

Ombitasvir, paritaprevir, ritonavir, dasabuvir and ribavirin in cirrhosis after complete destruction of hepatocellular carcinoma

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Abstract

We observed a sustained viral response (SVR) of ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin therapy, for 12 wk, in two cases with compensated liver cirrhosis and fully destroyed early hepatocellular carcinoma (HCC). Patients were infected with hepatitis C virus (HCV) genotype 1b and were previous null responders/relapsers to interferon-alpha/ribavirin (IFN/RBV). There was a rapid suppression of HCV RNA to undetectable levels within the first two treatment weeks. SVR was achieved even after marked reduction of the RBV dose. The treatment was well tolerated. Both subjects experienced worsening of liver disease during therapy, in different patterns: severe, transient, predominantly direct hyperbilirubinemia without cytotoxicity (case 1) or progressive increase of aminotransferases (grade 4) without severe hyperbilirubinemia (case 2).

Adverse events spontaneously resolved. The patients remained in a good clinical condition without hepatic decompensation. There was no re-occurrence of HCC. This is the first report for treatment of HCV cirrhosis after complete HCC destruction.

Key words: Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Ribavirin; Hepatitis C virus cirrhosis; Hepatocellular carcinoma

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Core tip: Interferon-free regimens based on a combination of different direct acting antivirals (DAAs) are intensively studied in patients with hepatitis C virus (HCV)-related cirrhosis who are previous null responders or relapsers to interferon/ribavirin. DAAs are very effective and relatively safe in compensated cirrhosis, but there are no data regarding patients with successfully treated hepatocellular carcinoma (HCC). These two cases are the first reports on the efficacy, safety and tolerability of an ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin therapy in subjects with HCV cirrhosis and fully destroyed early HCC, as well as on an evaluation of the serum level of total bile acids during therapy and 12 wk thereafter.

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INTRODUCTION

Recently developed interferon-alpha (IFN)-free regimens based on a combination of different direct acting antivirals (DAAs) bring hope for the successful treatment of patients with hepatitis C virus (HCV)-related cirrhosis who are null responders or relapsers to previous pegylated interferon-alpha (PegIFN) and ribavirin (RBV) dual therapy. New treatment regimens are very effective and relatively safe. The reported sustained viral response (SVR) rate in HCV genotype 1 cirrhotic patients is more than 90%^[1-3]. However, data obtained in registration trials need further careful evaluation, especially in terms of safety. A recent real-life study with first generation protease inhibitors plus PegIFN/RBV showed a significantly higher incidence of serious adverse events, including death, compared to registration phase III trials^[4]. In this study low platelet count (< 100 G/L) together with low albumin level (< 34 g/L) in cirrhotic patients were the most important predictors of serious adverse events associated with triple therapy^[4].

A three drug regimen (3-D) of fixed-dose ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A inhibitor) boosted by ritonavir, taken in combination with dasabuvir (non-nucleos(t)ide analogue inhibitor of NS5B) was approved in United States and European Union for the treatment of chronic HCV genotype 1 infection. This 3-D regimen ± RBV provides SVR rates over 90% 12 wk post therapy even in patients with compensated cirrhosis, liver transplants or HIV co-infection^[1,2]. The SVR rate in genotype 1b is 99% irrespective of the presence of cirrhosis, prior treatment status (naive or experienced) or type of prior treatment failure: partial/null response or relapse^[1,2].

The risk of hepatocellular carcinoma (HCC) in patients with chronic HCV infection is highest among subjects with cirrhosis^[5-7]. HCC is a major global health problem as it represents more than 90% of primary liver cancers, which is the sixth most common cancer, the third cause of cancer-related death, and accounts for 7% of all cancers^[8]. Patients with HCC are curable at early stage A according to the Barcelona clinic liver cancer (BCLC) staging classification^[8]. These subjects are candidates for surgery or local destructive treatment procedures. The latter are preferred, if significant portal hypertension, hyperbilirubinemia or significant comorbidity are present^[8].

Recently introduced IFN-free anti-HCV therapy provides the opportunity to achieve SVR in the vast majority of cirrhotic patients probably even after HCC destruction. Despite this significant treatment advance, there are still no data for the behavior of completely destroyed early HCC by local therapy during and after an IFN-free regimen, as well as regarding the efficacy, safety and tolerability of DAAs among cirrhotic patients with complete HCC destruction.

