Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir ± Ribavirin Combinations in Patients with Genotype 1 Hepatitis C and Inherited Bleeding Disorders

Abdullah Sonsuz[1], Selma Bozcan[1], İbrahim Hatemi[1], Sebati Özdemir[1], Billur Canbakan[1], Süleyman Yıldırım[1], İlkay Gültürk[1], Cem Ar[2]

[1]Department of Gastroenterology, İstanbul University-Cerrahpaşa Cerrahpaşa School of Medicine, İstanbul, Turkey
[2]Department of Hematology, İstanbul University-Cerrahpaşa Cerrahpaşa School of Medicine, İstanbul, Turkey

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ABSTRACT

Background: *Hepatitis C is one of the leading causes of death in patients with inherited bleeding disorders. Currently, direct-acting antiviral drugs used for the treatment of hepatitis C have become an effective and a reliable option for people with inherited bleeding disorders. The aim of this study is to report the efficacy and safety of ombitasvir + paritaprevir/ritonavir and dasabuvir combination in the treatment of hepatitis C in patients with inherited bleeding disorders.*

Methods: *In this retrospective study, we evaluated the efficacy and safety of the combination of ombitasvir + paritaprevir/ritonavir and dasabuvir in 10 adult patients with hemophilia A, 4 patients with hemophilia B, and 1 patient with von Willebrand disease who were infected with hepatitis C genotype 1.*

Results: *Five patients had genotype 1a and 10 patients had genotype 1b chronic hepatitis C. One patient had Child A cirrhosis, 14 patients had chronic hepatitis C without cirrhosis. Hepatitis C virus ribonucleic acid was negative in all patients at week 4 and at the end of the treatment. Sustained virologic response was obtained in all patients. Serious side effects were detected in 3 patients, which were intramuscular bleeding, erosive gastritis-related gastrointestinal bleeding, and pneumonia.*

Conclusion: *Ombitasvir + paritaprevir combined with ritonavir and dasabuvir ± ribavirin is an effective treatment for patients infected with genotype 1 hepatitis C who have coagulation disorders. Tolerance and side effects are similar to other treatment options.*

Keywords: *Chronic viral hepatitis, direct-acting antivirals, hemophilia, inherited coagulation disorders, von Willebrand disease*

INTRODUCTION

Regular or on-demand replacement of the missing coagulation factor with fresh frozen plasma or later with plasma-derived coagulation factor concentrates has been the mainstay of treatment in patients with severe hereditary bleeding disorders (HBD) since the late 1950s.[1] However, for years, infections related to the use of blood and blood products have been a major and frequent treatment complication.

In 1972, Kasper and Kipnis[2,3] published an article about the risks of factor concentrates pointing out that the prevalence of viral hepatitis had increased in hemophilia A and hemophilia B patients since the introduction of plasma-derived factors VIII and IX in 1967 and 1969, respectively.

In 1989 after the start of using hepatitis C antibody tests, it was reported that the prevalence of hepatitis C infection in people with hemophilia (PwH) was 70%.[4] In another study published 1 year later in United Kingdom, a similar rate (76.3%) was reported.[5]

Interferon α was used to treat hepatitis C patients with limited success in sustained virologic response rate and significant side effects in the earlier 1990s. Today, we use direct-acting antiviral drugs combinations to treat chronic hepatitis C patients. With the introduction of these drugs, the treatment response and tolerability have significantly improved.

