Real-world efficacy, safety, and clinical outcomes of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin combination therapy in patients with hepatitis C virus genotype 1 or 4 infection: The Turkey experience experience

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ABSTRACT

Background/Aims: *mbitasvir/paritaprevir/ritonavir (OMV/PTV/r) ± dasabuvir (DSV) ± ribavirin (RBV) combination has demonstrated excellent rates of sustained virologic response (SVR) and a very good safety profile in patients with the chronic hepatitis C virus (HCV) genotype 1 or 4 infections. We aimed to investigate the effectiveness and safety of OMV/PTV/r ± DSV ± RBV combination regimen in a real-world clinical practice.*

Materials and Methods: *Data from HCV genotype 1 and 4 patients treated with OMV/PTV/r ± DSV ± RBV (n=862) in 34 centers across Turkey between April 1, 2017 and August 31, 2018 were recorded in a large national database. Demographic, clinical, and virologic data were analyzed.*

Results: *The mean age of the patients was 55.63, and 430 patients (49.9%) were male. The majority had HCV genotype 1b infection (77.3%), and 66.2% were treatment-naïve. Non-cirrhosis was present at baseline in 789 patients (91.5%). SVR12 rate was 99.1% in all patients. Seven patients had virologic failure. No significant differences were observed in SVR12 according to HCV genotypes. HCV RNA was undetectable at treatment week 4 in 90.9%, at treatment week 8 in 98.5%, and at the end of treatment (EOT) in 98.9%. SVR12 ratio was significantly higher in the non-cirrhotic patients compared to that in the compensated cirrhotic patients. Rates of adverse events (AEs) in the patients was 59.7%.*

Conclusion: *The present real-life data of Turkey for the OBV/PTV/r ± DSV ± RBV treatment of patients with HCV genotype 1b, 1a, or 4 infection from 862 patients demonstrated high efficacy and a safety profile.*

Keywords: *Chronic hepatitis C, HCV genotypes 1 and 4, ombitasvir, paritaprevir, dasabuvir, real-world effectiveness*

INTRODUCTION

About 170-200 million people are known to be infected with the hepatitis C virus (HCV) infection worldwide. The chronic hepatitis C (CHC) infection carries the risks of hepatic fibrosis, cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma (HCC) (1). Chronic

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HCV infection is an important health concern in Turkey, as it is around the world (2-5). In Turkey, genotype 1b virus causes approximately 90% of the HCV infections; although types 2, 3, and 4 exist, they arein low prevalence. In recent years, there has been an increase in the HCV genotype 4 infections in Turkey (4-8).

Using combination therapy with pegylated interferon (PegINF) and ribavirin (RBV), the sustained virologic response (SVR) rate is 40-50% in patients infected with HCV genotype 1 and 60% in patients infected with HCV genotype 4.The First-generation protease inhibitors in combination with PegINF and RBV achieved low response rates in the patients infected with HCV genotype 1 or 4andthese regimens were characterized by less favorable safety profiles, which affected the adherence to the PegINF-based therapy (2, 6, 7).

The novel INF-free second-generation direct-acting antiviral (DAA) therapy consisting of ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) ± dasabuvir (DSV) ± RBV improved the efficacy, safety, and tolerability of the treatment of the chronic HCV infection. The regimen of OBV/PTV/r + DSV ± RBV was highly efficacious to treat the HCV genotype 1a or genotype 1b infection, including the patients with compensated cirrhosis. The observed SVR12 rate ranged from 92-100% (9-12). This combination has also proved very effective not only against genotype 1 but also against genotype 4. The patients with genotype 4 infection were recommended combination treatment with OBV/PTV/r + RBV, which also resulted in high SVR rates in the clinical and real-world trials (13-16).

Three of these medications target HCV at different phases of the viral life cycle and two of them are the protease inhibitors. OBV inhibits the viral NS5A phosphoprotein, which is involved in the viral assembly, PTV inhibits the viral NS3-4A serine protease involved in the proteolytic processing, and DSV inhibits the viral NS5B RNA-dependent RNA polymerase. Furthermore, ritonavir enhances the pharmacokinetic properties of PTV, increasing their availability through improved drug exposure (17).

MAIN POINTS

- *The regimen of OBV/PTV/r ± DSV ± RBV was highly efficacious to treat HCV genotype 1 and 4 infections, including patients with compensated cirrhosis.*
- *The patients with chronic HCV genotype 1 or 4 infections were treated with OBV/PTV/r ± DSV ± RBV for 12 weeks achieved 99.1% SVR12 in our study. Adverse events were mostly mild and did not require medical intervention This cohort is the first to present real-life data in our country.*

The objective of this study was to obtain real-life data describing the characteristics of patients treated with the OMV/PTV/r ± DSV ± RBV combination and evaluating its efficacy and safety in genotype 1 or 4 patients with the chronic HCV infection.

MATERIALS AND METHODS

Study patients

The patient aged over 18 years, female or male, with chronic HCV genotype 1 or 4 infection, treatment-naïve or previously treated with INF/RBV or PegINF/RBV, and with chronic hepatitis or compensated cirrhosis were eligible for the study.

The exclusion criteria were: Genotypenon-1/4 HCV infection, decompensated liver cirrhosis with Child-Pugh class B or C, evidence of HCC, concomitant medication that is contraindicated according to the manufacturer's recommendations, current pregnancy, lactation, and platelet count<25.000/mm^3.

The patients were enrolled for treatment with OBV/PTV/r ± DSV ± RBV according to the therapeutic guidelines of the National Health Application Notice of the Ministry of Health. The clinical records of the eligible patients were reviewed to assess the following aspects: baseline demographic characteristics (age, sex), HCV genotype-subtype, prior treatment status (treatment-naïve, treatment-experienced), baseline viral load, liver function tests (bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin), hemoglobin, platelet count, international normalized ratio (INR), degree of fibrosis according to the liver biopsy, history of antiviral treatment, co-infection status, underlying diseases, and concomitant medications.

Study design

A retrospective, non-randomized, multicenter, prospectively collected data, national study was performed to describe the demographic and clinical characteristics of the patients treated with OBV/PTV/r ± DSV ± RBV, and to obtain the real-world efficacy and safety data on the use of this combination in the treatment of the HCV infection.

The data were collected through a National Registry under the auspices of the Study Group for Viral Hepatitis of the Turkish Society of Clinical Microbiology and Infec-

tious Diseases. All the subjects provided written informed consent for the treatment. The study recorded data from all patients chronically infected with HCV genotypes 1 or 4 and who underwent treatment with OMV/PTV/r ± DSV ± RBV in 34 Turkish centers between April 1, 2017 and August 31, 2018. The data from 862 patients were included in the analysis. The follow-up (FU) ranged from 24–36 weeks depending on the treatment duration. The study was approved by the Ethics Committee for Clinical Research at the Kocatepe University, conforming to the protocols in accordance with the Declaration of Helsinki (Decision number: 2017-4).

The effectiveness data and safety were collected at different time points, both during and after the treatment completion.

