Short Communication

iMedPub Journals
http://www.imedpub.com

Archives of Clinical Microbiology
ISSN 1989-8436

2021
Vol. 12 No. S4:167

Effectiveness of Retreatment with Ombitasvir/Paritaprevir/ Ritonavir, Dasabuvir+Sofosbuvir+Ribavirin in Patients with Chronic Hepatitis C, Subtype 1b and Cirrhosis, Who Failed Previous with First- and Second-generation NS5A Inhibitors

Sergii V. Fedorchenko*, Tatiana Martynovych, Zhanna Klimenko and Iryna Soliank

Department of Viral Hepatitis and AIDS, The L.V. Gromashevskyi Institute of Epidemiology and Infectious Disease, Amosova, Kiev, Ukraine

***Corresponding author:** Fedorchenko SV

fedorchenkosv@i.ua

Department of Viral Hepatitis and AIDS, The L.V. Gromashevskyi Institute of Epidemiology and Infectious Disease, Amosova, Kiev, Ukraine

Citation: Fedorchenko SV, Martynovych T, Klimenko Z, Soliank I (2021) Effectiveness of Retreatment with Ombitasvir/Paritaprevir/ Ritonavir, Dasabuvir+Sofosbuvir+Ribavirin in Patients with Chronic Hepatitis C, Subtype 1b and Cirrhosis, Who Failed Previous with First- and Second-generation NS5A Inhibitors. Arch Clin Microbiol Vol.12 S4: 167.

Abstract

The use of Direct-Acting Antiviral agents (DAAs) in patients with chronic HCV GenoType (GT) 1 infection results in Sustained Virologic Response (SVR) rates of 95%-97%, but 3%-5% of patients experience virologic failure. We observed 41 patients infected with HCV subtype 1b who failed previous treatment with DAAs, including 37 subjects (90.2%) with liver cirrhosis. In total, 30(73.2%) subjects previously received NS5A inhibitors of the first generation (ledipasvir, daclatasvir, or ombitasvir) and 11 subjects (26.8%) received NS5A inhibitors of the second generation (velpatasvir). All patients received retreatment with a combination of ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) with Sofosbuvir (SOF) and Ribavirin (RBV). We compared SVR12 rates depending on fibrosis stage, presence of just single or double NS5A mutation (L31M/V/I and/or Y93H), and the generation of previously used NS5A inhibitors. Observed SVR12 rates were as follows: 97.6% (40/41 patients) overall; 100% in patients without cirrhosis (n=4) versus 97.3% in those with cirrhosis (n=37); 100% with single L31M/V/I or Y93H mutation (n=22) versus 94.4% with double mutations (n=18); 100% in patients who failed previous treatment with first-generation (n=30) versus 90.9% in those who failed previous treatment with second-generation NS5A inhibitors (n=11).

Keywords: Hepatitis C virus; Antiviral agents; Anti-hepatitis C virus DAA (directly acting antivirals); Mutation; Resistance

Received: July 23, 2021; **Accepted:** August 06, 2021; **Published:** August 13, 2021

Description

Genotype 1 is the most prevalent HCV genotype worldwide, with HCV subtype 1a prevailing in both Americas, Australia and several Western European countries (England, Denmark, Portugal, and Sweden) and HCV 1b subtype- in Central and East European countries [1,2]. Among Ukrainian patients with chronic hepatitis C 55-60% are infected with HCV 1b subtype, and 16% of those have cirrhosis [3].

About 5% of patients treated with first-generation DAAs develop virological breakthrough or relapse [4-6]. In patients who have received NS3 protease inhibitors, NS5A and/or NS5B polymerase inhibitors and have not achieved SVR, nucleotide substitutions in the nonstructural HCV RNA region, defined as Resistance-Associated Substitutions (RASs), are found in 90% of cases. RASs evolved in the NS5A region persist during years and are known to be the main cause of HCV resistance to DAAs, unlike NS3 and NS5B RASs that are not stable and have less clinical significance.

The current study aimed at evaluating the effectiveness of antiviral therapy using ombitasvir 25 mg/ paritaprevir 150 mg ritonavir 100 mg QD and dasabuvir 250 mg BID (3D)+sofosbuvir 400 mg QD (SOF)+ribavirin 1000-1200 mg QD divided in 2 doses (RBV) in patients with HCV-infection subtype 1b, cirrhosis, who had failed treatment with first-and/or second-generation NS5A inhibitors.

A total of 41 patients were included into the study. All subjects received retreatment with 3D+SOF+RBV, completed the assigned course and were evaluated 12 weeks after its completion (SVR12). There were 28 men (68.3%) and 13 women (31,7%), median age was 53, 9 ± 2,3 years. Thirty-seven patients (90.2%) had cirrhosis.

Thirty of 41 patients (73.2%) had only 1 line of treatment with the first-generation DAAs (NS5A and NS5B inhibitors). Eight of 41 patients (19.5%) experienced 3 lines of treatment: (PEG)+RBV; the first-generation DAAs ± RBV; the 3rd line treatment included second-generation DAAs sofosbuvir/velpatasvir. Three of 41 patients (7.3%) failed after the 1st line treatment with SOF/VEL.

Of 41 patients who started therapy, 40 individuals (97,6%) achieved both Rapid Virologic Response (RVR) on week 4 and SVR12 .

