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Effectiveness of 8- and 12-Week Treatment with Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Treatment-Naïve HCV Patients in a Real-Life Setting in Romania: the AMETHYST Study

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ABSTRACT

Background & Aims: The 12-week regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir (OPrD) has shown high efficacy and tolerability in clinical trials for the treatment of chronic hepatitis C virus (HCV). The shorter 8-week regimen has been recently incorporated into clinical guidelines and on-label indications, but real-world evidence on its use is limited. Given this knowledge gap, the AMETHYST study aimed to evaluate the effectiveness of the 8- and 12-week regimens of OPrD in treatment-naive patients with HCV with mild to moderate liver fibrosis in Romanian clinical practice.

Methods: This was a secondary data collection study analyzing data from a 1-year Patient Support Program in HCV in Romania. Patients received OPrD treatment for 8 or 12 weeks. The effectiveness endpoint was sustained virologic response 12 weeks post-treatment (SVR12).

Results: A total of 1,835 treatment-naive patients with HCV with mild or moderate fibrosis were included in the study. Of these, 426 and 1,375 completed the 8-week and 12-week regimens, respectively. SVR12 was 98.1% in the 8-week treatment group and 98.7% in the 12-week treatment group.

Conclusion: The study provides real-world evidence that 8-week and 12-week treatment regimens of OPrD are highly effective in treatment-naive patients with HCV with mild to moderate liver fibrosis.

Key words: hepatitis C virus – ombitasvir – paritaprevir – ritonavir – dasabuvir – real-world – sustained virologic response – 8-week and 12-week treatment.

Abbreviations: CP: core population; CPSFU: core population with sufficient follow-up data; HCV: hepatitis C virus; LLoQ: lower limit of quantification; OPrD: ombitasvir/paritaprevir/ritonavir plus dasabuvir; PSP: Patient Support Program; SVR12: sustained virologic response 12 weeks after the end of treatment; TE: transient elastography.

INTRODUCTION

The interferon-free combination of ombitasvir/paritaprevir/ritonavir plus dasabuvir (OPrD) for the treatment of chronic infection with hepatitis C virus (HCV) has demonstrated its efficacy in randomized controlled clinical trials, including in treatment-naive patients without cirrhosis [1-5]. Although efficacy can be defined as the capacity of a treatment to produce the desired effect in an ideal, controlled environment (eg, a randomized trial), effectiveness is defined as the extent to which a drug achieves its intended effect in a real-world context [6, 7]. Effectiveness trials usually include few or no exclusion criteria and a broader patient population from standard clinical practice, a group that is often underrepresented in clinical trials [7]. When measured in interventional settings versus routine clinical practice, drug effectiveness estimates differ. These differences are explained by the well-recognized lack of external validity of the clinical randomized trials on one hand and the numerous possible interactions of the real-life factors with the biological effect of the drug on the other [8].

The initial label recommendation of the OPrD combination was supported by the results of randomized clinical studies that included a 12-week treatment regimen [1, 3-5]. The current label states that a shortened regimen of 8 weeks is a therapeutic option that can be considered in previously untreated patients with mild to moderate liver fibrosis, based on the GARNET study results [9]. The 8-week regimen seems to be a more

convenient option in real-life settings, with the potential of reducing the overall health care burden and improving patient compliance [9]. However, the data on the shorter regimen of OPrD in routine practice shows conflicting results from several studies with relatively small sample sizes [10, 11].

In Romania, experience with the 8-week OPrD regimen began on September 1, 2018, when this option became eligible for health insurance reimbursement. Until then, only patients with advanced or severe fibrosis (stages F3 and F4, respectively) were included in the reimbursement criteria. To address the knowledge gap, the AMETHYST study, a retrospective analysis of data collected within the 1-year Patient Support Program (PSP), was conducted to evaluate the effectiveness of the 8- and 12-week OPrD regimens in a real-world setting in treatment-naive patients with chronic infection with HCV with mild to moderate fibrosis.