Therapy and follow-up

The patients received two tablets of OBV/PTV/r (Viekirax, 12.5mg/75mg/50mg per tablet; Fournier Laboratories Ireland Limited Anngrove, Carrigtwohill, CoCork, Ireland)once daily andtwo tablets of DSV (Exviera 250 mg; AbbVie Ireland NL B.V.,Sligo, Ireland) per day. The RBV dose that was administered was based on the bodyweight (<75 kg, 1000 mg/day;>75 kg, 1200 mg/day). The patients infected with genotype 1a were treated with OBV/PTV/r+DSV+RBV for12 weeks (the ones without cirrhosis) or for 24 weeks (the ones with compensated cirrhosis). All patients with genotype 1b infection were treated with OBV/PTV/r + DSV for 12 weeks. All patients with genotype 4 infection were treated with OBV/PTV/r + RBV for 12 weeks. In case of significant laboratory abnormalities at baseline (anemia, thrombocytopenia or chronic renal failure (CRF)), the treatment was started with a lower dose of RBV according to the product characteristics. The RBV dose was modified or discontinued during therapy in patients who developed severe adverse events (AEs) or laboratory abnormalities. The necessary modifications were made tothe medications used by the patients according to the interactions of the antiviral drugs. In the renal transplant recipients, the doses of tacrolimus were reduced according to the plasma concentrations.

The clinical signs, AEs, and laboratory parameters (biochemical, hematologic tests, and HCV RNA) were assessed at the baseline, weeks 4 and 8, end of treatment (EOT, week 12 or 24), and FU12(12 weeks after EOT) or until the premature discontinuation of the treatment.

Efficacy and safety analysis

The primary effectiveness endpoint was the achievement of SVR (HCV RNA undetectable or below detection threshold) at FU12.The secondary endpoints were to evaluate the virologic responses at week 4 (RVR, rapid virologic response), week 8, and EOT. The virologic failure was defined as the virologic relapse (undetectable HCV RNA at the end of treatment, but positive within 12 weeks post-treatment) and non-response (HCV RNA being detectable at the end of treatment). The quantitative HCV RNA measurement was performed using various commercial real-time PCR quantification kits. The detection threshold was 12–25 IU/mL in the stud ycenters.

Safety endpoints included AEs and laboratory abnormalities.

Statistical analysis

The analyses were carried out on the per-protocol population, which comprised 791 patients. Histogram, q-q plots, and Shapiro-Wilk's test were assessed to test the normality of the data. A logarithmic transformation (base 10) was applied to the HCV-RNA due to its highly skewed distribution. Levene's test was used to test the homogeneity of variance. Mauchly's test was used to test the sphericity. To compare the distribution of the virologic response among the genotypes, non-cirrhotic/cirrhotic, and type of treatment, either Pearson's chi-squared analysis or Fisher's exact test was applied. Bonferroni corrected *z* test was used for multiple comparisons. To compare the laboratory parameters among follow-up time points, either a repeated measure analysis of variance (ANOVA) or Friedman's test was performed. Bonferroni or Nemenyi test was applied for multiple comparisons. The analyses were conducted using TURCOSA (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) statistical software. A p value less than 5% was considered as statistically significant.

RESULTS

Patients' characteristics

The demographic and clinical baseline characteristics are shown in Table 1. A total of 862 patients with HCV were included in the study. The majority of the patients had HCV genotype 1b infection (77.3%) and 66.2% were treatment-naïve. Non-cirrhosis was present at baseline in 789 patients (91.5%). Eighteen of 862 patients in our cohort were HBsAg positive. Of all patients, four had HIV and one had hepatitis D (HDV) co-infection. The hepatitis B virus (HBV) DNA was negative in all HBsAg positive patients before the HCV treatment and the two patients who were using entecavir. Both the HBV DNA and HDV RNA were negative in the HDV co-infected patients. In

Table 1. Baseline demographic and clinical characteristics.

Gender (male), n (%)	94 (66.7)	307 (46.1)	29 (52.7)	430 (49.9)
Age (years)	49.60±15.61	56.94±14.15	55.22±14.93	55.63±14.68
	(19.00-85.00)	(18.00-87.00)	(23.00-85.00)	(18.00-87.00)
Treatment-naïve, n (%)	94 (66.7)	439 (65.9)	38 (69.1)	571 (66.2)
Non-cirrhotic	88 (93.6	406 (92.5)	29 (76.3)	523 (91.6)
Compensated cirrhotic	6 (6.4)	33 (7.5)	9 (23.7)	48 (8.4)
Treatment-experienced, n(%)	47 (33.3)	227 (34.1)	17 (30.9)	291 (33.8)
Non-cirrhotic	45 (95.7)	205 (90.3)	16 (94.1)	266 (91.4)
Compensated cirrhotic	2 (4.3)	22 (9.7)	1 (5.9)	25 (8.6)
HCV RNA, log_{10} IU/mL	5.88±0.81	5.81±0.86	6.09±0.66	5.84±0.84
	(3.53-7.61)	(3.11-7.69)	(4.46-7.22)	(3.11-7.69)
≥ 800.000, IU/L, n(%)	71 (50.4)	310 (46.5)	39 (70.9)	420 (48.7)
ALT, IU/L	44.00 (30.00-68.00)	41.00 (27.00-63.00) (nmd=3)	32.00 (22.00-56.00)	41.00 (27.00-63.00)
AST, IU/L	36.00 (27.00-53.00)	37.00 (26.00-54.00) (nmd=3)	31.00 (21.00-53.00)	36.00 (26.00-54.00)
Total bilirubin, mg/dL	0.69 (0.51-0.97) (nmd=12)	0.65 (0.49-0.83) (nmd=93)	0.73 (0.55-0.98) (nmd=3)	0.66 (0.49-0.87)
Albumin, g/dL	4.28±0.46 (3.00-5.60) (nmd=13)	4.23±0.44 (2.60-5.70) (nmd=86)	4.14±0.56 (3.00-5.60) (nmd=4)	4.23±0.45 (2.90-5.70)
Hemoglobin, g/dL	13.95±1.76 (10.00-17.80) (nmd=11)	13.84±1.63 (8.20-18.80) (nmd=44)	13.91±1.97 (10.40-17.90)	13.86±1.68 (8.20-18.80)
Platelet count, /1000 mm^3	209.50 (170.00-265.25) (nmd=7)	216.00 (168.00-264.00) (nmd=27)	216.00 (165.00-262.00)	215.00 (168.00-264.00)
INR	1.10 (1.00-1.22) (nmd=5)	1.01 (0.95-1.10) (nmd=42)	1.00 (0.94-1.16) (nmd=2)	1.02 (0.96-1.10)
Fibrosis stage*, n (%)				
F0	-	5 (0.8)	-	5 (0.6)
F1	12 (8.5)	82 (12.3)	7 (12.7)	101 (11.7)
F2	29 (20.6)	134 (20.1)	5 (9.1)	168 (19.5)
F3	35 (24.8)	179 (26.9)	14 (25.5)	228 (26.5)
F4	3 (2.1)	19 (2.9)	1 (1.8)	23 (2.7)
F5	3 (2.1)	28 (4.2)	6 (10.9)	34 (3.9)
F6	3 (2.1)	11 (1.7)	3 (5.5)	20 (2.3)
Unknown	56 (39.7)	208 (31.2)	19 (34.5)	283 (32.8)
Antiviral treatment history, n(%)				
Number of experiences				
1	40 (85.1)	157 (69.2)	16 (94.1)	213 (73.2)
>1	7 (14.9)	70 (30.8)	1 (5.9)	78 (26.8)
Treatment regimens				
PegINF+RBV	35 (74.5)	145 (63.9)	16 (94.1)	196 (67.4)
PegINF+RBV/ Peg INF+RBV	6 (12.8)	66 (9.9)	1 (5.9)	73 (25.1)

