks postcompletion of therapy. Instead these studies reported SVR at 13 weeks (study 2), 4-30 weeks (study 8), 12/24 weeks (study 16), and one did not report the specific time point (study 18). For all primary publications, intent-to-treat (ITT) analyses were favoured over modified intent-to-treat (mITT) or per-protocol analyses, where multiple values were available. Breakdown of safety data associated with real-world treatment with OBV/PTV/r±DSV±RBV was analysed for all GT1-infected patients, where available; data were unavailable for those with GT4 infection. Subgroup analyses, such as patients with or without cirrhosis, or patients with GT1a/b, were calculated only using studies that reported such breakdowns in the initial publication. For example, it is possible that more than 189 patients analysed in this study had Child-Pugh B or decompensated cirrhosis; however, 189 patients were specifically reported to have Child-Pugh B or decompensated cirrhosis in primary studies, and thus, the SVR rate for this population was calculated based on 189 patients. Similarly, the level of patient detail reported varied by primary data source, resulting in lower patient N available for analysis within each subgroup than the total N reported. For example, while a total of 5046 GT1 patients had reported SVR across 18 studies, only five studies (including 535 patients) reported SVR specifically for subtype GT1a, and seven such studies reported SVR specifically for the GT1b subgroup (including 1750 patients); this limited the subtype-specific analysis for GT1 to a total of 2285 patients, despite having SVR data for 5046 patients for GT1 as a whole.

For minority and special populations, patients with end-stage renal disease (ESRD) were defined as those reported to have stage 4 or 5 chronic kidney disease. The definition of anaemia reported by each primary publication is unknown, and could fluctuate. We did not define anaemia, but grouped all cases of anaemia together regardless of primary definition. For patients with decompensated cirrhosis in study 13 (McCombs et al.), genotype was not reported; it is only known that those patients (n=129) were treated with either the 2-DAA or 3-DAA regimens.

2.5 | Role of the funding source

AbbVie sponsored the study, contributed to its design, the collection, analysis and interpretation of the data, and participated in the writing, review and approval of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit the publication.

3 | RESULTS

3.1 | Patient population and primary data sources

A total of 5158 patients were treated with OBV/PTV/r±DSV±RBV across 25 primary publications, encompassing 20 unique cohorts in 12 countries. The patient population had HCV GT1 or GT4 infection and included those with compensated or decompensated cirrhosis, prior HCV treatment experience, and with ESRD on dialysis. A majority (n=5046) of patients had HCV GT1, while the remaining 112 had GT4 infection. Rate of SVR was reported in 19 publications; the raw SVR rates of each are reported in Figure 1, and additional details are available in Table S3. Briefly, rates of SVR ranged between 91.5 and 100%, with an overall SVR of 96.8% (95% CI, 96.3-97.3). Additionally, 1.3% of patients (n=67) had ESRD, 62.8% (n=3240) of patients had cirrhosis, and 3.7% (n=189) of patients had Child-Pugh B or decompensated cirrhosis.

3.2 | Analysis of sustained virologic response by patient subgroups

Sustained virologic response by patient subgroups can be seen in Figure 2. Rate of SVR was 93.8% (95% CI, 87.8-98.0) for patients with HCV GT1a (n=535), while those with GT1b (n=1750) or GT4 (n=112) infection had SVR rates of 97.9% (95% CI, 97.0-98.9) and 98.9% (95% CI, 94.2-100), respectively. Among GT1 patients dichotomized by prior HCV treatment experience, SVR rates were above 95% in both groups (Table S5 and S6). SVR rates for those with or without cirrhosis were similar for all genotypes and subtypes. The largest difference observed was in GT1a patients, where those with cirrhosis had an SVR rate of 93.9% (95% CI, 89.6-97.3, n=193) compared to 96.5% (95% CI, 91.8-99.5, n=125) for those without cirrhosis. Patients with cirrhosis and subtype 1b infection were the most prevalent across all cohorts and demonstrated an SVR rate of 98.0% (95% CI, 96.4-99.1) across 715 patients. GT1b patients without cirrhosis (n=337) had a 98.9% (95% CI, 96.9-100) SVR rate. The published cohort data included fewer patients with GT4 infection and cirrhosis, of which breakdown data were only available for 19 patients; 99% (95% CI, 82.3-100) of them achieved SVR. The rate of response was similar for

