Clinical and Experimental
HEPATOLOGY

Clin Exp HEPATOL 2017; 3, 3: 164–168
DOI: https://doi.org/10.5114/ceh.2017.70281
Received: 17.05.2017, **Accepted:** 04.07.2017, **Published:** 25.09.2017

Original paper

Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin for treatment of chronic hepatitis C 1 genotype in the Republic of Belarus

Dzmitry Danilau, Nadzeya Malich, Dzmitry Litvinchuk, Igor Karpov

Belarusian State Medical University, Belarus

Abstract

Aim of the study is to evaluate real-world efficacy of the ombitasvir/ paritaprevir/ ritonavir + dasabuvir ± ribavirin for treatment of chronic hepatitis C 1 genotype.

Material and methods: The study included 27 patients according to inclusion criteria. Main laboratory studies were performed in all patients at the baseline and during the treatment.

Results: Efficacy of the antiviral therapy was assessed by measuring the SVR12 and the SVR24 along with measuring of viral load during the treatment. The SVR12 and SVR24 rate was 100% (27/27).

Discussion: The results of the treatment were comparable to the results of pivotal, large-scale, randomized clinical trials. There were no serious adverse events during the treatment.

Key words: HCV, DAA, 3D, ombitasvir, paritaprevir, dasabuvir, SVR.

Address for correspondence:

Dr. Dzmitry Danilau, Belarusian State Medical University, Dzerzhinsky Ave. 83, 220016 Minsk, Belarus,
e-mail: d.danff@gmail.com

Introduction

Chronic hepatitis C is a widespread and costly, due to its complications, and healthcare problems. Globally, there are 71 million people living with chronic HCV infection. Moreover, most of them are unaware of their disease [1]. The prevalence of HCV differs among the distinct regions and groups of the patients (e.g. PWID, patients with hemophilia). Depending on the age of the patients, HCV prevalence peaks in the age range from 55 to 64. HCV is more prevalent among males in the majority of the countries, probably due to higher rates of exposition to the risk factors [2].

Hepatitis C virus is divided into 7 distinct genotypes, and there are several subgenotypes in each of the genotypes. Genotype 1 is the most widespread with the dominance of 1b subgenotype. The second is genotype 3. The rest of the HCV is presented by genotype 2, genotype 4, and genotype 6. The large part of genotype 4 is concentrated in Central Africa and Middle East region. The prevalence of genotype 5 and genotype 7 does not exceed 1% [2, 3].

Persistence of the virus and chronic inflammation causes continuous liver damage. Patients with chronic hepatitis C are at risk of developing cirrhosis and hepatocellular carcinoma. Moreover, HCV is a cause of the severe and potentially life-threatening extrahepatic manifestations.

Patients with chronic hepatitis C have about 15-20% risk to develop cirrhosis over 20 years of infection. Decompensation and hepatocellular carcinoma are frequent in patients with advanced liver disease due to chronic hepatitis C [4].

Since 2013-2014, HCV treatment strategies have been changed significantly. Novel direct acting agents possess higher efficacy along with better safety profile when compared to interferon-based treatment. Well tolerable interferon-free regimens allowed cure of HCV in patients who were previously ineligible for

interferon-based treatment, including those with advanced cirrhosis.

In 2015, European Medicines Agency approved combination of antiviral therapy for chronic hepatitis C 1 genotype with ombitasvir/paritaprevir/ritonavir plus dasabuvir [5]. Concomitant inhibition of the key viral proteins results in a potent suppression of HCV replication. Moreover, combination therapy provides a higher barrier to resistance than any of the drugs when used alone. Ombitasvir inhibits function of NS5A, paritaprevir is NS3/4A protease inhibitor, dasabuvir is a non-nucleoside NS5B palm polymerase inhibitor, and ritonavir acts as CYP3A inhibitor. More than 95% of non-cirrhotic previously untreated patients infected with 1 genotype of HCV achieved SVR12 after 12 weeks course of ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin [6].

Equal results were observed in patients with the history of interferon-based treatment failure, including those with no response [7]. Patients with cirrhosis and 1a genotype of HCV achieved SVR12 rates of more than 95% after the 24-week course of ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin [8]. In cirrhotic patients with 1b genotype, the 12-week treatment course of ombitasvir/paritaprevir/ritonavir + dasabuvir showed 100% SVR rates [9].

Patients without advanced fibrosis infected with HCV 1 genotype had 98% SVR rates after the even 8-week course of this regimen. Liver fibrosis (F3) was the only factor associated with SVR rates [10].

Similar efficacy of this regimen was observed in real-world study, where the overall rates of SVR12 were 99% [11].