METHODS

Study design and participants

A secondary data collection study within the PSP (sponsored by AbbVie SRL, Bucharest, Romania) for patients with HCV was performed. The eligibility criteria for PSP enrolment were adult individuals (≥18 years) with chronic infection with HCV who were treatment-naive, had mild (stage F1) or moderate (stage F2) fibrosis, and received treatment with OPrD as per the Romanian National Health Insurance House prescription protocol. The PSP started on September 1, 2018 and lasted 1 year. Medical doctors (n=212) from clinical centers across the country who had treated patients infected with HCV were included in the PSP database used in the AMETHYST study.

Within the PSP, only a minimal set of variables were collected: patient demographics (age and gender), clinical characteristics (fibrosis grade and associated comorbidities), and HCV RNA level, expressed as detectable or undetectable/unquantifiable at 12 weeks after treatment. The National Bioethics Committee for Medicines and Medical Devices and National Agency of Medicines and Medical Devices was notified regarding the AMETHYST study, as per local legislation. The current analysis included only patients who provided written informed consent within the PSP, allowing the use of data for research purposes and its publication in an anonymized manner.

Treatment and procedures

The treatment consisted of two tablets of 12.5 mg ombitasvir, 75 mg paritaprevir, and 50 mg ritonavir (Viekirax®; AbbVie Deutschland GmbH & Co. KG, Wiesbaden, Germany) once daily and one tablet of 250 mg dasabuvir (Exviera®; AbbVie Deutschland GmbH & Co. KG) twice daily for an 8- or 12-week period, according to the clinical judgement of the treating physician.

Per routine clinical practice, patients underwent pre-treatment clinical assessments of hepatic fibrosis with transient elastography (TE; FibroScan®, EchoSens, Paris, France) or FibroMax® (BioPredictive, Paris, France). Transient elastography evaluation was performed in fasting conditions for ≥4 hours; a cut-off of 7 kPa for stage 1 of fibrosis and a cut-off of 9.5 kPa for stage 2 of fibrosis was used [12, 13]. For FibroMax assessments, the cut-offs were 0.31 for stage F1 and 0.58 for stage F2 [13, 14]. Serum HCV RNA was measured before starting the treatment and 12 weeks after the end of treatment (ie, ≥70 days) for all patients using a polymerase chain reaction test with a lower limit of quantification (LLoQ) of <15 IU/mL. Sustained virologic response 12 weeks after the end of treatment (SVR12) was defined as an HCV RNA level below the LLoQ [13].

Statistical analysis

Statistical analyses were performed using R language, version 4.0.0. Data were summarized using univariate statistics, including mean, standard deviation, median, and range for continuous variables and frequency distributions for categorical variables. Interval variables were analyzed using the Student *t* test. Categorical variables were analyzed using either chi-square or Fisher exact test. For the measure of primary objective (the percentage of patients achieving SVR12), two-sided 95%CI was calculated. No data were imputed for the analysis of effectiveness of the 8- and 12-week OPrD regimen. No formal hypothesis was tested. The analysis was not powered for comparisons within treatment groups.

Two sets of analysis were defined: the core population (CP), which included all patients from the study who started the OPrD treatment within the PSP, and the core population with sufficient follow-up data (CPSFU), which consisted of all CP patients except those with no HCV RNA evaluation after day 70 post-treatment for reasons not related to safety or efficacy (ie, missing or lost to follow up).

RESULTS

Patient characteristics

A total of 1,835 treatment-naive patients with HCV with mild to moderate liver fibrosis who were participating in the PSP and who received ≥1 dose of OPrD were included in this analysis (CP). This population included 428 (23.3%) patients receiving the 8-week OPrD regimen and 1,407 (76.7%) patients receiving the 12-week regimen. Two patients (0.5%) in the 8-week group and 29 patients (2.1%) in the 12-week group were lost to follow-up and discontinued. Three deaths (0.2%) were registered in the 12-week treatment group. In all, 1,801 (98.1%) patients completed treatment and performed the HCV RNA evaluation at 12 weeks post-treatment (CPSFU).