Table 1. Baseline demographic and clinical characteristics. (Continue)

INF + RBV	5 (10.6)	12 (5.3)	-	17 (5.8)
INF+RBV/ PegINF+RBV	1 (2.1)	4 (1.8)	-	5 (1.7)
Treatment responses				
Relapses	11 (23.4)	84 (37.0)	6 (35.3)	101 (34.7)
Non-responders	6 (12.8)	65 (28.6)	8 (47.1)	79 (27.1)
Discontinued due to AEs	2 (4.3)	18 (7.9)	1 (5.9)	21 (7.2)
Partial responders	3 (6.4)	4 (1.8)	-	7 (2.4)
Breakthrough	-	2 (0.9)	1 (5.9)	3 (1.0)
Unknown	25 (53.2)	54 (23.8)	1 (5.9)	80 (27.5)
HBV co-infection, n (%)	2 (1.4)	15 (2.3)	1 (1.8)	18 (2.1)
HIV co- infection, n (%)	1 (0.7)	1 (0.2)	2 (3.6)	4 (0.5)
HBV-HDV co-infection, n (%)	-	1 (0.2)	-	1 (0.1)
Associated diseases n (%)	62 (44.0)	452 (67.9)	43 (78.2)	557 (64.6)
Number of diseases				
1	46 (74.2)	310 (68.6)	28 (65.1)	384 (68.9)
>1	16 (25.8)	142 (31.4)	15 (34.9)	173 (31.1)
Definition of disease				
Cardiovascular[π]	28 (19.9)	164 (24.6)	11 (20.0)	203 (23.5)
Diabetes mellitus	16 (11.3)	76 (11.4)	12 (21.8)	104 (12.1)
Chronic renal failure	15 (10.6)	51 (7.7)	11 (20.0)	77 (8.9)
Lung diseases[F]	7 (5.0)	39 (5.9)	1 (1.8)	47 (5.5)
Hematologic diseases[#]	-	17 (2.6)	4 (7.3)	21 (2.4)
Neurological diseases[h]	4 (2.8)	16 (2.4)	1 (1.8)	21 (2.4)
Psychiatric diseases[j]	3 (2.1)	16 (2.4)	1 (1.8)	20 (2.3)
Thyroid diseases[v]	3 (2.1)	16 (2.4)	1 (1.8)	20 (2.3)
Oncologic diseases[m]	2 (1.4)	14 (2.1)	-	16 (1.9)
Bone-joint diseases[α]	-	10 (1.5)	-	10 (1.2)
Dermatological diseases[g]	-	7 (1.1)	1 (1.8)	8 (0.9)
Substance use	1 (0.7)	6 (0.9)	-	7 (0.8)
Kidney transplantations	1 (0.7)	3 (0.5)	2 (3.6)	6 (0.7)
Rheumatologic diseases[b]	1 (0.7)	3 (0.5)	-	4 (0.5)
Other[u]	2 (1.4)	49 (7.4)	3 (5.5)	54 (6.3)
Modification of concomitant medications, n (%)	35 (24.8)	62 (9.3)	16 (29.1)	113 (13.1)

All data are presented as mean ± standard deviation (range) or median (1st–3rd quartiles), unless indicated otherwise.

Nmd: number of missing data; HCV: hepatitis C virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; PegINF: pegylated interferon; INF: interferon; RBV: ribavirin; AEs: adverse events; HBV: hepatitis B virus; HIV: human immunodeficiency virus; HDV: hepatitis D virus

*Ishak scoring system

[π]Hypertension, arrhythmia, valvular disease, aortic aneurism, heart failure, hyperlipidemia, peripheral vascular diseases;[F]Asthma, chronic bronchitis, silicosis; [#T]halassemia, hemophilia, lymphoma, multiple myeloma, anemia, polycythemia vera; [h]Epilepsy, Alzheimer's, Parkinson's, paresis, migraine, spina bifida, lumbar hernia, lumbar stenosis; [j]Depression, schizophrenia, mood disorder; [v]Hypothyroidism, hyperthyroidism, thyroiditis; [m]Solid tumors; [α]Osteoporosis, osteoarthritis, osteomyelitis, gout; gVitiligo, psoriasis, allergy; [bP]olyarthritis, ankylosing spondylitis, rheumatoid arthritis, Sjogren; [u]Familial Mediterranean fever, reflux, hydatid cyst, glaucoma, past tuberculosis, benign prostatic hypertrophy, cholelithiasis, renal artery stenosis, peptic ulcer, kidney stone, hyperparathyroidism, insulin resistance, hypersomnia, gastritis

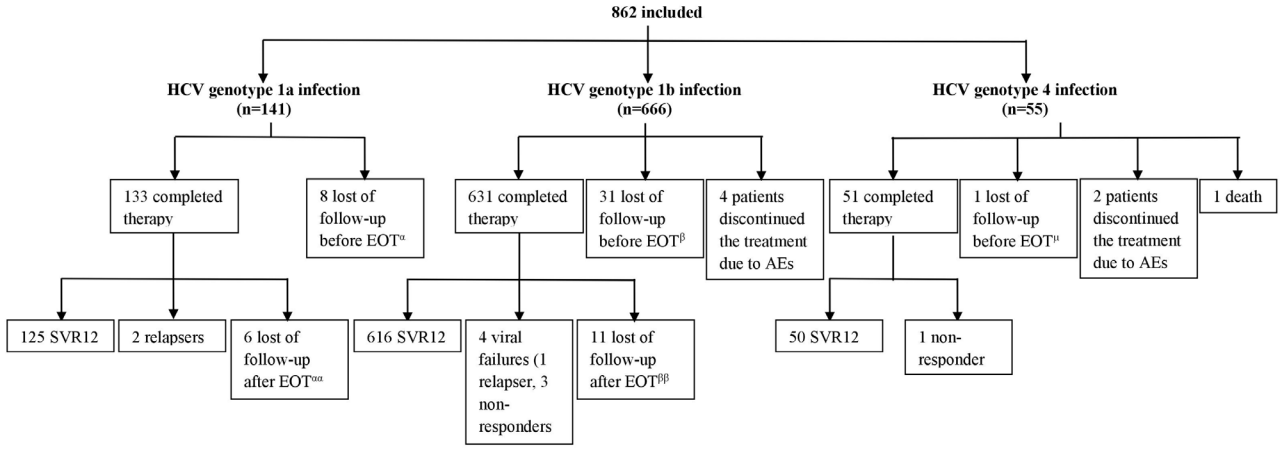


Figure 1. Study flowchart.

