Annals of Clinical Hepatology

Research Article
Published: 18 Jun, 2019

Twelve Weeks Treatment with Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Chronic Hepatitis C Genotype 2k/1b Patients is Highly Efficient and Safe

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Abstract

Aim: Hepatitis C Virus (HCV) infection is one of the most prevalent etiologies for liver cirrhosis and hepatocellular carcinoma. HCV is highly heterogeneous, with seven confirmed major genotypes and 67 confirmed subtypes. The importance of determining correctly each genotype and its subtype lies in choosing appropriately the combination and duration of anti-viral treatment. The recombinant HCV genotype 2k/1b was first described in St. Petersburg in 2002 among intravenous drug users. Treatment of HCV 2k/1b patients with Sofosbuvir and ribavirin resulted in a low rate of Sustained Virologic Response (SVR). The high efficacy of the 3D regimen (Ombitasvir/paritaprevir/ritonavir and dasabuvir) has been proven for genotype1b population; however, it has not been evaluated for patients with 2k/1b HCV genotype.

The aim of this study was to prospectively evaluate the efficacy and safety of twelve weeks treatment with Ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) for patients infected with HCV 2k/1b.

Methods: This is an open-label, single arm study. Seven patients received Ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily plus dasabuvir 250 mg twice daily for twelve weeks.

Results: Six patients achieved SVR without significant adverse events. One patient discontinued the treatment at week four due to headache and vomiting.

Conclusion: This study demonstrates that twelve weeks' treatment with Ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) of adult patients with HCV 2k/1b is highly efficient and safe.

Keywords: Direct acting antiviral treatment; Genotype 2k/1b; Hepatitis C; Sustained virologic response

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Received Date: *18 May 2019*
Accepted Date: *14 Jun 2019*
Published Date: *18 Jun 2019*

Citation:
Hazzan R, Reish I, Barak M, Daniel R, Strauss M, Zuckerman E. Twelve Weeks Treatment with Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Chronic Hepatitis C Genotype 2k/1b Patients is Highly Efficient and Safe. Ann Clin Hepatol. 2019; 3(1): 1010.

Introduction

Hepatitis C Virus (HCV) infection is one of the most prevalent etiologies of liver cirrhosis, hepatocellular carcinoma, liver failure and liver-related mortality [1]. HCV is also a prominent, global indication for liver transplantation.

HCV is highly heterogeneous, with seven confirmed major genotypes and 67 confirmed subtypes [2,3] and with up to 30% divergence in the nucleotide sequences [4]. Each genotype displays a different geographic distribution [2]. Since different HCV genotypes respond differently to the available antiviral therapies, accurate identification of the HCV genotype is required for choosing the type and duration of treatment. The recombinant HCV genotype 2k/1b was first described in St. Petersburg in 2002 in intravenous drug users [5].

Since most routine HCV genotype assays are based on a single genome region sequencing, the identification of the recombinant virus can be compromised [6,7], commercial genotyping assays that can amplify both the 5' and the 3' regions of the HCV genome or approaches using special sequencing strategy are required in order to ensure exact genotype identification [8]. However, when clinical laboratories use the second-generation VERSANT HCV Genotype 2.0 Assay for routine HCV genotyping, they misclassify the 2k/1b strains as HCV genotype 2a/2c [9,10]. Based on

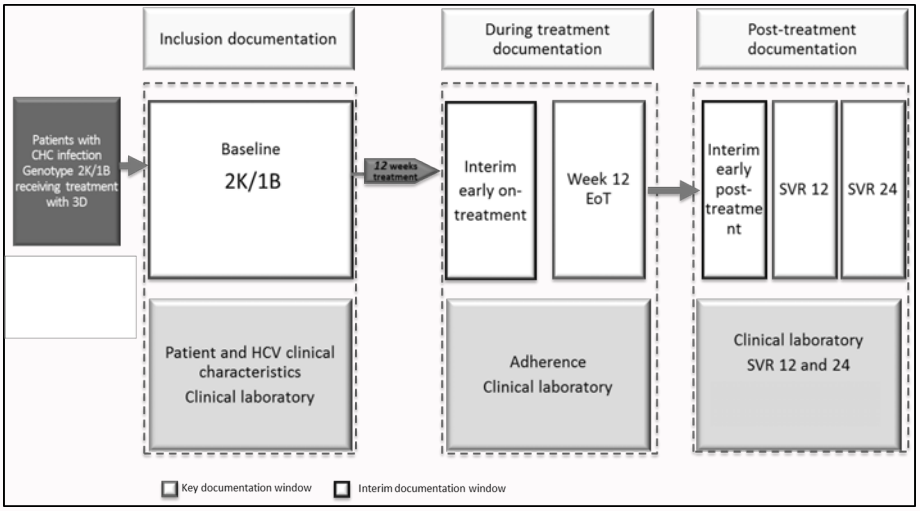

Figure 1: Study flowchart.
EOT: End of Treatment
SVR: Sustained Virologic Response

these findings, the number of patients infected with HCV 2k/1b may be underestimated.