In both the CP and CPSFU, the analysis of baseline characteristics showed significant differences across treatment groups for age and fibrosis in the CP and CPSFU (Tables I and II). In both populations, approximately half of the patients from the 8-week treatment group ranged from of 41 to 60 years of age (CP: 51.9%; CPSFU: 52.1%), whereas in the 12-week treatment group almost two-thirds of patients were in the range of 51 to 70 years of age (CP: 65.5%; CPSFU: 65.7%; Fig. 1).

In each population, the most common comorbidity reported was hypertension (22.6% each in the CP and CPSFU). Other specific comorbidities with incidence >5% included cardiovascular diseases (coronary artery disease, chronic ischemic cardiopathy, arrhythmia of all causes, etc, with an overall incidence of 7.0% in the CP and 7.1% in the CPSFU),

Table I. Baseline demographic and clinical characteristics in the core population

Characteristic	Treatment group		p*	Total N=1,835
	8-week n=428	12-week n=1,407		
Gender, n (%)				
Male	108 (25.2)	289 (20.5)	p=0.046	397 (21.6)
Female	320 (74.8)	1,118 (79.5)		1,438 (78.4)
Age, years				
Mean ± SD (95% CI)	51.8±13.1 (50.5–53.0)	59.8±11.2 (59.2–60.4)	p<0.001	57.9±12.2 (57.4–58.5)
Median (min, max)	51 (19, 86)	61 (19, 84)		60 (19, 86)
Fibrosis stage, n (%)				
F1	159 (37.1)	329 (20.5)	p<0.01	488 (26.6)
F2	269 (62.9)	1,078 (76.6)		1,347 (73.4)

CI: confidence interval; F1: mild fibrosis; F2: moderate fibrosis; SD: standard deviation
*To compare the distribution of gender and fibrosis across treatment groups, chi-square tests were conducted. Student *t* tests were used to compare the mean ages across groups, and a medium size effect was noted (Cohen *d* = 0.69).

Table II. Baseline demographic and clinical characteristics in the core population with sufficient follow-up data

Characteristic	Treatment group		p*	Total N=1,801
	8-week n=426	12-week n=1,375		
Gender, n (%)				
Male	107 (25.1)	285 (20.7)	p=0.064	392 (21.8)
Female	319 (74.9)	1,090 (79.3)		1,409 (78.2)
Age, years				
Mean ± SD (95%CI)	51.8±13.1 (50.6–53.1)	59.7±11.2 (59.1–60.3)	p<0.01	57.8±12.1 (57.3–58.4)
Median (min, max)	51 (19, 86)	61 (19, 84)		59 (19, 86)
Fibrosis, n (%)				
F1	159 (37.3)	322 (23.4)	p<0.01	481 (26.7)
F2	267 (62.7)	1,053 (76.6)		1,320 (73.3)

*To compare the distribution of gender and fibrosis across treatment groups, chi-square tests were conducted. Student t tests were used to compare the mean ages across groups, and a medium size effect was noted (Cohen *d* = 0.67). For abbreviations see Table I.

gastrointestinal disorders (cholelithiasis, chronic gastritis, esophagitis, liver steatosis, etc, with an overall incidence of 6.2% and 6.3%, respectively) and diabetes mellitus (5.8% and 5.6%). Chronic kidney disease and thyroid-related diseases, including hypo- and hyperthyroidia, had an overall incidence <5 % in each population. The CPSFU results are shown in Table III.