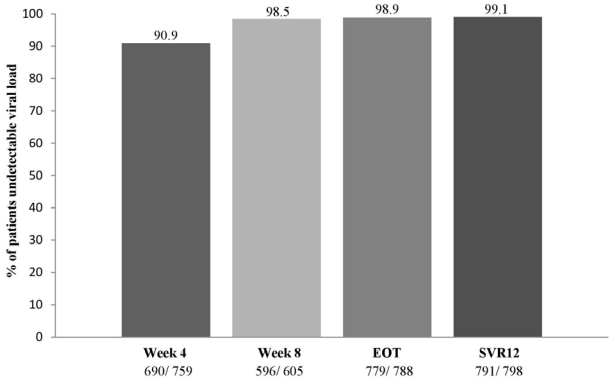


Figure 2. Efficacy of ombitasvir paritaprevir ritonavir ± dasabuvir ± ribavirin at different time points during treatment and 12 weeks after treatment.

13.1% of the patients, concomitant medications were modified due to drug-drug interactions.

Efficacy and safety outcomes

Out of 862 analyzed patients, 57 patients did not return for the viral loadFU12, 6patients stopped antiviral therapy because of the AEs,7patients had virologic failure, and one patient died (Figure 1).

The virologic rates per protocol analysis were calculated in the patients. The FU12 data were available for 798 patients, among whom 791 (99.1%) achieved SVR12. The HCV RNA was undetectable at treatment week 4 in 90.9%, at treatment week 8 in 98.5%, and at EOT in 98.9% (Figure 2). The RVR rates were significantly higher in the patients infected with HCV genotype 1a or 1b than that in the patients infected with genotype 4 ($p<0.001$). No significant differences were observed at treatment week 8, EOT, and FU12virologic responses according to HCV genotypes ($p=0.630$, $p=0.785$, and $p=0.410$, respectively).The RVR and SVR12 ratios were significantly higher in the non-cirrhotic patients as compared to that in the compensated cirrhotic patients ($p=0.004$ and $p=0.016$, respectively).There was no significant difference in the on-treatment or EOT or FU12 weeks responses between the treatment-naïve and treatment-experienced patients ($p=0.599$, $p=0.166$, $p=1.000$, and $p=0.431$, respectively) (Table 2).

The SVR rates according to the presence or absence of cirrhosis in the treatment-naive or -experienced patients are shown in Figure 3a-d. For genotype 1a patients, the SVR rates were 99.2% and 85.7%, respectively, for those without or with compensated cirrhosis, and 98.4% overall. For genotype 1b patients, the SVR12 rates were 99.5% and 98.0%, respectively, for those without or with compensated cirrhosis, and 99.4% overall. For genotype 4 patients, the SVR12 rates were 100% and 88.9%, respectively for those without or with compensated cirrhosis, and 98.0% overall. The SVR12 ratios were not significantly different between those without and with compensated cirrhosis in genotype 1a, genotype 1b, and genotype 4 patients. The SVR12 ratio in the treatment-naïve and non-cirrhotic patients infected with genotype 1a or genotype 4 was higher than in the compensated cirrhotic

Table 2. Virologic responses according to patients' characteristics.

	Virologic responses (negative/tested (%))			
Variable	Week 4 (RVR)	Week 8	EOT	Week 12 (SVR12)
All patients	690/759 (90.9)	596/605 (98.5)	779/788 (98.9)	791/798 (99.1)
Genotypes				
Genotype 1a (n=141)	119/123 (96.7)[a]	108/109 (99.1)	132/133 (99.2)	125/127 (98.4)
Genotype 1b (n=666)	533/587 (90.8)[a]	455/463 (98.3)	597/604(98.8)	616/620 (99.4)
Genotype 4(n=55)	38/49 (77.6)b	33/33 (100)	50/51 (98.0)	50/51(98.0)
p	< 0.001	0.630	0.785	0.410
Non-cirrhotic/compensated cirrhotic				
Non-cirrhotic (n=789)	633/689(91.9) [a]	543/551(98.5)	713/720 (99.0)	727/731(99.5)
Compensated cirrhotic (n=73)	57/70 (81.4) [b]	53/54 (98.1)	66/68 (97.1)	64/67 (95.5)
p	0.004	0.571	0.178	0.016
Response of previous therapy				
Treatment-naïve (n=571)	438/484 (90.5)	376/384 (97.9)	506/512 (98.8)	510/516 (98.8)
Treatment-experienced (n=291)	252/275 (91.6)	220/221 (99.5)	273/276 (98.9)	281/282 (99.6)
p	0.599	0.166	1.000	0.431

RVR: rapid virologic response at week 4 of treatment; EOT: end of treatment; SVR12: sustained virologic response at week 12 post-treatment

Different superscripts in the same column indicates a statistically significant difference between the genotypes and cirrhosis status.

patients infected with same genotypes. However, the differences were not significant (p=0.120 and p=0.235, respectively).In the patients infected with genotype 1b,the SVR12 ratewas higher in the treatment-experienced, non-cirrhotic patients as compared to that in the compensated cirrhotic patients (p=0.096). The SVR12 rates in the treatment-experienced patients were higher than that in the treatment-naïve patients for all different HCV genotype infections, but the differences were not statistically significant (p=0.108 for genotype 1a patients, p=0.291 for genotype 1b patients, and p=0.177 for genotype 4 patients). As compared to all genotypes, there was no difference in the SVR12 rates between the treatment-naïve and treatment-experienced patients (p=0.254 and p=0.866, respectively). SVR12 was achieved in 74 of 77 patients (96.1%) with CRF. Two patients left the FU and one patient died in this group. SVR12 was obtained in four patients (100%) with HIV co-infection and in five of six patients (83.3%) with kidney transplant. A transplant patient was lost to FU.

Table 3 summarizes the differences between the baseline and different time points during the antiviral therapy. In the patients, the mean ALT level significantly decreased from 41.00 IU/L at baseline to 20.00 IU/L after week 4 of the treatment and to 17.00 IU/L at EOT (p<0.001). The AST and hemoglobin values decreased from baseline to FU12 (p<0.001, p<0.001). The platelet count increased between baseline and FU12 (p<0.001).

Seventy-one patients (8.2%) failed to achieve SVR12. The causes for the lack of SVR12 response could be virologic failure in seven patients (four non-responders, three relapses), death of one CRF patient infected with genotype 4at week 6 of the treatment because of gastric bleeding unrelated to the liver disease, withdrawal from the treatment due to AEs in six patients (four patients infected with HCV genotype 1b and two patients with HCV genotype 4), and loss of FU in 57 patients (40 of the patients were before EOT, 17 of them after EOT). The six patients with virologic failure were treatment-naïve and one was treatment-experienced. Four were infected with HCV genotype 1b, two with genotype 1a, and one with genotype 4 among them. Three patients had the liver cirrhosis (Table 4).