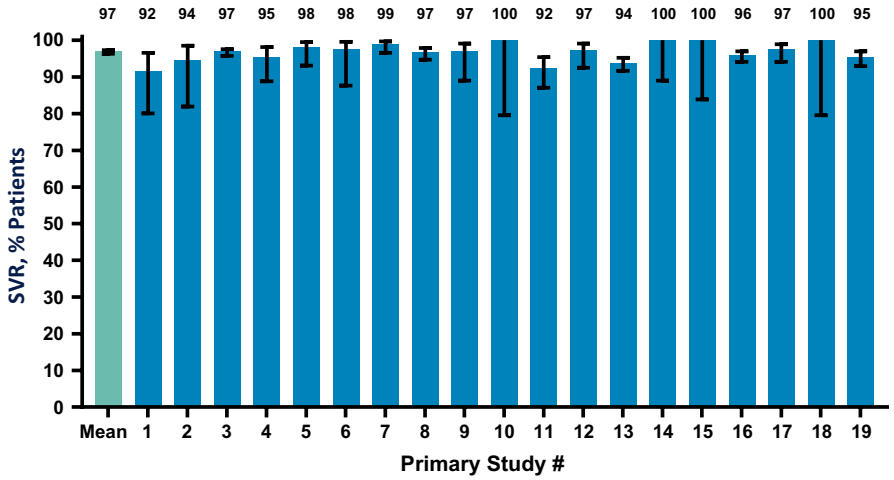

FIGURE 1 Real-world SVR rates from primary studies. Each primary publication that reported SVR is shown here. There were 25 primary publications used for meta-analysis in this study; only 19 were used to calculate SVR due to cohort overlap or publications that did not report SVR. Corresponding study details for this figure are shown in Table S3. The 19 SVR values reported in this graph represent 19 unique cohorts across 12 countries, totalling 5158 patients. The overall weighted SVR value (mean) was 97%. Confidence intervals at a significance level of 0.05 were calculated using Wilson score for binomial proportions