The most common cause of failures of DAA treatment are RASs in the NS5A region, and L31M and Y93H are the most significant of them. These very mutations are most often registered in patients with HCV subtype 1b in case of failure of the most commonly used first -generation DAAs treatment regimens: SOF/LED, SOF/DAC, 3D [7]. Simultaneous presence of double mutation (L31M and Y93H) in the NS5A region is responsible for the reduction of second generation DAA effectiveness (SOF/VEL) [8]. In HCV subtype 1b infection L31M substitution in NS5A leads to potential development of resistance to ledipasvir, ombitasvir, velpatasvir but not to daclatasvir. Y93H mutation is strongly associated with resistance to daclatasvir, ledipasvir, ombitasvir and possibly to velpatasvir [9].

In patients infected with HCV GT1a, a single Y93H/N substitution in NS5A increases ombitasvir EC50 10 000 folds, and even reinforcement of 3D regimen with ribavirin and prolongation of treatment duration may not be enough to overcome clinical resistance. That is why we studied the proposed regimen only for re-treatment of patients with GT1b, and the results cannot be extrapolated to patients with GT1a.

Patients with cirrhosis who failed treatment with NS5A inhibitors are the most difficult target for retreatment especially if pangenotypic regimens of the second-generation DAAs (glecaprevir/pibrentasvir,sofosbuvir/ velpatasvir/voxilaprevir) are not registered in the country, or they are not reimbursed by the state healthcare system.

The presented study dedicated to the effectiveness of retreatment included the most difficult patients with HCV-infection subtype 1b: Cirrhosis was diagnosed in 37 of 41 individuals-90,2%. Eight of them had three unsuccessful attempts of treating hepatitis C using PEG/RBV and DAA. For 8 of the patients the third attempt to treat hepatitis C using the second-generation DAA (SOF/VEL) with, or without RBV for 12 weeks finished with relapse. Genetic sequencing at the start of 3D+SOF+RBV therapy revealed the presence of two most significant mutations in the NS5A region L31M/V/I or Y93H of 40 patients (97,5%), while C316N mutation was detected with the highest frequency in the NS5B region of 23 patients (74,2%) and L159F in-14 patients (45,2%).

In our study 30 out of 41 individuals previously failed treatment with the first- generation DAA. In one of them clinically relevant NS5A RASs were not detected. Single mutations L31M (L31I) or Y93H in NS5A region were detected in 22(75,9%) individuals. Simultaneous presence of both NS5A–mutations was detected only in 7 persons (24,1%). At the same time, in all eleven individuals who had recurrence after therapy with second generation DAA (SOF/VEL), L31M/V and Y93H were detected simultaneously (100%).

The present study has demonstrated high effectiveness of 3D+SOF+RBV in patients with HCV subtype 1b infection, cirrhosis, who failed DAA treatment with the first-or second- generation NS5A inhibitors. Grade of fibrosis, the presence of a single NS5A RASs (L31M/V/I or Y93H), or double NS5A RASs (L31M/V and Y93H), as well as the generation of previously used NS5A inhibitors did not impact SVR12 achievement.

Conclusion

Retreatment with 3D+SOF+RBV was highly effective and safe in patients with chronic HCV GT1b infection, including those with liver cirrhosis, who failed previous treatment with DAA containing NS5A inhibitors. Fibrosis stage and single or simultaneous presence of NS5A RASs L31M/V/I and Y93H at the baseline, as well as the generation of previously used NS5A inhibitors, did not impact SVR12 rates.

References

1. Aghemo A, Dore GJ, Hatrakis A, Wedemeyer H, Razavi H (2015) Estimating HCV disease burden-volume (editorial). J Viral Hepat 22: 1-3.
2. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, et al. (2017) Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modeling study. The Lancet 2: 161-176.
3. Fedorchenko SV. Hronicheskay HCV-infekcia. [Chronic HCV-infection.].Kiev, Monograph VSI “Medicina”, 2010, 270p.
4. Aghemo A, Bruno R, Colombo M, Medagli M, Puoti M, et al. (2016) Treatment of patient with chronic hepatitis C infection in Lombardia: A report by the Lombargia Hepatitis Network. Eur Rev Med Pharmacol Sci 20: 17-19.
5. Calleja JL, Crespo J, Antoran RB, Rincon D, Perello C, et al. (2017) Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. J of Hepatol 66: 1136-1148.
6. Buggisch P, Sarrazin C, Mauss S, Hinrichsen H, Simon KG, et al. (2015) Sofosbuvir-based treatment under real life condition in Germany. J of Hepatol 62: S622.
7. Dietz J, Susser S, Vermehren J, Peiffer KH, Grammatikos G, et al. (2018) Patterns of resistance-associated substitution in patients with chronic HCV infection following treatment with direct-action antivirals. Gastroenterol 154: 976-988.

8. Hezode C, Rean N, Svarovskaia ES, Doehle BP, Shanmugam R, et al. (2018) Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase 3 studies. J of Hepatology 68: 895-903.

9. Sorbo MC, Cento V, Maio DVC, Howe AY, Garcia F, et al. (2018) Hepatitis C virus drug resistance associated substitutions and their clinical relevance: Update 2018. Drug Res Upd 37: 17-39.