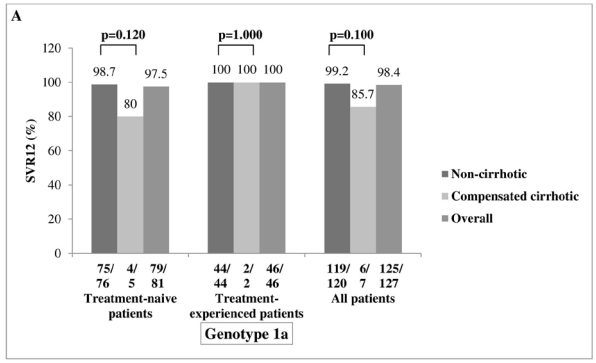
The AEs and laboratory abnormalities observed during the treatment or FU are shown in Table 5. There was at least one AE in 515 patients (59.7%). One CRF patient died after she achieved RVR due to gastric bleeding. In our cohort, six patients (0.7%) stopped the therapy within 3 weeks after the start of the treatment because of the AEs or laboratory abnormalities; two patients had jaundice and hepatotoxicity (total bilirubin, 5.6 mg/dL; ALT,

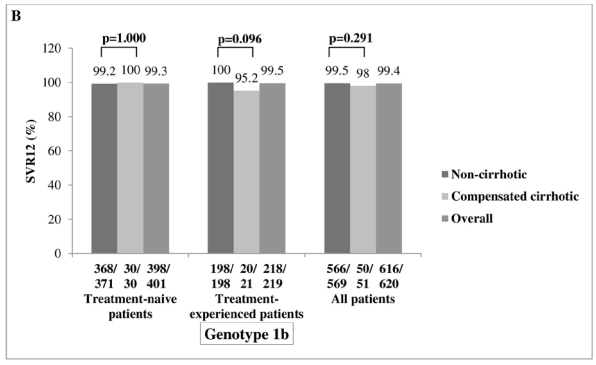
Table 3. Changes in the median laboratory parameters between baseline and 12 weeks post-treatment.

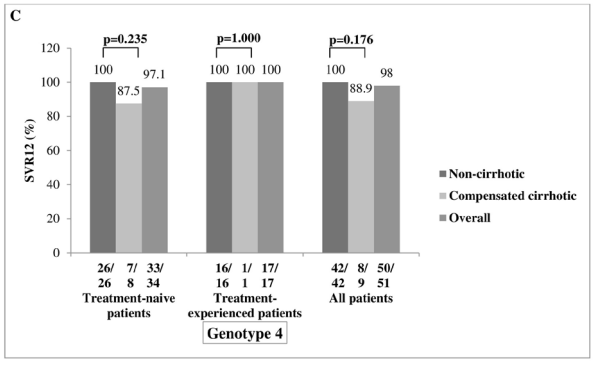
Variables	Follow-up time points					
	Baseline	Week 4	Week 8	Week 12	FU12	p
Genotype 1a (n= 127)						
ALT, IU/L (number of complete cases= 94)	44.50 (30.75-67.50)[a]	25.50 (15.75-43.00)[b]	22.00 (12.68-34.50)[b]	20.00 (14.00-33.00)[b]	25.00 (16.00-33.00)[b]	<.001
AST, IU/L (number of complete cases= 91)	39.00 (29.00-54.00)[a]	25.00 (17.00-38.00)[b]	22.00 (15.00-33.00)[cd]	18.00 (13.00-29.00)[c]	25.00 (17.00-33.00)[bd]	<.001
Hemoglobin, g/dL (number of complete cases= 63)	13.88 ± 1.90[a]	12.91 ± 1.99[bc]	12.71 ± 2.35[bc]	12.58 ± 1.92[b]	13.14 ± 1.98[c]	<.001
Platelets count, /1000 mm^3(number of complete cases= 78)	209.5 (166.8-272.0)	219.0 (175.5-278.0)	217.0 (174.8-267.3)	221.5 (177.5-272.0)	222.5 (197.0-288.3)	.088
Genotype 1b (n= 620)						
ALT, IU/L (number of complete cases= 485)	41.00 (28.00-62.50)[a]	19.00 (13.00-34.00)[b]	17.00 (12.00-30.00)[c]	16.00 (12.00-24.00)[d]	18.00 (13.00-27.00)[c]	<.001
AST, IU/L (number of complete cases= 482)	37.00 (25.75-54.00)[a]	21.00 (16.58-32.00)[b]	19.0 0 (16.00-27.00)[c]	18.00 (15.00-25.00)[d]	20.00 (16.00-25.00)[c]	<.001
Hemoglobin, g/dL (number of complete cases = 401)	13.81 ± 1.64[ab]	13.83 ± 1.67[a]	13.71 ± 1.71[b]	13.66 ± 1.71[b]	13.79 ± 1.68[b]	.002
Platelet count, /1000 mm^3(number of complete cases= 422)	215.0 (164.8-260.0)[a]	217.0 (178.0-262.5)[b]	214.0 (171.0-257.0)[a]	219.5 (176.8-264.0)[b]	216.0 (178.0-266.0)[b]	.001
Genotype 4 (n= 51)						
ALT, IU/L (number of complete cases= 48)	32.00 (22.25-55.50)[a]	16.00 (12.00-27.50)[b]	14.50 (11.25-19.75)[b]	15.00 (12.00-19.75)[b]	17.00 (12.00-23.00)[b]	<.001
AST, IU/L (number of complete cases= 48)	31.00 (21.25-53.00)[a]	18.00 (14.00-22.00)[b]	16.00 (12.00-21.75)[b]	16.00 (12.00-19.00)[b]	18.50 (14.00-22.75)[b]	<.001
Hemoglobin, g/dL (number of complete cases= 48)	14.07 ± 2.04[a]	13.19 ± 2.33[b]	13.00 ± 2.13[b]	12.85 ± 2.08[b]	13.28 ± 2.20[b]	<.001
Platelet count, /1000 mm^3(number of complete cases= 48)	217.0 (167.5-269.5)	242.0 (192.3-295.8)	220.5 (187.0-282.5)	231.5 (186.3-284.5)	237.0 (186.0-278.0)	.081
Total (n= 798)						
ALT, IU/L (number of complete cases= 627)	41.00 (28.00-64.00)[a]	20.00 (13.00-34.00)[b]	17.00 (12.00-31.00)[c]	17.00 (12.00-25.00)[d]	19.00 (13.00-27.00)[c]	<.001
AST, IU/L (number of complete cases= 621)	37.00 (26.00-54.00)[a]	21.00 (16.00-32.00)[b]	19.00 (15.00-27.00)[c]	18.00 (14.00-24.00)[d]	20.00 (16.00-26.00)[c]	<.001
Hemoglobin, g/dL (number of complete cases= 512)	13.84 ± 1.71[a]	13.65 ± 1.81[b]	13.52 ± 1.88[b]	13.45 ± 1.81[b]	13.67 ± 1.79[b]	<.001
Platelet count, /1000 mm^3(number of complete cases= 548)	214.0 (166.0-261.0)[a]	217.5 (178.0-267.0)[b]	214.0 (175.0-259.5)[b]	220.0 (177.3-267.0)[b]	218.5 (181.3-269.8)[b]	<.001