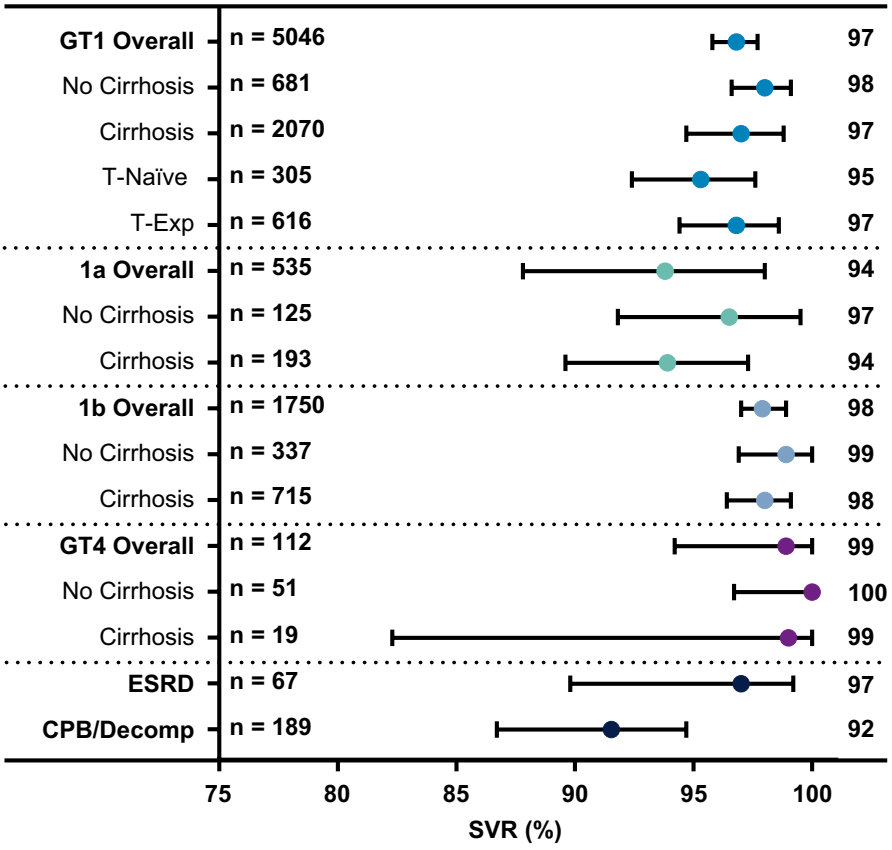

FIGURE 2 Real-world SVR rates by subgroup. The Freeman-Tukey transformed SVR and corresponding 95% confidence intervals are shown by patient subgroups; untransformed values are shown for patients with ESRD and CPB/decompensated cirrhosis. Overall SVR rates for GT1 and GT4 patients treated with OBV/PTV/r±DSV±RBV were 97% and 99%, respectively. Large confidence interval spread can be impacted by relatively few studies reporting SVR data for those individual subgroups, despite relatively high patient numbers, or by insufficient patient numbers (eg, n=19 for GT4 patients with cirrhosis). Note: the number of patients in each subgroup is based on data from primary publications that specifically reported breakdowns of SVR by subgroups; thus, subgroup N numbers may not total to overall N numbers. Abbreviations: CPB, Child-Pugh B cirrhosis; Decomp, decompensated cirrhosis; ESRD, end-stage renal disease; GT, genotype; SVR, sustained virologic response; T, prior HCV treatment

noncirrhotic patients with GT4 infection, as 100% (51/51) achieved SVR. Among patients that received the label-recommended OBV/PTV/r±DSV±RBV regimen, 98% (431/440) achieved SVR; in comparison, 92% (151/165) of patients treated off-label achieved SVR. Off-label was defined as patients treated with the OBV/PTV/r±DSV±RBV regimen for which treatment is not recommended by the USPI or SmPC. Furthermore, although patients with Child-Pugh B or decompensated cirrhosis are not recommended for treatment with the OBV/PTV/r±DSV±RBV regimen, those 189 patients with available data were not included in the off-label treated group; those patients are discussed separately below.

3.3 | Analysis of safety and adverse events

Overall, in GT1 patients, 3.12% (95% CI, 2.49-3.90) of 2370 patients across seven studies experienced at least one serious adverse event ([SAE]; Table 1). Study drug was discontinued by 2.50% (95% CI, 2.10-2.96) of the 5170 GT1 patients in which data were available. Drug discontinuation was the only safety metric where data were available specifically for patients with GT4 infection. Among 42 patients for which data were available in this population, there was no discontinuation. For 3440 patients where data were reported, only 0.96% (95% CI, 0.68-1.34) of patients experienced hepatic decompensation; of note, 70% of these 3440 patients had cirrhosis. Overall, the virologic relapse rate across 3524 GT1-infected patients in nine studies was 1.28% (95% CI, 0.96-1.70). Twenty-five of 4690 (0.53% [95% CI 0.36-0.79]) patients died during treatment or follow-up.

3.4 | Analysis of patients with renal disease or Child-Pugh B cirrhosis

The OBV/PTV/r±DSV regimen does not require dose modification for those with ESRD, with or without dialysis,[32] and is prescribed for those patients with concomitant HCV infection. In the analysis, among two studies that reported patients with ESRD, 97% (65/67) achieved SVR (Figure 2); 22% (15/67) of those patients experienced anaemia during treatment. In real-world clinical practice, OBV/PTV/r±DSV-based regimens were also utilized to treat patients with Child-Pugh B or decompensated cirrhosis, despite their contraindication in that population. Here, 92% (173/189) of patients within that population treated with OBV/PTV/r±DSV±RBV achieved SVR across two studies. Information on the rate of hepatic decompensation was only available for 39 patients with Child-Pugh B cirrhosis, of which only one patient (2.6%) experienced this event.