According to the recent meta-analysis of a real-world efficacy of ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin, the overall rate of SVR12 in patients with 1 genotype was 96.8%. The SVR12 rates in patients with 1a genotype were 94%, and the SVR12 rates in patients with 1b genotype was 98% [12].

The antiviral therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin is well-tolerated by patients, including those with cirrhosis. The most frequent adverse events on this regimen were fatigue, headache, nausea, and pruritus. Serious adverse events occurred in 2.1% patients without cirrhosis, and in 0.6% treatment was stopped due to adverse events. The rate of serious adverse events was 6.2% in patients with cirrhosis. In addition, 1.9% patients with cirrhosis discontinued treatment due to serious adverse events [6-9].

Systemic exposure to the drugs in this regimen changes significantly in patients with decompensated cirrhosis, and thus, ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin are not recommended for use in patients with cirrhosis Child-Pugh B, and contraindicated in patients with cirrhosis Child-Pugh C [5].

This antiviral regimen may be used in patients with severe renal impairment, including hemodialysis patients [13].

This article provides the information about the first use of ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin for the treatment of chronic hepatitis C in the Republic of Belarus.

Material and methods

This study included 27 eligible patients who were treated for chronic HCV-infection 1 genotype with ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin between 2015 and 2016.

Inclusion criteria:

1. Patients with chronic hepatitis C 1 genotype, including those with cirrhosis Child-Pugh A or B;
2. Patient's willingness to being treated.

Exclusion criteria:

1. Decompensated liver disease (Child-Pugh C);
2. HIV-coinfected or HBV-coinfected patients;
3. History of hepatocellular carcinoma (including patients with remission of HCC);
4. Patients with previous DAAs-based treatment.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and National Research Committee, and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Statistical analysis was performed with R Statistical Package version 3.4.0.

Results

Among participants, 55.6% (15/27) were males, and 44.4% (12/27) were females. Mean age was 47.2 years, ranging from 30 to 68 years.

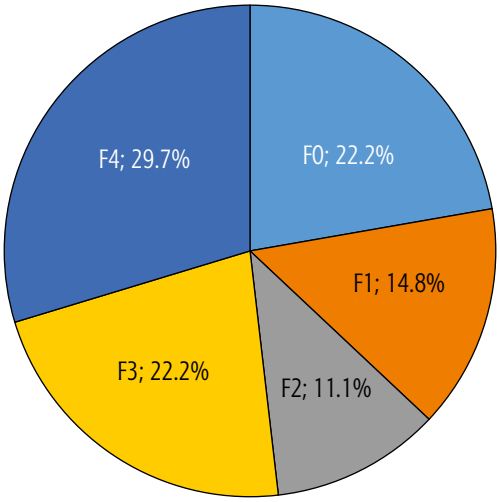

Fig. 1. Distribution of the patients by the stages of fibrosis (n = 27)

History of previous interferon-based treatment failure had 40.7% (11/27) of patients, among them, 54.5% (6/11) with the null response, 18.2% (2/11) with partial response, and 18.2% (2/11) with relapse. One patient (1/11) discontinued previous interferon-based treatment due to bacterial infection (acute sinusitis).

Median of baseline viral load was 1 312 320 IU/ml with interquartile range 594 561 IU/ml – 2 710 385 IU/ml, minimum of 8520 IU/ml, and maximum 29 000 000 IU/ml.

A part of the patients (37%; 10/27) had elevated level of total bilirubin at baseline. Median total bilirubin was 15 μmol/l (interquartile range, 11.76-20.86 μmol/l). Also, 33% (9/27) had increased baseline level of ALT. Medial ALT level was 52.8 IU/l (interquartile range, 42.3-78 IU/l).

Table 1. Individual characteristics of the patients before treatment initiation

Patient	Age, years	Sex	HCV genotype	Fibrosis stage	Viral load, PCR RNA, IU/ml	ALT, IU/l
1	39	M	1b	F1	1312320	33.9
2	63	F	1b	F3	8520	159.1
3	43	F	1b	F4	2100000	100
4	46	F	1b	F2	2700000	70.5
5	66	F	1b	F3	1947840	78
6	56	F	1a	F3	7712813	31.2
7	41	F	1b	F0	517390	56
8	37	F	1b	F1	10000000	52.8
9	60	M	1b	F4	670000	46.4
10	68	F	1b	F2	120000	28.6
11	38	M	1a/1b	F3	1300000	90.8
12	43	M	1b	F4	2140000	111.9
13	42	M	1b	F0	2240000	80.1
14	39	F	1b	F1	3700000	42.3
15	39	M	1b	F0	1043195	48.3
16	30	M	1b	F2	710000	42.1
17	43	M	1b	F0	204510	44.8
18	42	F	1b	F0	628100	24.8
19	64	F	1b	F3	82100	45
20	45	M	1b	F4	2720770	67
21	55	M	1b	F4	245190	95
22	46	M	1b	F4	1416919	56
23	38	M	1b	F4	1078307	53
24	56	M	1b	F4	561021	19
25	59	F	1a	F3	3200000	52
26	37	M	1b	F1	3600000	38.5
27	40	M	1b	F0	29000000	50.8