Current The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) (www.HCVGuidelines.org) guidelines recommend following combinations for the treatment of genotype 1 hepatitis C infections: (i) elbasvir/grazoprevir; (ii) glecaprevir/pibrentasvir; (iii) ledipasvir/sofosbuvir; and (iv) sofosbuvir/velpatasvir.[6,7] EASL guidelines recommend the combination of paritaprevir/ritonavir/ombitasvir with dasabuvir (PrOD) as a treatment option

Corresponding author: ***Selma Bozcan****, e-mail:* ***selmabozcan@yahoo.com***
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only for hepatitis C genotype 1b, but in the past guidelines of EASL and AASLD, this combination was recommended in all genotype 1 patients.[6,8,9]

These guidelines do not include any special recommendations for hemophilia patients or those with other bleeding disorders. The combination of ledipasvir/sofosbuvir, one of the recommended combinations for genotype 1 hepatitis C infection, has been used in patients with a bleeding disorder with success and has shown no difference from other patients in terms of treatment efficacy, side effects, and drug tolerance.[10,11] However, no data is available on the use of the combination of paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) ± ribavirin in hepatitis C patients with inherited bleeding disorder. Furthermore, there is some evidence from former studies done with protease inhibitors used to treat HIV-positive PwH denoting that protease inhibitors might increase bleeding tendency.[12,13] It needs to be clarified however whether the protease inhibitors specifically used in the treatment of hepatitis C have such adverse effects.

The aim of this study was to evaluate the efficacy and tolerability of ombitasvir, paritaprevir, and ritonavir combination used for the treatment of genotype 1 hepatitis C infection in people with bleeding disorders.

MATERIALS AND METHODS

A total of 15 people with HBD having genotype 1 hepatitis C infection were treated with ombitasvir, paritaprevir, ritonavir, dasabuvir ± ribavirin between August 2016 and November 2018 were included in this study. Patients were followed at the Hematology department for their inherited bleeding disorders and were referred to the Hepatology outpatient clinic due to chronic HCV infection.

Pretreatment information on clinical examination findings, liver ultrasonography, biochemical tests were obtained from patient files and electronic records and AST to Platelet Ratio Index (APRI) score (Aspartate aminotransferase (AST) to platelet ratio index) was calculated for each patient. Anti-HCV, HCV-RNA, HCV genotype and subtype determination, HBsAg, Anti-HBs, Anti-HBc, and Anti-HIV results were used for virologic assessment. Liver biopsy was avoided in all of the patients due to their coagulation defect.

Main Points

- *Combination of PrOD ± ribavirin appears to be an effective treatment option in genotype 1 HCV infected patients with inherited bleeding disorders.*
- *PrOD ± ribavirin combination seems to be safe and well tolerated in patients with inherited bleeding disorders.*
- *Although there are former studies done in protease inhibitor taking HIV-positive PwH, suggesting that protease inhibitors might increase bleeding tendency, no serious bleeding tendency was observed in this study.*

In Turkey, when this study was conducted PrOD combination was the only reimbursed option for genotype 1 patients who were treatment naïve or who were in stage Child A compensated cirrhosis even they were treatment naïve or previously treated. For patients with genotype 1a, ribavirin was also added at a dose of 1000 or 1200 mg daily according to the weight. Treatment duration was set to 12 weeks for non-cirrhotic patients and 24 weeks for genotype 1a cirrhotic patients.

HCV-RNA levels were measured at the fourth week, at the end of the treatment period and at 12 weeks after the completion of treatment. During antiviral treatment, patients were regularly assessed every 2 weeks for possible adverse events and any unexpected clinical as well as biochemical findings. Because of the data about increased bleeding tendency in HIV patients using protease inhibitor,[12,13] patients were strictly evaluated for signs and symptoms of bleeding during their visits.

Patient characteristics are given in Table 1. The age of the patients ranged between 32 and 63 years (mean 44.6 ± 8.7 years). Ten of 15 patients had hemophilia A, 4 had hemophilia B, and 1 had von Willebrand disease. All hemophilia patients had factor activity levels ≤ 1%. The patient with von Willebrand disease had type III disease. All patients had been receiving tertiary prophylactic factor replacement therapy.