3.5 | Statistical heterogeneity

Statistical heterogeneity (I^2) was low for all SVR meta-analyses except for patients with GT1 infection and cirrhosis (I^2=73.1%), and GT1a overall (I^2=76.9%). For safety analyses, although heterogeneity was low for meta-analysis of virologic relapse, considerable heterogeneity (I^2≥75%) was observed for analyses of anaemia, serious adverse events, drug discontinuations and hepatic decompensation.

4 | DISCUSSION

Real-world evidence can provide insights into the effectiveness and safety of therapeutic regimens in a broader patient population and a more diverse clinical setting. This is critical because it is not unusual for clinical trials to demonstrate higher efficacy than what is observed with real-world experience. Pooled analyses of OBV/PTV/r±DSV±RBV treatment in phase 3 clinical trials within patients with HCV GT1a or GT1b infection demonstrated an overall SVR12 rate of 97%.[13,14] The present meta-analysis of real-world data from over 5000 patients demonstrates that OBV/PTV/r±DSV±RBV treatment resulted in SVR for 96.8% of patients with HCV GT1 or GT4 infection, confirming similarly high efficacy in phase 3 trials and the real world.

In total, for GT1 patients, neither cirrhosis nor prior HCV treatment experience had statistically significant impact on rate of SVR in the real-world, recapitulating findings from clinical trials.[10,33,34] Patient compliance and follow-up are often lower in the real world than in carefully controlled clinical trials, making virologic failure a bigger risk. The real-world relapse rate here was still low at just above 1% across nine studies and over 3500 patients, consistent with the relapse rate for GT1 patients observed in clinical trials (0.8%).[35]

Hepatitis C virus Subtype 1b is the most prevalent HCV infection worldwide, and thus, the largest subset of real-world patients treated with OBV/PTV/r+DSV±RBV (n=1750) fell into that group. Ninety-eight per cent of GT1b patients achieved SVR, with no appreciable difference in effectiveness between those with or without cirrhosis, a finding consistent with clinical trials in this population.[13,15] Recently, the TURQUOISE-III study demonstrated treatment with a RBV-free

TABLE 1 Real-world safety and adverse events[a]

Event	Rate (%)	95% CI	n/N	Studies
Virologic relapse	1.28	0.96-1.70	45/3524	9
Hepatic decompensation	0.96	0.68-1.34	33/3440	5
Drug discontinuation	2.50	2.10-2.96	129/5170	12
Serious AEs	3.12	2.49-3.90	74/2370	7
Death	0.53	0.36-0.79	25/4690	6

AE, adverse event; CI, confidence interval; HCV, hepatitis C virus; GT, genotype; n, number of event occurrences; N, total number of patients.

[a]All patients in this analysis had HCV GT1; 95% CI calculated with Wilson Score.

regimen of OBV/PTV/r+DSV led to 100% SVR12 for 60 GT1b patients with cirrhosis,[15] leading to an US Food and Drug Administration (FDA) and European Medicines Agency (EMA) label change for that population. High efficacy was recapitulated here with real-world evidence, although most patients with HCV GT1b infection in this study received RBV.

Patients with GT1a had a lower SVR rate compared to those with GT1b or GT4. This is not unexpected; in the era of DAA-based HCV therapies, patients with HCV GT1a have been more difficult to cure than those with GT1b and GT4, primarily due to the development of resistance.[36] Additionally, the presence of cirrhosis had a larger impact on SVR rate for GT1a than for GT1b or GT4; those with GT1a infection and cirrhosis had an overall SVR rate of more than 2% lower than their counterparts without cirrhosis. Nonetheless, the SVR of patients with GT1a infection, regardless of cirrhosis status, remained high (≥94%).