Studies to identify the prevalence of recombinant HCV genotypes are sparse, but in Georgia it was reported that 76% of the patients with defined genotype 2 harbors the 2k/1b chimeric variant [9]. Due to migration, a relatively high prevalence (17% to 25%) of patients infected with HCV genotype 2k/1b recombinant was observed in Germany and Israel [7]. Recently, an extensive study aimed to describe the geographical distribution of genotype 2k/1b revealed the geographic origin of 50 patients infected with 2k/1b. The vast majority of these patients (88%; n=44/50) originate from the former Soviet-Union. Eighteen patients were of Russian origin, while 11 patients originate from Georgia, four patients were Ukrainian, three were Azerbaijani, three were Chechens, two were Armenian, two were Kazakhstani, and one was from Tadzhikistan. The remaining six patients were from Western Europe (Germany n=2; Greece n=1, Romania n=1 and Israel=2) [7].

Treatment of viral chimera with sofosbuvir and ribavirin led to virologic relapse in 25/27 patients (93%) in Germany [8]. Conversely, ten other patients harboring 2k/1b genotype were treated with genotype 1-targeted Direct Acting Antiviral (DAA) regimens. Two of these patients responded to daclatasvir/sofosbuvir, two to paritaprevir/Ombitasvir/dasabuvir (3D) therapy, and four out of five patients achieved SVR with Ledipasvir/sofosbuvir ± ribavirin therapy and one was lost to follow-up [8]. Four out of eleven Israeli patients with the chimera virus were treated with Pegylated interferon (PegIFN-alfa) and ribavirin for up to 24 weeks: Two patients achieved SVR and two failed to respond. Of the 25 patients who relapsed on sofosbuvir and ribavirin from Germany, 14 received salvage therapy with an NS5A-inhibitor plus sofosbuvir or 3D, with or without ribavirin (Ledipasvir/sofosbuvir n=2; Ledipasvir/sofosbuvir/ribavirin n=3; daclatasvir/sofosbuvir/ribavirin n=1; paritaprevir/Ombitasvir/dasabuvir n=5; velpatasvir/sofosbuvir n=3), with 13 of them achieving SVR12, while in one patient treatment was still ongoing [8]. The 3D regimen includes 3 DAAs with distinct, non-overlapping mechanism of action. Ombitasvir is a potent NS5A inhibitor that is co-formulated with paritaprevir, a potent NS3 (nonstructural protein 3)/4A protease inhibitor co-dosed with ritonavir to boost drug exposure; Dasabuvir is a non-nucleoside NS5B Ribonucleic Acid (RNA) polymerase inhibitor [11,12]. The high efficacy of the 3D regimen has been proven in registration clinical trials for 1b population [13]. The aim of this study was to prospectively assess the efficacy and safety of the 3D regimen as a treatment for the recombinant HCV genotype 2k/1b.

Methods

Study design and patients

The study was designed by the investigators and the sponsor (AbbVie Biopharmaceuticals LTD), and was conducted according to Good Clinical Practice guidelines, the declaration of Helsinki, and all applicable regulations, with independent ethics committee and institutional review board approval. All authors had access to the study data and had reviewed and approved the final manuscript.

This is an open-label, single arm study. The study included 1 group of HCV genotype 2k/1b- infected subjects who were untreated or failed to respond to previous therapy with peg IFN-alfa and Ribavirin (RBV). Patients were treated with the 3D regimen according to the label recommendation for genotype 1b for 12 weeks. All subjects received Ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily). Subjects were assessed for virologic response, clinical outcome and adverse events. Subjects were followed for up to 24 weeks after the end of treatment (Figure 1). All patients provided written informed consent. Eligible patients were ≥ 18 years of age, with HCV RNA>15 IU/mL and a laboratory result at screening indicating infection with HCV genotype 2k/1b subtype. Patients were excluded if they had evidence of HCV genotype or subtype other than genotype 2k/1b, or if they tested positive for hepatitis B surface antigen or anti-HIV antibody at screening.

Previous study drug administration was also a reason for exclusion, as was a history of organ transplant, hepatocellular carcinoma, severe renal impairment, clinically significant disorders or co-morbidities other than HCV infection.

HCV genotyping

HCV genotyping was performed by real-time based assays (Abbott Real Time HCV Genotype II, Abbott Molecular, Illinois, USA) according to manufacturer instructions. Briefly, RNA was

Table 1: Summary of patients' demographic parameters, genotype, fibrosis stage and previous treatment.