One of the patients had been previously treated with interferon + ribavirin but had relapsed later; the rest were treatment-naïve patients. Five patients were identified as genotype 1a and 10 as genotype 1b. HCV-RNA levels ranged from 10 428 IU/mL to 17 700 000 IU/mL (mean ± SD 5 572 962 ± 5 826 075 IU/mL). Based on clinical and laboratory findings, 1 patient was cirrhotic while 14 patients were non-cirrhotic.

Written informed consent was obtained from all patients. Ethical approval for this study was obtained from the institutional ethical committee.

Table 1. Patient Characteristics

No	Age	Bleeding Disorders	Factor level (%)	APRI score	HCV-RNA (IU/mL)	Cirrhosis	Hepatitis B Serology			Anti-HIV	Naïve/ Treatment experienced	Genotype	Treatment Regime		Treatment Duration (week)
							HBsAg (+)	Anti-HBc (+)	Anti-HBs (+)				OBV/ PTV/R+DSV	Ribavirin	
1	58	HA	0.4	0.14	388 215	-	-	+	-	-	-	1a	+	+	12
2	53	HA	1	0.15	1 603 184	-	-	-	+	-	-	1b	+		12
3	44	HA	0.4	0.35	17 700 000	-	-	-	-	-	-	1b	+		12
4	30	HA	0.2	0.31	1 050 924	-	-	-	+	-	-	1b	+		12
5	63	HA	0.3	0.37	10 744 072	-	-	+	+	-	-	1b	+		12
6	32	HA	0.3	0.08	2 820 000	-	-	+	+	-	-	1b	+		12
7	43	HA	0.7	7.46	10 428	+	-	-	+	-	+	1a	+	+	24
8	43	HB	1.7	0.97	17 700 000	-	-	-	-	-	-	1a	+	+	12
9	40	HB	1.2	0.36	183 466	-	-	-	+	-	-	1a	+	+	12
10	40	HA	0.4	0.43	6 711 515	-	-	-	-	-	-	1b	+		12
11	44	VWD	1	0.14	1 250 218	-	-	+	-	-	-	1b	+		12
12	42	HA	0.2	0.553	5 837 598	-	-	+	-	-	-	1b	+		12
13	52	HA	1	0.28	7 283 841	-	-	-	-	-	-	1a	+	+	12
14	48	HB	28	0.169	4 738 000	-	-	-	-	-	-	1b	+		12
15	38	HB	NA	0.322	9 876 101	-	-	-	+	-	-	1b	+		12

HA, hemophilia A; HB, hemophilia B; VWD, von Willebrand disease; OBV/PTV/R+DSV, ombitasvir/paritaprevir/ritonavir + dasabuvir.

RESULTS

Treatment Compliance

In 11 patients (73%), the treatment was completed at planned duration and with planned drug doses. One patient treated with a combination containing ribavirin required a dose adjustment because of a decrease in the hemoglobin level. One patient reduced the ribavirin dose to 600 mg by his own decision at the ninth week of treatment due to exacerbation of pre-existing arthritis; he could not be convinced that this was not necessary. In 1 patient, we stopped all antiviral drugs for 4 days and ribavirin for 12 days due to an episode of acute upper gastrointestinal bleeding which caused anemia. Another patient stopped the treatment 4 weeks earlier than planned, which was 12 weeks, and informed us only after the completion of the treatment period (Table 2).

Virologic and Biochemical Response

Evaluation at the fourth week of treatment revealed that all patients were HCV-RNA (–). Aminotransferases level of 6 patients (40%) had been found to be high at the beginning of the treatment; all went down to normal level at the fourth week except 1 patient who had a mild elevation (42 IU/L). Treatment duration was 12 weeks in 14 non-cirrhotic patients and 24 weeks in 1 patient who had compensated cirrhosis, HCV-RNA was negative at the end of the treatment period in all patients. Aminotransferases levels were normal in all patients at the end of treatment. HCV-RNA results were negative in all patients 12 weeks after the end of the treatment, indicating a sustained virologic response. Virologic and biochemical responses of patients are shown in Table 3.