Similar to the findings in GT1b, patients with GT4 infection achieved very high rates of SVR with minimal impact of cirrhosis status on effectiveness. One limitation of this study was the relatively low number of GT4-infected patients with available data (n=70), especially those with cirrhosis (n=19). With limited analysis within this population, GT4-specific safety data could not be reported for OBV/PTV/r±DSV±RBV. Historically, GT4-infected patients have very high rates of SVR in clinical trials,[17,37-39] which align with the SVR rate observed in the real-world population, despite the small number of patients available for analysis here.

Other factors that influence patients' ability to achieve SVR are serious adverse events (SAEs), especially those leading to drug discontinuation. Within the two placebo-controlled clinical trials designed to study safety, the reported rates of SAEs for patients treated with OBV/PTV/r±DSV±RBV were 2.3 and 2.6 per cent.[33,34] Here, the observed rate across seven studies was similar, at just above 3%, despite a high percentage of cirrhotic patients. Notably, the rate of drug discontinuation remained low (2.5%) within a population of over 5000 patients. A low death rate was also observed (0.5%) considering the high percentage of patients with cirrhosis. While mortality was a reported outcome for nearly 4700 patients, high variation in follow-up time between studies made it difficult to determine whether deaths occurred during treatment and the standard 12-week post-treatment period of clinical trials, or during extended 24- to 36-week post-treatment follow-up periods observed in some studies.

Although the presence of cirrhosis had little impact on the effectiveness of OBV/PTV/r±DSV±RBV, hepatic decompensation is an added risk for patients in that population. Estimated rates of annual hepatic decompensation for patients with compensated cirrhosis are 5%-7% overall,[40,41] with the potential for higher rates among those undergoing treatment with DAAs.[42] Less than 1% rate of hepatic decompensation was observed across more than 3400 patients within cohorts that reported this event, suggesting that treatment of GT1 patients with OBV/PTV/r±DSV±RBV does not increase risk for decompensation. Documented manifestations of decompensation were available for 23 patients; there were eight patients with variceal bleeding, eight with ascites, six with hepatic encephalopathy and one patient that exhibited multiple signs. It is important to note that while most studies did not report specific event rates for cirrhotic patients, about 70% of these 3440 patients had cirrhosis (some with decompensated cirrhosis, despite contraindication), meaning the true rate of hepatic decompensation in the cirrhotic subpopulation could be closer to 1.37% (or slightly higher, depending on subsequent follow-up), assuming all patients that experienced decompensation had cirrhosis. The potential for drug-induced liver damage cannot be ruled out, particularly for patients whose decompensation is reversed upon drug discontinuation, which could occur in rare cases of decompensation events among those patients without a history of cirrhosis. However, based on a follow-up time of 24-36 weeks, either of the calculated rates of decompensation is in line with, if not below, the naturally expected rate of decompensation for cirrhotic patients. This real-world finding is supported by a meta-analysis of cirrhotic patients in clinical trials with OBV/PTV/r±DSV±RBV, where a decompensation rate of only 1.2% was reported within a population of 1066 Child-Pugh A cirrhotic patients.[43]

Of special interest are populations such as HCV-infected patients with renal impairment and stage 4 or 5 chronic kidney disease (CKD) on dialysis. OBV/PTV/r±DSV±RBV is recommended for use in patients with ESRD because it does not require dose modification for patients with any degree of renal impairment,[32] unlike sofosbuvir-containing regimens that are not recommended in this patient population.[44-46] The real-world SVR rate for patients with stage 4 or 5 chronic kidney disease, including those on dialysis, was similar to the combined SVR rate in all patient subgroups (97%), and nearly identical to that demonstrated in phase 3 clinical studies for patients with ESRD.[47] Additionally, the rate of anaemia in this population, observed here, is within the range generally reported for patients with ESRD (~20%-50%).[48,49]