All data are presented as mean ± standard deviation (range) or median (1^{st}-3^{rd} quartiles),unless indicated otherwise. Different superscripts in the same row indicates a statistically significant difference among time points.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FU12: follow-up 12 week







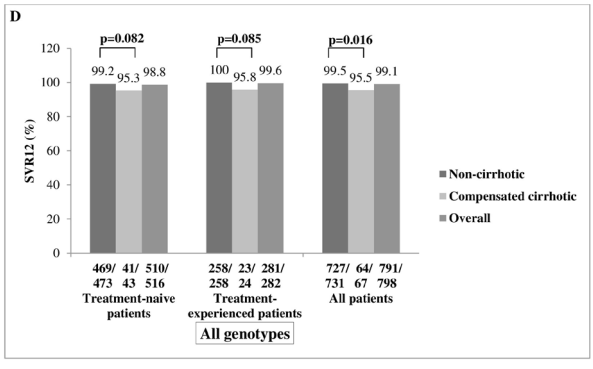


Figure 3. Rates of virological response to ombitasvir paritaprevir ritonavir dasabuvir ribavirin.

Table 4. Demographic and clinical characteristics of patients with virologic failure.

Gender	Male	Female	Male	Female	Male	Female	Male
Age, years	42	66	52	65	65	66	58
Genotype	1a	1a	1b	1b	1b	1b	4
Response tocurrent therapy	Relapse	Relapse	Relapse	Non-responder	Non-responder	Non-responder	Non-responder
Previous antiviral treatment	Treatment-naïvenon -cirrhotic	Treatment-naïve, compensated cirrhotic	Treatment-naïve, non-cirrhotic	Treatment-naïve, non-cirrhotic	Treatment-naïve, non-cirrhotic	Treatment -experienced, compensated cirrhotic	Treatment -naïve, compensated cirrhotic
HCV RNA, IU/mL							
Day 0	1.314.359	1.142.000	6.318.000	428.400	2.560.000	3.800.000	540.000
Week 4	-	Undetected	118000	-	511	2.700.000	5.139.000
Week 8	Undetected	Undetected	Undetected	127.000	Undetected	4.200.000	Undetected
Week 12	Undetected	Undetected	Undetected	298.000	6.390	5.870.000	3156000
FU 12	857.845	2.680.000	4.567.000	527.000	487.000	3.990.000	6.177.000
ALT	27	89	22	123	36	99	59
AST	19	103	22	100	30	157	67
Hemoglobin	14	12.10	16.20	13.10	14.30	12	13.10
Platelet count	161.000	90.000	219.000	176.000	255.555	64.000	100.000

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Table 5. Adverse events and laboratory abnormalities.

Patients, n (% patients with at least one event or one laboratory abnormality)/Total patients	Genotype 1a (n=141)	Genotype 1b (n=666)	Genotype 4 (n=55)	Total (n=862)
Any AEs	93 (66.0)	384 (57.7)	38 (69.1)	515 (59.7)
AEs or laboratory abnormalities leading to treatment discontinuation	-	4 (0.60)	2 (3.6)	6 (0.7)
Adverse events				
Asthenia	17 (12.1)	68 (10.2)	5 (9.1)	90 (10.4)
Pruritus	9 (6.4)	38 (5.7)	2 (3.6)	49 (5.7)
Headache	7 (5.0)	38 (5.7)	1 (1.8)	46 (5.3)
Fatigue	7 (5.0)	34 (5.1)	3 (5.5)	44 (5.1)
Nausea	4 (2.8)	34 (5.1)	1 (1.8)	39 (4.5)
Insomnia	5 (3.5)	18 (2.7)	-	23 (2.7)
Anorexia	2 (1.4)	18 (2.7)	2 (3.6)	22 (2.6)
Diarrhea	4 (2.8)	10 (1.5)	2 (3.6)	16 (1.9)
Dizziness	3 (2.1)	11 (1.7)	-	14 (1.6)
Mild rash	3 (2.1)	4 (0.6)	3 (5.5)	10 (1.2)
Abdominal pain	-	8 (1.2)	-	8 (0.9)
Cough	-	6 (0.9)	1 (1.8)	7 (0.8)
Fever[α]	-	6 (0.9)	-	6 (0.7)
Arthralgia	1 (0.7)	4 (0.6)	-	5 (0.6)
Dry skin	4 (2.8)	-	1 (1.8)	5 (0.6)
Palpitation	2 (1.4)	1 (0.2)	-	3 (0.3)
Vomiting	-	1 (0.2)	1 (1.8)	2 (0.2)
Chest pain		2 (0.3)		2 (0.2)
Other[αα]	1 (0.7)	37 (5.6)	-	38 (4.4)
Hemoglobin				
<10-8 g/dL	14 (9.9)	-	7 (12.7)	21 (2.4)
<8-6.5 g/dL	2 (1.4)	-	1 (1.8)	3 (0.3)
Total bilirubin				
>1.5-3 x ULN	6 (4.3)	28 (4.2)	4 (7.3)	38 (4.40)
>3-10 x ULN	-	2 (0.3)[βμ]	2 (3.6)[βμ]	4 (0.5)
ALT				
>3-5 x ULN	1 (0.7)	7 (1.1)	-	8 (0.9)
>5-20 x ULN	-	1 (0.2)[β]	1 (1.8)[β]	2 (0.2)
AST				
>3-5 x ULN	1 (0.7)	7 (1.1)	-	8 (0.9)
>5-20 x ULN	-	1 (0.2)[β]	1 (1.8)[β]	2 (0.2)

AEs: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: Upper limit of normal.

[α]Two urinary tract infections, one acute sinusitis; [αα]Epigastric pain, myalgia, appetite and weight gain, rectal pain, dyspepsia, sweating, hot flashes, night bad dream vision, blood pressure elevation, constipation, dry mouth, edema in lower extremities, darkening of urine color, imbalance, reduction in daily activity, dyspnea; [β]Treatment was discontinued; [μ]Transaminases were high in one patient

363 IU/L; AST, 352 IU/L; and total bilirubin, 11.7 mg/dL, ALT, 476 IU/L; AST, 389 IU/L, respectively) and therapy was stopped after 14 days; two patients had jaundice (total bilirubin: 10.8 mg/dL and 9.1 mg/dL, respectively) and therapy was stopped after 21 days; one patient developed arrhythmia (drug-drug interaction was considered) and therapy was stopped after 9 days; and one patient had vomiting and therapy was stopped after 14 days.