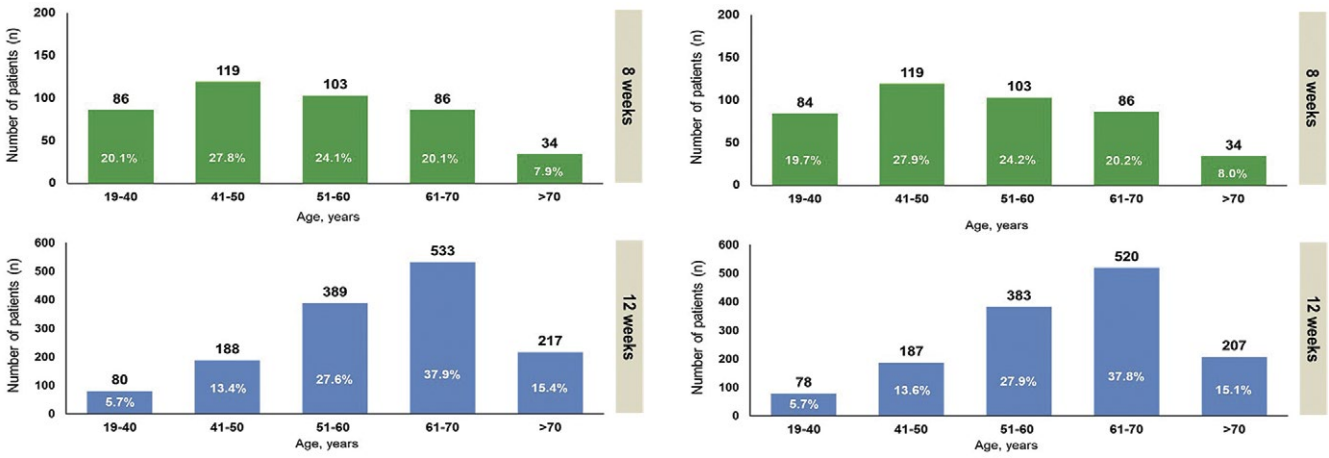

Fig. 1. Age distribution by treatment group in the CP (A) and CPSFU (B). CP: core population; CPSFU: core population with sufficient follow-up data.

Table III. Comorbidities rates in the CPSFU

Disease category, n (%)	CPSFU N=1,801
Hypertension	407 (22.6)
Diabetes	101 (5.6)
Thyroid diseases	74 (4.1)
Cardiovascular diseases	128 (7.1)
Chronic kidney disease	40 (2.2)
Gastrointestinal disorders	114 (6.3)
Depressive/anxious disorders	56 (3.1)
Cancer	35 (1.9)
HBV co-infection	12 (0.7)
Other disorders	249 (13.8)

CPSFU: core population with sufficient follow-up; HBV: hepatitis B virus.

Effectiveness analysis

In the CP, the SVR12 rates were 97.7% (418/428) in the 8-week treatment group and 96.4% (1,357/1,407) in the 12-week treatment group. In the CPSFU, the rates were 98.1% (418/426) and 98.7% (1,357/1,375), respectively. In the CPSFU, several subgroup SVR12 analyses were performed in each treatment group. The SVR12 status differed significantly by gender in each group (Fig. 2) but did not significantly differ by age or fibrosis stage (Fig. 3).

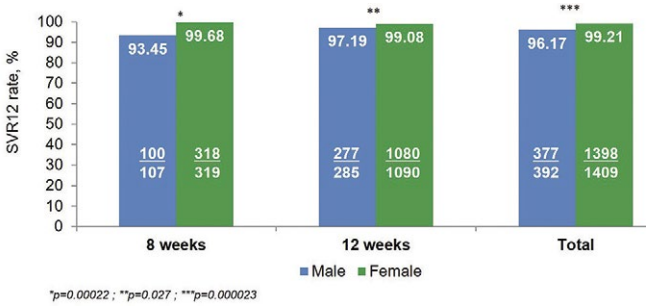

Fig. 2. SVR12 analysis by gender in each CPSFU treatment group. CPSFU: core population with sufficient follow-up data; SVR12: sustained virologic response 12 weeks post-treatment.