Of great clinical importance is new, emerging real-world evidence that demonstrates significantly higher SVR rates for patients treated with the label-recommended regimen of OBV/PTV/r±DSV±RBV,[50] which could serve to help increase real-world SVR rates even further for patients treated off-label. This was supported by findings from this meta-analysis, which demonstrated that those treated with the label-recommended regimens had a 98% SVR rate, compared to 92% when there was deviation from the label. Nonetheless, even in the current treatment landscape, the real-world SVR rate for patients treated with the 2-DAA or 3-DAA regimens was high, regardless of genotype and historic negative predictors such as cirrhosis or prior treatment experience. Moreover, the rates of virologic relapse, hepatic decompensations, SAEs and drug discontinuations were approximately the same as previously demonstrated in clinical trials, or lower than expected.

Limitations of this analysis included the level of detail reported in each primary publication, as well as differing definitions of endpoint reporting between primary publications, resulting in different patient numbers available for meta-analysis per endpoint. In addition, not all studies reported SVR outcomes as ITT but some only a modified ITT (see Tables S3 and S4), and many of the studies were not available as full publications, only as posters, allowing only limited analyses from some cohorts. Furthermore, meta-analyses have an inherent degree of heterogeneity, usually assumed to be sampling

error; however, variability in study design and outcome reporting can also impact data heterogeneity. In this meta-analysis, many of the safety outcome analyses had considerable heterogeneity as measured by the I^2 statistic; much of the observed heterogeneity seen within safety outcomes can likely be attributed to the small number included studies, and variability in results and reporting between studies. Given that these primary studies were real-world observational cohorts, underlying differences in patient characteristics, study design and methods may have also contributed to statistical and clinical heterogeneity; however, such heterogeneity is difficult to evaluate due to lack of detailed available data from each individual source. In this study, only the SVR analyses of GT1a patients and GT1 patients with cirrhosis exhibited considerable heterogeneity ($I^2 \geq 50\%$). However, the results for SVR12 (particularly for GT1-infected patients) can be considered robust, as they include more than 5000 patients, and the associated confidence intervals had narrow ranges.

In summary, the present meta-analysis of real-world data for OBV/PTV/r±DSV±RBV treatment of patients with HCV GT1 or 4 infection from over 5000 patients demonstrated high effectiveness and a safety profile similar to that observed in phase 3 clinical studies.

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AUTHOR CONTRIBUTIONS

AP, ZZ and HW contributed to the design of the study. AP, HW and ZZ contributed to data collection and ZZ participated in data analysis. AP, MM, ZZ, YB, HW, AC, EZ, DD, RF, SKR and JLC contributed to the scientific content, critical reading and editing of the manuscript.

REFERENCES

1. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61:77-87.
2. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;61(1 Suppl):S45-S57.
3. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet*. 2015;385:1124-1135.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45:529-538.
5. Bezemer G, Van Gool AR, Verheij-Hart E, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. *BMC Gastroenterol*. 2012;12:11.
6. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol*. 2012;26:401-412.
7. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol*. 2016;65(1 Suppl):S95-S108.
8. Pawlotsky JM, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol*. 2015;62(1 Suppl):S87-S99.
9. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r–ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med*. 2014;370:1983-1992.
10. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370:1973-1982.
11. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. 2015;313:1223-1231.
12. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370:1604-1614.
13. Jacobson IM, Dufour JF, Wedemeyer H, et al. 99.7% sustained virologic response rate in 369 HCV genotype 1b-infected patients treated with label-recommended regimen of ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin. *Am J Gastroenterol*. 2015;110(S1):S850-S851.
14. Rustgi V, Wedemeyer H, Pockros P, et al. Sustained virologic response rate of 96% in HCV genotype 1a-infected patients treated with ombitasvir/paritaprevir/r and dasabuvir with ribavirin. *Am J Gastroenterol*. 2015;110(S1):S862.
15. Feld JJ, Moreno C, Trinh R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. *J Hepatol*. 2016;64:301-307.
16. Asselah T, Hézode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. *Lancet Gastroenterol Hepatol*. 2016;1:25-35.
17. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet*. 2015;385:2502-2509.