The most common AEs were asthenia, skin pruritus, headache, and fatigue. The AEs were mostly mild and did not require medical intervention. The incidence of laboratory abnormalities was uncommon in the patients. Because of anemia, the RBV dose was reduced in 13 (1.5%) patients (nine patients infected with genotype 1a and four patients infected with genotype 4) and RBV was discontinued in seven(0.8%) patients (six patients infected with genotype 1a and one patient infected with genotype 4). Erythrocyte transfusion was performed in five (0.6%) patients (three with HCV genotype 1a infection, and two with genotype 4 infection).

Three of 18 patients with HBV co-infection were lost to FU. The HBV reactivation was observed in two of 15 patients (13.3%) with HCV genotype 1b infection. The hepatitis flare did not occur in these patients; however, the oral antiviral treatment for the HBV infection was initiated.

DISCUSSION

The patients with the HCV infection are at the risk for progression to cirrhosis, transplantation, liver-related, and all-cause mortality. The use of DAAs has considerably improved the therapeutic outcomes for patients with the chronic HCV infections. High SVR12 levels were achieved in the treatment-naïve or -experienced patients with chronic HCV genotype 1/4 infections, including patients without cirrhosis or with cirrhosis who received OBV/PTV/r ±DSV ± RBV (9-15).The real-world evidence can provide insights into the effectiveness and safety of the therapeutic regimens in a broader patient population and in a more diverse clinical setting (18). Numerous real-world experiences have been reported from many Western countries thus far; however, no report of real-world data from Turkey is currently available. This cohort is the first to present real-life data in our country.

The current study analyzed the real-world effectiveness of OBV/PTV/r ± DSV ± RBV in 862 patients with HCV genotype 1a/1b/4 infections who were being treated in 34 health care centers in Turkey. The SVR12 rate was 99.1% in all patients. The study population included a considerable number of treatment-naïve (66.2%) and non-cirrhotic patients (91.5%). High SVR12 rates were obtained in HCV genotype 1a, genotype 1b, and genotype 4 infected patients (98.4%, 99.4%, and 98%, respectively). The SVR12 ratios were 98.8% in the treatment-naïve patients, 99.6% in the treatment-experienced patients, 99.5% in the non-cirrhotic patients, and 95.5% in the cirrhotic patients. The SVR12 ratio was significantly higher in the non-cirrhotic patients as compared to that in the compensated cirrhotic patients. There was no significant difference in the SVR 12 ratio between the treatment-naïve and -experienced patients and different genotype infected patients. The analysis of the real-world effectiveness of OBV/PTV/r ± DSV based regimens demonstrated overall 96–100% SVR rates in the patientswith HCV genotype 1 or 4 infection, which is equivalent to the efficacy observed in phase III clinical trials (16, 17, 19-25).Thus, the current study results were similar to the high SVR12 rates noted in the real-world studies.

In our study, the virologic response rates were 90.9% in week 4 of treatment, 98.5% in week8 of treatment, and 98.9% in EOT. Neither different genotypes nor previous antiviral treatments were associated with a significant difference in the virologic response rate at week 8 of the treatment and EOT. However, the RVR rates were significantly higher in the patients infected with genotype 1 than that in the patients infected with genotype 4, and in the non-cirrhotic patients as compared to that in the compensated cirrhotic patients. In Spain, a real-world study reported RVR rate of 93.1% and EOT rate of 98% in the patients infected with genotype 1 (20). In this study, there was no significant difference between the patients without and with cirrhosis on the treatment or EOT responses. In another Spanish study of 72.9% of cirrhotic patients, the RVR rate was 77.6% and the EOT rate was 97.3% (17). In a real-life experience study conducted by Jancoriene et al. (19), in genotype 1infected non-transplant patients, the rate of EOT response was found to be 97.1% in the treatment-naïve patients, and 100% in the patients with treatment-experienced PegINF + RBV.

Seven patients had virologic failure in our study. Our results confirm similar low rates of virologic failure in the individuals treated with OBV/PTV/r ± DSV ± RBV, as previously observed in the clinical trials and real-world data (17, 18, 20, 21, 24, 26, 27).

In our cohort, the results demonstrated high SVR12 rates with OBV/PTV/r ± DSV ± RBV in all the patients irrespec-

tive of cirrhosis status, previous treatment history or different HCV genotype infections. In Turkey, the HCV patients are managed by experienced clinicians in the referral centers because of the national program for the HCV treatment, which may result in better treatment adherence and higher response rates. A meta-analysis of 20 unique patient cohorts across 25 studies encompassing 5,158 patients reported the overall SVR12 rates of 96.8% (95% confidence interval (CI): 95.8-97.7) in genotype 1 infected patients and 98.9% (95% CI 94.2-100) in genotype 4infected patients (18).The SVR12 rates were consistently high irrespective of the cirrhosis status or prior HCV treatment experience.

The OBV/PTV/r + DSV ± RBV combination has demonstrated a very good safety profile in the clinical trials. The Phase III studies showed a discontinuation rate ranging from 0–2.4% and a percentage of serious AEs between 0.5% and 6.2% (28).The AE rate was 72.2% in the study by Flisiak R et al. (26) and 42.7% in the study by Jancoriene L et al. (19).In our study, 59.7% of the patients reported at least one AE and most of the AEs were mild or moderate. The frequency of the discontinuation due to AEs in the current study was low (0.7%) and lower than other real-life studies (2.2-2.5%) (18, 19, 26).

The drug-drug interaction is another important issue for the OBV/PTV/r ± DSV ± RBV therapy. The routine medication was modified at the baseline due to potential drug-drug interactions in 113 (13.1%) patients in our cohort. In the study by González-Colominas E et al. (29), at least one potential drug-drug interaction was reported in 62.1% of the patients and concomitant medication was modified before the HCV treatment in 27.7% of the patients.

The OMV/PTV/r ± DSV combination does not require dose modification for those with end-stage renal disease, with or without dialysis. This combination was found to be highly effective and safe in the patients with CRF (18,30). The real-world SVR rate for the patients with stage 4 or 5 CRF, including those on dialysis have been reported to be 97% (18). In our study, SVR12 rate was found to be 96.1% in the patients with CRF.

In Turkey, the DAA regimens are not easily accessible because of their high costs and the national legal restrictions for patients who can receive the HCV treatment free of charge. The present study has some limitations. First, the number of patients infected with genotype 4 and those with compensated cirrhotic were relatively low when compared with many real-world cohorts. Second, the study was uncontrolled, retrospective, and there was no external monitoring of the collected data. Third, the quantification of the HCV viral load and genotyping were conducted at several laboratories. Nevertheless, this study is of great value as it reports the effectiveness and safety outcomes in real life clinical practice in our country. The efficacy of OMV/PTV/r ± DSV ± RBV was very high in our cohort of patients with non-cirrhosis or compensated cirrhosis, and with underlying diseases, such as chronic renal failure, HIV, and transplantation.