DISCUSSION

The AMETHYST study was conducted to provide real-world data describing the outcomes of the OPrD treatment regimen with durations of 8 and 12 weeks in treatment-naive patients with HCV with mild to moderate liver fibrosis. To our knowledge, this is the first assessment of the 8-week OPrD regimen conducted in Romania since September 2018 (when financial reimbursement of OPrD treatment became effective) that included treatment-naive patients with stages F1 and F2 fibrosis. Previous local studies exploring the 12-week regimen of OPrD in various populations, such as patients with compensated liver cirrhosis [15] with a focus on older patients (>70 years) [16] and patients with HCV with renal disease [17], observed good tolerance and efficiency in these categories of patients.

The 8-week OPrD regimen resulted in high rates of the SVR12 (>97% in the CP and >98% in the CPSFU), when measured according to various subgroups. Additionally, the results observed in the 12-week OPrD regimen were consistent with those reported in clinical trials, supporting OPrD effectivenesss [1, 2, 18].

Based on the phase 3b GARNET study results [9], the European Association for the Study of the Liver guidelines [19] and the OPrD label have been updated to include the 8-week regimen for the patients infected with HCV genotype 1b, previously untreated, with mild to moderate liver fibrosis. In the GARNET study, which was a multinational, single-arm, open-label trial with 166 patients, the SVR12 was 98% [9]. In the first real-world study of the 8-week OPrD treatment regimen conducted in 200 treatment-naive patients with mild to moderate fibrosis, the overall SVR12 rate in the intention-to-treat population was 96% [10]. In a recent analysis of a post-marketing observational study conducted across 13 countries [11] in which only 82 patients were treated with the 8-week regimen of OPrD, the SVR12 was 96.3% in the intention-to-treat population. Our study has the advantage of a larger sample size, with 428 patients receiving the 8-week OPrD regimen and 1,407 receiving the 12-week regimen. The SVR12 observed in our study, irrespective of treatment duration or population subset, compares similarly with the rates reported in the above-mentioned real-world studies [10, 11]. With few patients discontinuing treatment (around 2% in each treatment group), our study underlines the effectiveness of the OPrD combination in treatment-naive patients with HCV with mild or moderate liver fibrosis who completed the treatment, irrespective of its duration.

The AMETHYST study results highlight the demographics of patients for whom the 8- versus the 12-week treatment regimen was prescribed. The 8-week treatment regimen was recommended to a significantly younger population of patients (median age 51.0 vs 61.0 years; $p<0.01$). Additionally, the group stratification by gender revealed significant differences in sustained virologic rates, with higher SVR12 in female patients (Fig. 2). In our analysis, both groups showed a majority of women. This unbalanced distribution may contribute to this finding, while previous research [20–22] has shown that men and women are affected differently by HCV infection, with women experiencing overall slower disease progression, increased viral clearance, and higher sustained virologic rates than men over the course of various treatment regimens.

Because of its retrospective, observational nature, this analysis has several limitations. Despite the relatively large sample size, this analysis was not designed to ensure adequate power for subgroup comparisons. Another drawback of this study was the use of data from a PSP with a limited collection of baseline variables and no genotyping or other laboratory indicators or adverse events specifically assessed or recorded for the scope of a study. Therefore, we could not explore potential reasons for treatment discontinuation and non-response or the real-life tolerability and safety aspects of the OPrD regimen. Additionally, the PSP was conducted at the national level and, owing to variations in clinical experience among physicians, the severity of liver fibrosis was not evaluated in a uniform way. Both FibroScan and FibroMax were used variously, and this study did not collect any information regarding the type of test used to diagnose of the severity of fibrosis, only its grade.