Here we present the treatment results of a 12-wk therapy with ombitasvir, paritaprevir/ritonavir, dasabuvir and RBV in two patients who were diagnosed with: (1) compensated cirrhosis and genotype 1b HCV infection; (2) previous null response or relapse to IFN/RBV; (3) early stage HCC; and (4) complete destruction of HCC by local therapy

CASE REPORT

Case report 1

A 68-year-old female presented with HCV-related liver cirrhosis (genotype 1b), moderate arterial hypertension and type-II diabetes mellitus. She was anti-HBc total positive, but negative for hepatitis B surface antigen (HBsAg) and anti-HIV 1/2 and had no history of alcohol or drug abuse. Liver cirrhosis was morphologically proved in 2001 during cholecystectomy. At the time of diagnosis there were no data of esophageal varices. In 2002 IFN/RBV was administered. The patient was a primary null responder to this dual therapy. For a further 13 years she received supportive treatment. Over the years a regular follow-up was performed and

Table 1 Laboratory findings in case 1

	BL	Week 1	Week 2	Week 4	Week 8	Week 12 (ETR)	Week 12 post therapy (SVR-12)	Week 24 post therapy (SVR-24)
Hgb (g/L)	106	107	97	85	79	89	105	111
WBC (G/L)	3.2	2.4	3.7	5.8	5.3	3.5	4.5	4.7
PLT (G/L)	80	69	111	123	136	94	81	91
TBil/DBil (μmol/L)	16/10	98/47	66/34	41/25	42/9	13/7	10/5	12/5
ALT (U/L)	49	28	20	23	25	15	11	15
Alb (g/L)	39	39	42	41	36	38	44	44
PT (s)	14.4	14.2	14.9	15.8	14.5	15.1	14.2	15.3
HCV RNA (IU/mL)	496183		UND	UND		UND	UND	UND
FIBROMAX™	A2/F4					A0/F4		
TBA (μmol/L)	27					39	33.5	

BL: Treatment baseline; ETR: End of treatment response; SVR-12: Sustained virological response 12 wk post therapy; SVR-24: Sustained virological response 24-wk post therapy; UND: Undetectable; Hgb: Hemoglobin; WBC: White blood cell count; PLT: Platelet count; TBil: Total bilirubin; DBil: Direct bilirubin; ALT: Alanine aminotransferase; Alb: Albumin; PT: Prothrombin time; HCV: Hepatitis C virus; TBA: Total bile acids.

the patient remained in a good clinical condition with low viral load (HCV RNA < 800000 IU/mL), normal or slightly elevated alanine aminotransferase (ALT) [$< 2 \times$ upper limit of normal (ULN)] and with compensated liver disease (no evidence of ascites, jaundice, encephalopathy or varices bleeding).

In September 2013 abdominal ultrasound (US) and a contrast enhanced computed tomography (CT) scan showed a liver nodule in the third hepatic segment with dimensions 14 mm \times 8 mm and typical signs of HCC (enhanced density in arterial phase with washout in venous phase). US-guided biopsy confirmed HCC. The patient was at stage A according to BCLC classification. At that time she had significant portal hypertension (grade II esophageal varices and platelets < 100 G/L) and was not suitable for surgery, but there were clear indications for local HCC therapy. Angiography revealed a clearly visible hepatic artery branch vessel ensuring the arterial blood supply of the single HCC nodule. The discussed vessel was very suitable for embolization, so transarterial chemoembolization (TACE) was performed. The control CT scan in March 2014 revealed a residual vital HCC nodule in the third hepatic segment. Three sessions of radiofrequency ablation (RFA) were performed subsequently in March 2014, October 2014 and at the beginning of January 2015. After the last session of RFA, the HCC lesion was completely destroyed and a control CT scan showed no data for vital tissue within the ablated malignant nodule, nor at the tumor edge. The CT showed only a zone of ablation-induced necrosis with axial dimensions of 36 mm \times 47 mm.

At the end of January 2015 the patient started to receive antiviral therapy with ombitasvir, paritaprevir/ritonavir, dasabuvir and ribavirin 800 mg for 12 wk. Serum HCV RNA fell to undetectable levels at treatment week 2 and the subject remained aviremic throughout the therapy, as well as 12 and 24 wk thereafter. This was associated with complete normalization of aminotransferases and reduction of the liver disease activity grade from A2 to A0 (FibroMax™) - Table 1.

The most significant adverse events were anemia, transitory direct hyperbilirubinemia with jaundice and marked fatigue.

The anemia was RBV-related as it was properly managed by RBV dose modification. RBV was administered in a lower initial daily dose (800 mg instead of 1000 mg) due to a grade 1 anemia at baseline, but nevertheless the anemia became grade 2 and the RBV dose was reduced to 400 mg daily at week 4. This resulted in initial stabilization of the hemoglobin (Hgb) level, but at treatment week 8 the anemia became more severe - grade 3 (Hgb < 80 g/L) and the RBV dose was reduced again to 200 mg daily and remained the same until week 12. At the end of treatment the anemia was grade 2 and during the follow-up period the Hgb level progressively increased to its baseline level.