Side Effects

Patients were evaluated for side effects during the outpatient clinic visits every 2 weeks by using standard treatment assessment forms, and all had a detailed physical examination. The most common complaint was fatigue and was reported by 33% of patients. This was followed by headache (20%), itching (13%), insomnia (13%), and anorexia (13%). The most frequent side effects

Table 2. Treatment Compliance

	n	%
Patients completing the total schedule at the planned dose	11	73
Early termination of the treatment	1	7
Temporary interruption of the treatment	1	7
Dose reduction (ribavirin)	2	14

Table 3. Biochemical and Virologic Response

	Before Treatment	4 Weeks	12 (24) Weeks	+12 Weeks
HCV-RNA (+)	15 (100%)	0	0	0
ALT/AST elevations	7 (46.6%)	1 (6.6%)	0	0

HCV-RNA, hepatitis C virus ribonucleic acid.

associated with antiviral treatment are given in Table 4. Bleeding episodes were observed in 2 patients during the treatment. The first one was a 63-year-old patient with hemophilia A who developed intramuscular bleeding. He was treated for genotype 1b hepatitis C in the non-cirrhotic stage, spontaneous bleeding developed into the gastrocnemius muscle at the end of the second week of the antiviral treatment and was kept under control by local measures and additional factor VIII replacement. Antiviral treatment was not stopped for this complication but due to temporary anemia after bleeding, ribavirin dose reduction was made. The other patient was a 32-year-old male and had genotype 1a HCV infection with compensated liver cirrhosis (Child A). He experienced a upper GI bleeding at the seventh week of antiviral treatment. Endoscopic examination revealed erosive gastritis. The patient had to be hospitalized for 1 week to be observed under intensified factor VIII replacement. He received 4 units of packed red blood cells in addition to standard bleeding measures. Antiviral treatment consisting of PrOD was stopped for 4 days during this bleeding episode; the treatment was restarted on the fifth day when the condition of the patient was stabilized. However, an interruption of 12 days of ribavirin treatment was necessary due to low hemoglobin levels.

DISCUSSION

Many patients with hemophilia and other inherited bleeding disorders who have been infected with hepatitis C in the past before the implementation of effective control and prevention measures still carry the virus. These patients continue to live with risks associated with chronic liver disease. In a large clinical series of 6018 patients published from the United Kingdom, liver disease (including hepatitis and liver cancer) constitutes the third leading cause of death in people with severe hemophilia and the fourth leading cause of death in all PwH.[14] The life expectancy of PwH has been reported to have increased from 64.0 to 71.2 years in the 2000-2007 period compared to the 1990-1999 period when 45% of deaths resulted from HIV infection, and an additional 13% were reported to be caused by hepatitis C, confirming that transfusion-transmitted diseases are still a major clinical problem, even if the rate of occurrence of new cases has declined.[15] Several recent studies have highlighted the importance of liver disease among causes of death in hemophilia patients with hepatitis C, indicating the high risk for developing hepatocellular cancer.[16-19]

For the past 25 years, treatment of PwH infected with hepatitis C has also undergone significant changes in line with developments in chronic hepatitis C treatment. The first studies on the treatment of hepatitis C in PwH began in the 1990s. The fact that 3 of the pioneering studies published between 1990 and 1995 included only 25 patients receiving treatment indicates how slow the progress was in this area.[20-22] A meta-analysis published in 2008 evaluated the results of 824 hemophilic hepatitis C patients from 14 prospective cohorts, 1 retrospective study, and 18 randomized controlled trials. Considering HIV (–) patients in this meta-analysis, the reported sustained virologic response rates with the combination of pegylated interferon + ribavirin were 45% and 79% for genotype-1 hepatitis C and for other genotypes, respectively.[23] It should be noted that one of the reasons which makes hepatitis C treatment problematic for PwH is that some of these patients concomitantly had HIV