Table 2. The efficacy of ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in treatment for chronic hepatitis C 1 genotype

Treatment outcome	Number of patients successfully achieved the point	Number of patients who failed to achieve the point*
End of treatment response	92.6% (25/27)	7.4% (2/27)
SVR12	100% (27/27)	0
SVR24	100% (27/27)	0

**It is speculated that positive PCR RNA HCV represents amplification of unviable components of viral RNA rather than the presence of intact virions; it is supported by the fact that patients with positive RNA HCV at the end of the treatment achieve SVR12 afterwards.*

All patients had undergone liver fibrosis evaluation by means of non-invasive tests, i.e. elastography (Acoustic Radiation Force Impulse Elastography or FibroScan®) and FibroTest®. 37% (10/27) patients had F0-F1 fibrosis, 11.1% (3/27) had F2 fibrosis, 22.2% (6/27) had F3 fibrosis, and 29.6% (8/27) had F4 fibrosis. Among patients with cirrhosis (F4), 7 patients had cirrhosis Child-Pugh A, and 1 patients had cirrhosis Child-Pugh B (Fig. 1). Therefore, more than one-half of the patients was considered to be "difficult-to-treat" due to significant morphological alterations in the liver. All patients had 1 genotype of HCV, among them, 88.8% (24/27) had 1b subgenotype, 7.4% (2/27) had 1a subgenotype, and 1 patient (3.8%) had 1a/1b coinfection. Table 1 shows individual characteristics of the patients at the baseline.

All patients received following regimen of antiviral therapy with ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin based on HCV subgenotype and the stage of liver fibrosis:

- ombitasvir/paritaprevir/ritonavir + dasabuvir, 12 weeks – 62.9% (17/27),
- ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin, 12 weeks – 29.6% (8/27),
- ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin, 24 weeks – 7.4% (2/27).

There were several treatment modifications in the group of the patients with ombitasvir/paritaprevir/ritonavir + dasabuvir, 12 weeks. Two patients (patient 13 and patient 15) had delayed viral clearance at intermediate checkpoints during the treatment; therapy was extended for 1 week in these patients (total 13 weeks). Patient 19 had detectable, but uncountable viral load (less than 15 ME/ml) at week 8, and the treatment was prolonged in this patient for additional 4 weeks (total, 16 weeks).

Among all patients, 25 had an undetectable viral load using high-sensitive PCR at the completion of the treatment course (i.e. achieved the end of treatment response). Patient 16 had positive qualitative HCV RNA PCR, but unmeasurable by quantitative PCR (under the detection threshold).

Patient 27 had positive PCR RNA HCV at all checkpoints during 12-weeks course of ombitasvir/paritaprevir/ritonavir + dasabuvir. It was decided to extend the treatment to 24 weeks, but at week 20, the patient had stopped treatment on his own. This patient had positive quantitative, but unmeasurable (< 100 ME/ml) PCR RNA by the treatment discontinuation. At 12 week after treatment discontinuation, this patient has had negative RNA PCR (i.e. has achieved SVR12). Figure 2 shows treatment results.