A rapid elevation of total bilirubin, including direct bilirubin, occurred within the first treatment week causing moderate jaundice. Direct bilirubin was a predominant fraction of the total bilirubin at baseline. This pattern continued through treatment week 4 and resolved with ongoing DAA therapy. Hyperbilirubinemia was not accompanied by increased aminotransferase activity and was not associated with a decreased albumin level or prolonged prothrombin time. The serum level of total bile acids was highly elevated at baseline, and was additionally increased during therapy from 27 to 39 μmol/L but decreased after treatment discontinuation - Table 1. There were no clinical signs of liver decompensation (ascites, encephalopathy or bleeding). The patient had predominantly direct hyperbilirubinemia and during the bilirubin peak level at week 1 she showed no significant changes in the Hgb level, so the initial rapid elevation of bilirubin could not be explained by RBV-induced hemolysis - Table 1. Paritaprevir effects on bilirubin transporters (OATP1B1 and 1B3) may result in the elevation of indirect bilirubin, which is the typical pattern, independent of RBV-related effects on hemolysis.

The patient experienced marked fatigue that started during the first treatment week and progressively

Table 2 Dynamic of alpha fetoprotein levels in case 1

	Aug 2013	Nov 2013	Mar 2014	Jun 2014	Aug 2014	Oct 2014	Jan 2015	Apr 2015	Jul 2015	Oct 2015
AFP (ULN < 5.5 IU/mL)	15	14	19	13	13	20	77	4	4.05	4.36

ULN: Upper limit of normal; AFP: Alpha fetoprotein.

Table 3 Alterations of alpha fetoprotein levels in case 2

	Apr 2012	July 2012	Aug 2012	Sep 2012	Feb 2012	Sep 2013	Apr 2014	Jan 2015	Apr 2015	Jun 2015	Sep 2015
AFP (ULN < 5.5 IU/mL)	86	120	153	167	16	3	2	3	2	1.5	1.2

ULN: Upper limit of normal; AFP: Alpha fetoprotein.

increased until treatment week 4. Fatigue persisted relatively unchanged during the entire treatment course and rapidly disappeared within the first weeks of post-treatment follow-up.

During therapy and in post-treatment follow-ups, the patient was carefully evaluated with respect to previously diagnosed HCC. Alpha-fetoprotein (AFP) decreased from 77 IU/mL (normal value < 5.5 IU/mL) to normal serum level of 4.0 IU/mL at week 12 (Apr 2015) and remained normal for 24 wk thereafter (with follow-ups in Jul and Oct 2015) - Table 2. The control contrast-enhanced abdominal US showed a well-delineated zone of prior ablations with dimensions of 4 cm × 3 cm in June 2015 and with a diameter of 2.6 cm in Sep 2015. There were no signs of HCC recurrence or newly developed liver nodules.

Case report 2

A 76-year-old male was diagnosed with hepatitis C (genotype 1b) in 2001. He had a history of arterial hypertension and type II diabetes with onset in 2002. In 2008 he started insulin therapy. In 2011 tamsulosin 0.4 mg daily was initiated for the treatment of benign prostatic hyperplasia. The patient's history did not reveal alcohol or drug abuse. He was anti-HBc total positive, but negative for HBsAg or anti-HIV 1/2.

In 2002 a liver biopsy was performed and data for chronic hepatitis with fibrosis stage 2 were found. In 2002/2003 the patient was treated with IFN/RBV for 48 wk. He proved a relapser to dual therapy. During further supportive treatment the patient remained with persistently elevated aminotransferase levels above 3 × ULN.

In 2009, liver cirrhosis (Child-Pugh A) was diagnosed based on an abdominal US examination and endoscopic evidence of portal hypertension - grade I - II oesophageal varices. In Apr 2012 an elevated AFP of 86 IU/mL (ULN < 5.5 IU/mL) was found. There were no clinical or US signs of hepatic decompensation (ascites, jaundice, encephalopathy or varices bleeding), nor was there any evidence of portal vein thrombosis. However, a subsequent contrast-enhanced US and a CT scan showed two nodules in the sixth hepatic segment. Both of them were below

3 cm in diameter and with typical signs of HCC. Based on the above findings, the patient was diagnosed with early HCC stage A according to BCLC classification. He was not suitable for surgery due to significant portal hypertension, advanced age and significant comorbidity, mainly related to diabetes. He was indicated for local HCC therapy and received two TACE sessions in September 2012 and in December 2012. A full HCC destruction was achieved and documented by regular control US and CT examinations, performed over a 3-mo interval from Jan 2013 to Aug 2014. There were no data for vital tissues within previously destroyed HCC lesions, including their margins. During the subsequent regular US examinations on a 3-mo interval (the last one in Sep 2015) there were no signs for new liver nodules. Alterations of the AFP level in case 2 are presented in Table 3.