In summary, the present real-life data of Turkey for OBV/PTV/r + DSV ± RBV treatment of the patients with HCV genotype 1b, 1a, or 4 infection from 862 patients demonstrated high efficacy and a safety profile. The patients with chronic HCV infection, with or without compensated cirrhosis and who were treated with OBV/PTV/r + DSV ± RBV for 12 or 24 weeks achieved 99.1% SVR12.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Afyon Kocatepe University, Date: 07.04.2017 and Number 2017/4.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept –B.A., N.D.; Design - B.A.; Supervision - B.A., N.D.; Resource -B.A., N.D.; Materials -B.A., N.D.; Data Collection and/or Processing - B.A., N.D., O.Y., M.K.Ç., İ.Ç., Ş.B., O.U., A.B., R.M., F.Ş., A.A., G.E., N.T., H.B., S.K., F.K, all outher group members; Analysis and/orInterpretation - B.A., G.Z., X.X.; Literature Search - B.A.; Writing - B.A.; Critical Reviews - N.D., O.Y., M.K.Ç., İ.Ç.

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REFERENCES

1. Zare F, Fattahi MR, Sepehrimanesh M, Safarpour AR. Economic burdenof hepatitis C virus infection in different stages of disease: A report from Southern Iran. Hepat Mon 2016; 16: e32654. [Crossref]
2. Aygen B, Yıldız O, Akhan S, et al. Retreatment of chronic hepatitis C infection with telaprevir: Preliminary results in Turkey. Balkan Med J 2015; 32: 266-72. [Crossref]
3. Aygen B, Nemirtürk N, Türker N, et al. Management of chronic hepatitis C virus infection: A consensus report of the Study Group for Viral Hepatitis of the Turkish Society of Clinical Microbiology and Infectious Diseases-2017 Update. Klimik J 2017; 30 (Suppl 1): 2-36. https://doi.org/10.5152/kd.2017.12
4. Aygen B, Yildiz O, Akhan S, et al. Impact of interleukin 28B genotype on the virological responses in chronic hepatitis C treatment. Gastroenterol Res 2014; 7: 123-30. [Crossref]
5. Taheri S, Aygen B, Korkmaz K, Yildiz O, Zararsiz G, Canatan H. Characterization of the interleukin-28B gene rs12979860 C/T polymorphism in Turkish chronic hepatitis C patients and healthy individuals. Balkan Med J 2015; 32: 147-55. [Crossref]
6. Aygen B, Yıldız O, Gökahmetoğlu S, Taheri S, Türe Z. Telaprevir combination therapy in patients infected with hepatitis C virus genotype 4. J Immunol Clin Microbiol 2016; 2: 57-61. [Crossref]
7. Aygen B, Yıldız O, Gökahmetoğlu S, Taheri S, Baltac S. Sofosbuvir plus ledipasvir treatment in patients with hepatitis C genotype 4d infection who previously failed to achieve sustained virological response with telaprevir or boceprevir combination therapies. Austin Pharmacol Pharm 2018; 3: 1012.
8. Ciccozzi M, Zehender G, Polat C, et al. Phylogenetic analysis of HCV-4d in Turkey: The curious case of Kayseri province. J Med Virol 2014; 86: 454-60. [Crossref]
9. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir,and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014; 147: 359-65. [Crossref]
10. 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: 1594-603. [Crossref]
11. 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: 1983-92. [Crossref]
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: 1604-14. [Crossref]
13. Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): A randomised, open-label trial. Lancet 2015; 385: 2502-9. [Crossref]
14. 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): Amulticentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016; 1: 25-35. [Crossref]
15. 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. [Crossref]
16. Crespo J, Calleja JL, Fernández I, et al. Real-world effectiveness and safety of oral combination antiviral therapy for hepatitis C virus genotype 4 infection. Clin Gastroenterol Hepatol 2017; 15: 945-9.
17. Perelló C, Carrión JA, Ruiz-Antorán B, et al. Effectiveness and safety of ombitasvir, paritaprevir, ritonavir ± dasabuvir ± ribavirin: An early access programme for Spanish patients with genotype 1/4 chronic hepatitis C virus infection. J Viral Hepat 2017; 24: 226-37.
18. Wedemeyer H, Craxí A, Zuckerman E, et al. Real-world effectiveness of ombitasvir/paritaprevir/ritonavir+/-dasabuvir+/-ribavirin in patients with hepatitis C virus genotype 1or 4 infection: A meta-analysis. J Viral Hepat 2017; 24: 936-43. [Crossref]
19. Jancoriene L, Polubenko K, Kazenaite E, et al. Direct-acting antivirals ombitasvir / paritaprevir / ritonavir + dasabuvir with or without ribavirin in hepatitis C virus (HCV) genotype 1-infected treatment-naive or treatment-experienced patients with or without cirrhosis: Real-life experience in Lithuania and Latvia. Hepat Mon 2018; 18: e62105. [Crossref]
20. Calleja JL, Crespo J, Rincón D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. J Hepatol 2017; 66: 1138-48. [Crossref]
21. Preda CM, Popescu CP, Baicus C, et al. Real-world efficacy and safety of ombitasvir, paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis. Liver Int 2018; 38: 602-10. [Crossref]
22. Hong CM, Liu CH, Su TH, et al. Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C in Taiwan: Real-world data. J Microbiol Immunol Infect 2018; 10.1016/j.jmii.2018.09.005. [Epub ahead of print] [Crossref]
23. Weil C, Mehta D, Koren G, et al. Sustained virological response to ombitasvir/paritaprevir/ritonavir and dasabuvir treatment for hepatitis C: Real-world data from a large healthcare provider. J Viral Hepat 2018; 25: 144-51. [Crossref]
24. Gheorghe L, Iacob S, Curescu M, et al. Real-life use of 3 direct-acting antiviral regimen in a large cohort of patients with genotype-1b HCV compensated cirrhosis.J Gastrointestin Liver Dis 2017; 26: 275-81. [Crossref]
25. 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: 34-7. [Crossref]
26. Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, et al. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirinin hepatitis C: AMBER study. Aliment PharmacolTher 2016; 44: 946-56. [Crossref]
27. Ioannou GN, Beste LA, Chang MF, et al. Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology 2016;151: 457-71. [Crossref]
28. Smith MA, Lim A. Profile of paritaprevir/ritonavir/ombitasvir plus dasabuvir in the treatment of chronic hepatitis C virus genotype 1infection. Drug Des Devel Ther 2015; 9: 6083-94. [Crossref]
29. González-Colominas E, Londoño MC, Morillas RM, et al. Potential drug-drug interactions of ombitasvir, paritaprevir/ritonavir ± dasabuvir ± ribavirin in clinical practice. J Gastroenterol Hepatol 2018; 33: 1100-7. [Crossref]
30. Muñoz-Gómez R, Rincón D, Ahumada A, et al. Therapy with ombitasvir/paritaprevir/ritonavir plus dasabuvir is effective and safe for the treatment of genotypes 1 and 4 hepatitis C virus (HCV) infection in patients with severe renal impairment: A multicentre experience. J Viral Hepat 2017; 24: 464-71. [Crossref]