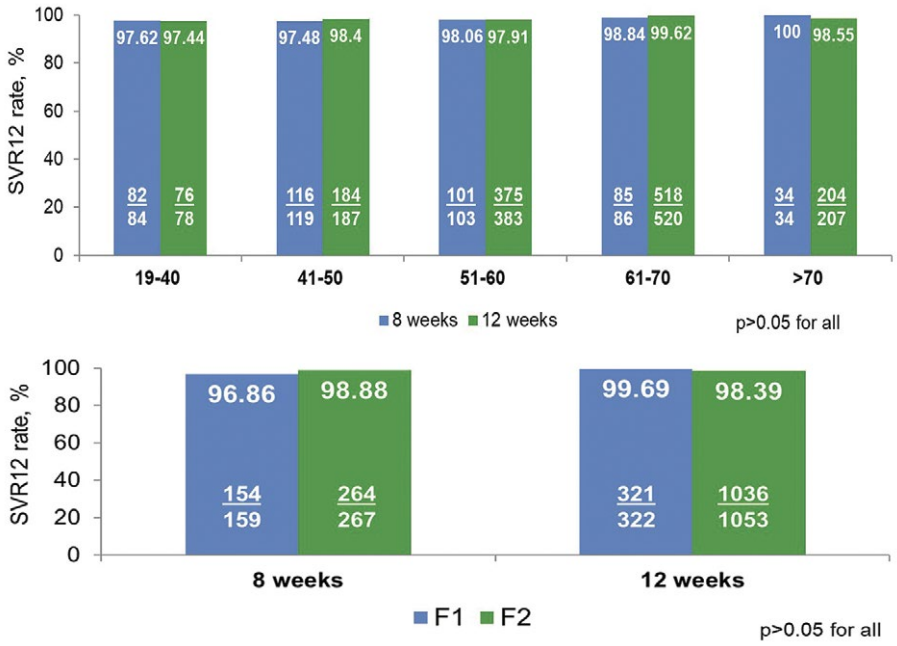

Fig. 3. SVR12 analysis by age (A) and fibrosis stage (B) in each CPSFU treatment group. CPSFU: core population with sufficient follow-up data; F1: mild fibrosis; F2: moderate fibrosis; SVR12: sustained virologic response 12 weeks post-treatment.

Thus, the study cannot inform further on the type of tests used in clinical practice to assess the grade of fibrosis. This analysis of patients with chronic HCV who were included in the PSP and who received treatment under a routine clinical practice setting provides useful information for clinicians and the therapeutic decision-making process. A non-invasive method, such as TE, has become standard and allows for stratification of patients into mild, moderate, severe, and advanced (cirrhosis) subgroups [12]. For those in the mild and moderate subgroups, the option of treatment with shorter duration (eg, 8 weeks) may be more attractive, with the potential of reducing side effects and complications while increasing patient compliance.

CONCLUSIONS

Our analysis indicates that the 8-week and 12-week treatment regimens of OPrD are both highly effective among treatment-naive patients with HCV with mild to moderate liver fibrosis in real-world settings. These data support the use of the shortened antiviral treatment duration in this population of patients.

Conflicts of interest: A.T., C.S., L.I., I.S., C.C., Z-A.S., A.S-C., L.G. were speakers scientific for AbbVie. A.T., C.S., L.I., I.S., M-C.L., E.M., A.S-C., L.G. were scientific advisors for AbbVie. A.T., L.I., I.S., C.C., Z-A.S., A.S-C., L.G. were speakers for Gilead. A.T., I.S., A.S-C., L.G. were scientific advisors for Gilead. C.S. received travel grants from Gilead. C.C., C.M. received educational grants from AbbVie and Gilead. A.S-C. was principal investigator in HCV clinical trials by AbbVie and/or Gilead. L.G. was speaker and scientific consultant for Merck. L.B., M.D., C.P. no conflict to declare.

Authors' contributions: All authors had equal input into the manuscript, the study concept and protocol and the study report. A.T., L.I., C.S., I.S., L.B., M.D., M-C.L., E.M., C.C., C.M., Z-A.S., C.P. and L.G. provided most of the patients whose data were analyzed. A.T, L.I., I.S., A.S-C. were advisors for the scientific part and reviewed the literature data. All authors reviewed the draft of the manuscript, red and agreed to the final version of it.

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