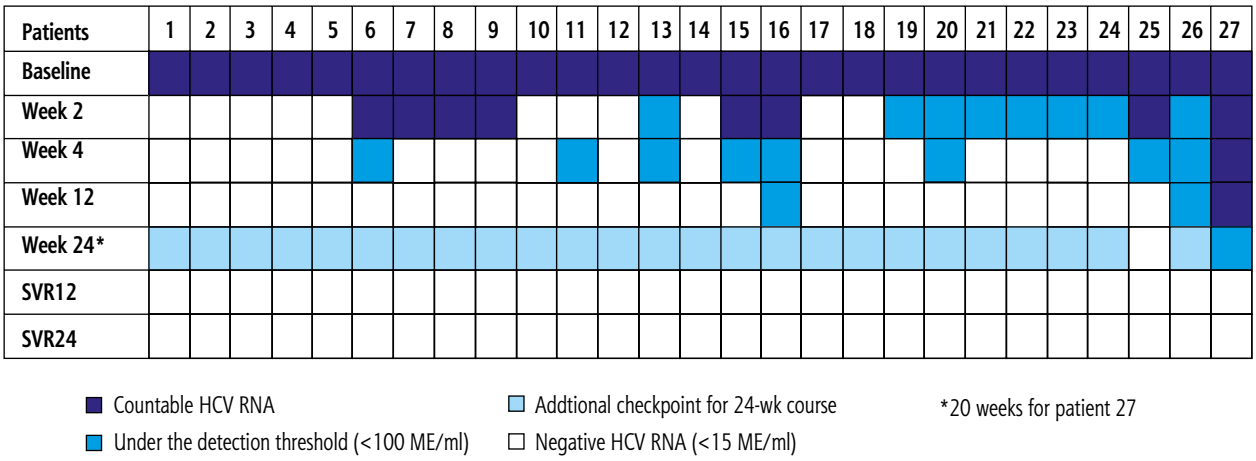

Fig. 2. Dynamics of viral load during the treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin (*n* = 27)

Discussion

Treatment was tolerated well by all patients. There were no adverse events that required treatment discontinuation.

The elevated level of ALT in some of the patients at baseline had the tendency to decline during the treatment.

Two patients had a significant elevation of ALT at week 2 of the treatment (probably, due to the presence of non-alcoholic steatohepatitis in these patients). One more patient with rheumatoid arthritis had severe ALT flare during the treatment with ombitasvir/ paritaprevir/ ritonavir + dasabuvir. However, in this case, additional use of hepatotoxic antirheumatic drugs was present. Therefore, it cannot be stated certainly, that only ombitasvir/ paritaprevir/ ritonavir + dasabuvir was the only cause of the ALT flare in this patient.

There was the declining trend in hemoglobin level during the treatment, mainly because of the use of ribavirin in the part of the patients. Nevertheless, no critical declining of hemoglobin was observed, even in patients with cirrhosis. Sustained virologic response at 12 weeks and 24 weeks after completion the treatment course (SVR12, SVR24) was observed in all 27 patients (including the patients who had detectable RNA HCV at the end of the treatment). One patient with cirrhosis Child-Pugh B (patient 3) achieved SVR24. Table 2 shows treatment results.

In this real-world study, we observed 100% efficacy (SVR12 and SVR24) of the antiviral treatment with ombitasvir/ paritaprevir/ ritonavir + dasabuvir ± ribavirin. It may be claimed that very high rates of SVR were achieved along with good safety profile, taking into account presence of the patients with cirrhosis, history of previous failure of interferon-based treatment, and comorbidities.

Conclusions

This study summarizes the first clinical experience of antiviral treatment for chronic hepatitis C with ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in the Republic of Belarus. The overall observed safety profile of ombitasvir/paritaprevir/ritonavir + dasabuvir was acceptable. Patients with additional use of ribavirin showed no serious decline of hemoglobin levels.

Even patient with cirrhosis Child-Pugh B achieved SVR24 in a result of ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin therapy without any serious adverse events or deterioration of liver function. To date, ombitasvir/paritaprevir/ritonavir + dasabuvir is the only anti-HCV option available for treatment of the patients with renal insufficiency including hemodialysis patients in the Republic of Belarus.

Disclosure

Authors report no conflict of interest.

References

1. Hepatitis C WHO Fact Sheet Updated April 2017. WHO. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/
2. Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol 2016; 14: 122-132.
3. Nakano T, Lau GMG, Lau GML, et al. An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region. Liver Int 2012; 32: 339-345.
4. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014; 61: S58-68.
5. EUROPEAN MEDICINES AGENCY Viekirax (ombitasvir, paritaprevir, and ritonavir tablets). EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003839/human_med_001838.jsp&mid=WC0b01ac058001d124.
6. 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.
7. 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.
8. 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.
9. 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 12weeks. J Hepatol 2016; 64: 301-307.
10. Welzel TM. Ombitasvir, paritaprevir, and ritonavir plus dasabuvir for 8 weeks in previously untreated patients with hepatitis C virus genotype 1b infection without cirrhosis (GARNET): a single-arm, open-label, phase 3b trial. Lancet Gastroenterol Hepatol 2017; 2: 494-500.
11. Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, et al. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C: AMBER study. Aliment Pharmacol Ther 2016; 44: 946-956.
12. Wedemeyer H, Craxí A, Zuckerman E, et al. Real-World effectiveness of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in patients with hepatitis C virus genotype 1 or 4 infection: a meta-analysis. J Viral Hepat 2017; doi:10.1111/jvh.12722.
13. Kohli A, Alshati A, Georgie F, et al. Direct-acting antivirals for the treatment of chronic hepatitis C in patients with chronic kidney disease. Therap Adv Gastroenterol 2016; 9: 887-897.