Table 4. Side Effect and Adverse Events

Symptoms	(n)	(%)
Fatigue	5	(33%)
Headaches	3	(20%)
Itching	2	(13%)
Insomnia	2	(13%)
Anorexia	2	(13%)
Weight loss	1	(7%)
Myalgia	1	(7%)
Hair loss	1	(7%)
Diarrhea	1	(7%)
Serious infection	1	(7%)
Mean decrease of Hgb for the whole group	0.7 ± 0.8	
Decrease of Hgb in patients using ribavirin	1.4 ± 0.9*	
Decrease of Hgb in patients not using ribavirin	0.4 ± 0.6	
Decrease of Hgb in patients with bleeding attacks	2 (13%)**	

*Hemoglobin decreased more than 2 g/dL in 2 of 5 patients who were using ribavirin. The mean hemoglobin reduction was between 1.4 ± 0.9 g/dL.
**Upper GI bleeding due to erosive gastritis in 1 patient and intramuscular bleeding in 1 patient.

infection.[24] Human immunodeficiency virus infection is one of the conditions that significantly affect the natural course of hepatitis C and treatment response. Although the actual success rate of hepatitis C treatment in PwH is similar to that of other patients, PwH, especially those in the cirrhotic stage, have been infrequently considered as candidates for the treatment of HCV due to the poor safety and tolerability profile of former treatment options.

The treatment regimen with direct-acting antiviral agents is usually tailored according to the genotype/subtype of the virus: drugs used in case the patient was previously treated, the severity of liver disease, and other co-existing medical conditions.[6] Today, ledipasvir + sofosbuvir combination is the most frequently used option for treating genotype 1 HCV infection in PwH.[10,11] Information is limited on the efficacy and safety of more recent combinations of elbasvir + grazoprevir combination and glecaprevir and pibrentasvir.[25,26] Cases using the latter combination are infected with genotype III HCV, but the drug combination is known to be effective against all genotypes.

There is no data on the use of PrOD combination in genotype 1 hepatitis C infected patients with inherited bleeding disorders. There is no contraindication limiting the use of these drugs in PwH, however, prior observations with antivirals, such as ritonavir, used in the treatment of HIV infections revealed that there might be an increased tendency for bleeding. An FDA newsletter published in 1996 and some subsequent publications highlighted the increased tendency of bleeding in HIV (+) PwH receiving protease inhibitors and reported bleeding episodes in some patients.[12,27,28] Although subsequent studies have somewhat showed that antivirals could safely be used in HIV-infected PwH, the risk of bleeding caused by ritonavir or other protease inhibitors is still a controversial issue today.[29] In all product information in combination products, such as HIV protease inhibitors, including tipranavir, indinavir sulfate, saquinavir mesylate, fosamprenavir calcium, or lopinavir + ritonavir, there is a warning notice about the risk of bleeding for PwH and the general population.

In our retrospective case series, the rate of sustained virologic response was 100%. This is similar to the response rate of treatment with the combination of ledipasvir + sofosbuvir in PwH infected with genotype I hepatitis C and appears to be a powerful alternative to standard treatment.[11,30] This can be clearly seen if studies in which PwH were treated with direct-acting agents are analyzed. (Table 5).

Table 5. Treatment of Genotype 1 HCV Infection in Hereditary Bleeding Disorders

Drug Combination	Year	n	SVR, *n* (%)	References
Daclatasvir + asunoprevir	2017	18	16 (89)	Lee et al[31]
Ledipasvir + sofosbuvir	2017	8	8 (100)	Lee et al[31]
Ledipasvir + sofosbuvir	2016	14	14 (100)	Stedman et al[30]
Ledipasvir + sofosbuvir	2017	104	103 (99)	Walsh et al[11]