18. Waked I, Shiha G, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. *Lancet Gastroenterol Hepatol*. 2016;1:36-44.
19. Bansal S, Singal AK, McGuire BM, Anand BS. Impact of all oral anti-hepatitis C virus therapy: a meta-analysis. *World J Hepatol*. 2015;7:806-813.
20. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 2001;345:41-52.
21. Zoulim F, Liang TJ, Gerbes AL, et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. *Gut*. 2015;64:1824-1833.
22. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014;370:1889-1898.
23. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370:1879-1888.
24. Younossi ZM, Park H, Gordon SC, et al. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C. *Am J Manag Care*. 2016;22(6 Spec No.):SP205-SP211.
25. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real world effectiveness of ledipasvir/sofosbuvir in 4365 treatment-naive genotype 1 hepatitis c infected patients. *Hepatology*. 2016;64:405-414.
26. Mauss S, Schewe K, Rockstroh JK, et al. Sofosbuvir-based treatments for patients with hepatitis C virus (HCV) mono-infection and human immunodeficiency virus (HIV)-HCV co-infection with genotype 1and 4 in clinical practice – Results from the GErmanhepatitis C COhort(GECCO). The Liver Meeting (AASLD). 2016.
27. Tacke F, Gunther R, Buggisch P, et al. Treatment of HCV genotype 2 with sofosbuvir and ribavirin results in lower sustained virological response rates in real life than expected from clinical trials. *Liver Int*. 2017;37:205-211.
28. Pogorzelska J, Flisiak R. Real-world experience with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection. *Clin Exp Hepatol*. 2016;2:34-37.
29. Freeman M, Tukey J. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607-611.
30. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67:974-978.
31. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
32. VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) [package insert]. AbbVie, North Chicago, IL.
33. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370:1594-1603.
34. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370:1604-1614.
35. Poordad F, Agarwal K, Younes Z, et al. Low relapse rate leads to high concordance of sustained virologic response (SVR) at 12 weeks with SVR at 24 weeks after treatment with ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin in subjects with chronic hepatitis C virus genotype 1 infection in the AVIATOR study. *Clin Infect Dis*. 2015;60:608-610.
36. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology*. 2010;138:447-462.
37. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373:2599-2607.
38. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. *Lancet Infect Dis*. 2015;15:1049-1054.
39. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis c virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med*. 2015;163:1-13.
40. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Aliment Pharmacol Ther*. 2010;32:344-355.
41. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44:217-231.
42. Hoofnagle JH. Hepatic decompensation during direct-acting antiviral therapy of chronic hepatitis C. *J Hepatol*. 2016;64:763-765.
43. Poordad F, Nelson DR, Feld JJ, et al., editors. Pooled Safety Assessment of Ombitasvir/Paritaprevir/Ritonavir +/− Dasabuvir +/− Ribavirin in HCV-Infected Patients with Child-Pugh A Compensated Cirrhosis. EASL OPTIMIZE; 2016 12 April 2016; Barcelona, Spain.
44. SOVALDI (sofosbuvir) [package insert]. Gilead Sciences. Foster City, CA; 2014.
45. EPCLUSA (sofosbuvir and velpatasvir) [package insert]. Gilead Sciences. Foster City, CA; 2016.
46. HARVONI (ledipasvir and sofosbuvir) tablets [package insert]. Gilead Sciences. ed. Foster City, CA; February 2016.
47. Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterology*. 2016;150:1590-1598.
48. Clase CM, Kiberd BA, Garg AX. Relationship between glomerular filtration rate and the prevalence of metabolic abnormalities: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Nephron Clin Pract*. 2007;105:c178-c184.
49. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9:e84943.
50. Hinrichsen H, Wedemeyer H, Christensen S, et al. Real-world safety and effectiveness of ombitasvir/paritaprevir/r with dasabuvir and/or ribavirin in the German hepatitis C registry. The International Liver Congress (EASL); 2016.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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