Patient number	Gender	Age	COB	genotype	Fibrosis Stage (fibroscan)	Cut-off value (KPa)	Previous treatment	Baseline HCV RNA level (IU/ml)	SVR12 HCV RNA level (IU/ml)
1	Male	47	Russia	2K/1B	F4	25	untreated	1.7×10^6	ND
2	Male	61	Israel	2K/1B	F3-F4	8.8	untreated	1.5×10^6	ND
3	Female	22	Ukraine	2K/1B	F0-F1	6.5	untreated	3.2×10^6	ND
4	Male	52	Israel	2K/1B	F0-F1	4.6	untreated	2.4×10^6	ND
5	Male	41	Russia	2K/1B	F0-F1	6.6	peg IFN/RBV	1×10^6	ND
6	Female	40	Georgia	2K/1B	F0-F1	3.9	untreated	1.7×10^6	ND
7	Male	46	Azerbaijan	2K/1B	F0-F1	7	peg IFN/RBV	2.9×10^6	Early discontinuation

extracted from serum samples using the Abbott m2000sp instrument followed by multiplexed Reverse Transcription Polymerase Chain Reaction (RT-PCR) using the kit amplification reagent packs and the Abbott m2000rt instrument. The Abbott Real Time HCV Genotype II kit (Abbott-RT-HCV) is a commonly used FDA-approved platform for HCV genotyping that relies on consensus primer amplification of the HCV 5'-Untranslated Region (5'-UTR) and specific primers for HCV genotype 1a and 1b NS5b, located at the 3'-Untranslated Region (3'-UTR) sequences. Amplicons are detected using genotype specific fluorescent labeled probes against 5'-UTR of genotypes 1 to 6 and NS5B of subtypes 1a and 1b. By using 2 pairs of primers from the 5-UTR and the NS5b regions this assay can detect also recombinant HCV genotype 2/1 strains.

HCV RNA viral load detection

HCV RNA viral load was determined using the Abbott Real Time HCV assay (Abbott Molecular, Inc. (Des Plaines, IL) according to the manufacturer's specifications. Abbott Real Time HCV assay uses RT-PCR technology combined with homogeneous real time fluorescent detection for the quantitation of HCV RNA. The assay is standardized against the Second WHO International Standard for Hepatitis C Virus RNA (NIBSCCode 96/798) and results are reported in International Units/mL (IU/mL). HCV RNA <Lower Limit of Quantification (LLOQ) is 12 IU/ml.

Assessments

The SVR at 12 weeks post-treatment was used to assess treatment efficacy.

SVR12, defined as a sustained virologic response when found less than the LLOQ.

Serum samples were collected and examined for HCV RNA viral load at baseline, week four, end of treatment, 12 weeks post-treatment and 24 weeks post treatment.

Adverse event monitoring, vital signs measurements, physical examination, and laboratory tests were performed throughout the study to assess safety and tolerability.

Results

HCV genotype 2k/1b- infected subjects who were untreated (5/7) or failed to respond to peg IFN/RBV (2/7) were treated with Ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily) (3DAA) for 12 weeks. HCV RNA level was determined at baseline and 12 weeks post treatment. Six patients completed 3DAA treatment without any adverse events. HCV RNA was not detected at 12 weeks after the end of treatment (SVR12) (Table 1). One patient discontinued treatment early, at week 4, due to headache and vomiting.

Discussion

Recombinant HCV genotype 2/1 strains represent a challenge for Direct Antiviral therapy (DAA). Over the past years, different Direct Acting Antiviral drugs (DAAs) targeting the HCV non-structural proteins NS3, NS5A, or NS5B became available, leading to notable improvement in sustained virologic response rate [14].

One of the main requirements when choosing the optimal treatment for each patient is the precise determination of the HCV genotype and its subtype. The accurate determination of both allows the optimal combination treatment and treatment duration. Patients infected with un-diagnosed chimeric viruses may be treated inappropriately [15].

Since its first description in 2002 [5], the inter-genotypic recombinant HCV strain 2k/1b has been detected rarely, but consistently, in HCV infected patients [9,15]. So far, 50 2k/1b HCV patients were detected in eleven different countries [8]. Eighty nine percent of these patients originate from countries of the former Soviet Union. Treatment of viral chimera 2k/1b with the DAA's sofosbuvir/ribavirin or daclatasvir/sofosbuvir led to relatively low SVR rate [8]. However, treatment with other DAAs such as Ledipasvir/sofosbuvir; Ledipasvir/sofosbuvir/ribavirin; daclatasvir/sofosbuvir/ribavirin; paritaprevir/Ombitasvir/dasabuvir; velpatasvir/sofosbuvir has demonstrated high SVR rate [8]. The aim of this study was to evaluate for the first time the efficacy and safety of the 3D regimen for the treatment of the 2k/1b chimera virus. Seven new patients infected with 2k/1b HCV were identified. As expected [8], most of patients originated from the Soviet Union area, two patients originated from Russia, one from Ukraine, one from Georgia, and one from Azerbaijan. Two patients were born in Israel. Five patients were untreated while two other were not responders to peg IFN/RBV treatment. All patients were treated with 3DAA treatment for 12 weeks. All six patients who completed 3DAA treatment without any adverse events showed high SVR rate. One patient discontinued treatment after four weeks due to headache and vomiting. In conclusion, the 3D regimen was found to be highly efficient and safe for untreated patients as well as for patients who failed treatment with peg IFN/RBV.

Acknowledgment

This study was supported by AbbVie Biopharmaceuticals LTD.

Dr. Hazzan, Prof. Zuckerman and Dr. Inbal Lasry Reish wrote the manuscript and edited the text of the manuscript. Dr. Mira Barak edited the text of the manuscript. Rasha Daniel and Dr. Merav Strauss collected the laboratory data and performed the laboratory testing and molecular analysis.

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