With regard to safety and tolerability, the most common side effects (>10%) were non-life-threatening problems such as weakness, headache, pruritus, and insomnia. The frequency of the side effects was similar to that of the combination of ledipasvir + sofosbuvir used to treat HCV in PwH. In a study involving the similar number of patients and using a combination of ledipasvir + sofosbuvir, fatigue was reported in 50%, headache in 36%, and insomnia in 21% of the patients.[11] One patient in our series refused to take ribavirin because he thought that this drug was increasing his psoriatic arthritis symptoms. Actually, there is no evidence that this problem is directly related to the treatment. Exacerbation of psoriasis and psoriatic arthritis were not uncommon in hepatitis C patients when they used pegylated interferon + ribavirin. However, this was associated with interferon and not with ribavirin. In the same patient, pneumonia developed in the seventh week of treatment and was the only serious infection encountered in our case series.

Increased risk of bleeding was observed during the HIV treatment of inherited bleeding disorders but there is no data on HIV (–) hepatitis C patients treated with these drugs. In the presented case series, 2 drugs of the combination (paritaprevir and ritonavir) are protease inhibitors, of the other drugs included in the combination, ombitasvir is an NS5A inhibitor and dasabuvir is an NS5 B inhibitor. The combination of PrOD consists of 2 separate drugs, named VIEKIRAX (ombitasvir/paritaprevir/ritonavir) and EXVIREA (dasabuvir) in our country. The prescribing information of these pharmaceutical products includes a warning neither for PwH nor for the risk of bleeding.

Intramuscular hemorrhage in 1 patient and non-variceal upper gastrointestinal hemorrhage in another patient were 2 important complications in our study. However, none of the bleeding events has been directly related to the treatment. Intramuscular hemorrhage is a relatively common problem for PwH and accounts for 10%-23% of all hemorrhagic episodes.[32] The patient who had intramuscular hemorrhage had multiple

episodes of intramuscular hemorrhage in the past and defined this episode to be not different from prior episodes with regard to the severity and the response to factor replacement.

The patient who had upper gastrointestinal bleeding due to erosive gastritis had also a prior history of multiple intramuscular bleeds and an intracranial bleeding episode, which should merit attention. Erosive gastritis is a common condition seen in gastroscopy of cirrhotic patients, and it is the fourth most frequent cause of non-variceal upper gastrointestinal system bleeding (15%-25% of upper gastrointestinal bleeding) in these patients after duodenal ulcer, gastric ulcer, and portal hypertensive gastropathy.[33] The patient had skipped ribavirin for 12 days due to low hemoglobin levels, and he still had Sustained virologic response (SVR) which might support the finding of some recent studies claiming that the addition of ribavirin to DAA regimens is not associated with higher SVR rates.[34] Addition of ribavirin is label-recommended for genotype 1a, 1b for cirrhosis, and genotype 1a without cirrhosis in order to achieve higher SVR rates but benefits of adding ribavirin to DAA regimens requires further investigation.

Treatment for Hepatitis C in patients with inherited bleeding disorders with ledipasvir and sofosbuvir combination has also an increased tendency for bleeding.[11] In a case series of 104 patients using ledipasvir and sofosbuvir combination, severe bleeding was reported in 5% of the cases, including haemarthrosis in 2 cases, upper gastrointestinal hemorrhage in 1 case, hematoma and lower GI bleeding in 1 case for each complication.[11] When all bleeding episodes are considered including minor bleeds, the rate of bleeding in this case series increases to 20%. However, the authors noted that none of these bleeding episodes was related to antiviral treatment.

Although we didn't find an increased rate of bleeding episodes in PwH treated with protease inhibitors, the small sample size and retrospective nature of the study are the main limitations.

In conclusion, the combination of PrOD ± ribavirin appears to be an effective and safe treatment option for HCV-positive people with an inherited bleeding disorder. Although 2 bleeding episodes were observed during the treatment period, it seems that PrOD combination reported in this article has a similar safety profile and efficacy rate as other treatment options, currently available for patients with inherited bleeding disorders.

Ethics Committee Approval: Ethical approval for this study was obtained from institutional ethical committee.

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