After the last TACE session the patient remained in a good clinical condition and with compensated liver disease without clinical or US signs of ascites, jaundice, encephalopathy or GI bleeding.

In January 2015, a 12-wk antiviral therapy with ombitasvir, paritaprevir boosted by ritonavir, dasabuvir and RBV 1000 mg/d (according to body weight) was initiated. HCV RNA was undetectable at treatment week 2 and the subject was persistently aviremic during further therapy, as well as at weeks 12 and 24 post treatment. The dynamic of laboratory parameters during antiviral therapy is presented in Table 4.

The most significant adverse event during therapy was a marked elevation of aminotransferases which occurred at treatment week 4, reached a maximal level at week 6 (ALT toxicity grade 4), followed by progressive reduction to baseline level at week 12 - Table 4.

A mild direct hyperbilirubinemia was also observed. It occurred within the first treatment week and reached maximal levels at treatment week 12. The hyperbilirubinemia was accompanied by mild prolongation of prothrombin time at week 6, but there was no parallel reduction of the serum albumin level. The serum level of total bile acids was initially normal, increased about 4 times from 4.5 to 19 μmol/L at the end of therapy and returned to the initial level during

Table 4 Laboratory findings during treatment (case 2)

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 12 (ETR)	Week 12 post therapy (SVR-12)	Week 24 post therapy (SVR-24)
Hgb (g/L)	132	130	115	99	104	103	131	125
WBC (G/L)	5.7	6.4	8.8	5.1	4.5	6.2	6.7	8.1
PLT (G/L)	183	166	304	320	278	308	168	182
Tbil/Dbil (μmol/L)	7/3.6	19/13	24/13	16/10	9/4	34/23	5.2/2.3	6.4/2.6
ALT (U/L)	99	61	53	265	510	45	14	16
PT (s)	13.5	13.7	13.1	15.6	16.3	13.4	14.7	14.4
Alb (g/L)	42	40	49	45	42	43	47	47
HCV RNA (IU/mL)	1799000		UND	UND		UND	UND	UND
FIBROMAX™	A3/F4					A3/F4		
TBA (μmol/L)	4.5					19	5.2	

the post-treatment follow-up.

Another important problem during therapy was potential drug-drug interactions related to tamsulosin as this drug is a substrate of CYP3A4. Co-administration of a 3-D regimen and tamsulosin has not been studied, but exposure to tamsulosin increases 2.8 fold with ketoconazole, which is a CYP3A4 inhibitor similar to ritonavir. The current recommendation was to avoid use of tamsulosin with 3-D, so we discontinued tamsulosin prior to the antiviral therapy. At treatment week 1, a severe dysuria occurred. There were no US signs of urine retention and the prostate-specific antigen level remained within normal ranges. Antibacterial therapy with ciprofloxacin was initiated to treat a potential urinary tract infection, although there were no marked laboratory data confirming it. The dysuria became more severe. The antibiotic therapy was discontinued and treatment with tamsulosin was resumed with a lower dose of 0.4 mg every other day. Within a few days the dysuria resolved and the patient remained in a good clinical condition during further therapy.

DISCUSSION

The three-drug regimen of ombitasvir, paritaprevir/ritonavir and dasabuvir plus RBV is a spectacular treatment advance for genotype 1 patients with compensated HCV cirrhosis. It is associated with a high SVR rate of 91.8% and 95.9% after treatment for 12 and 24 wk, respectively^[1]. However, there are still many open questions regarding IFN-free therapy in liver cirrhosis. It is unknown whether the elimination of HCV infection will be sustained over the years and what the long-term treatment impact on chronic liver disease will be, including a regression of fibrosis and cirrhosis. It is also not clear which cirrhotic patients will mostly benefit from therapy in terms of prolonged survival and a slowing down of the progression to HCC. And finally there are no safety and efficacy data in subjects with cirrhosis who were successfully cured from early HCC.

To the best of our knowledge this is the first report of a 3-D regimen in patients with HCV cirrhosis and early HCC that had been completely destroyed by local treatment procedures in advance. Our results suggest

that IFN-free therapy might be a suitable treatment option for this specific patient subgroup. In both cases we observed a rapid suppression of serum HCV RNA to undetectable levels within the first two weeks of antiviral therapy. SVR was achieved even after marked reduction of the RBV dose to only 200 mg/daily in the first case.

Generally, the treatment was well tolerated, but both subjects experienced signs of worsening of liver disease during therapy which was manifested in two different patterns: a severe, early, transient predominantly direct hyperbilirubinemia without cytolysis (case 1) or progressive increase of serum aminotransferases (grade 4) without severe hyperbilirubinemia (case 2). The reported incidence of grade 3-4 hyperbilirubinemia and grade 3-4 ALT elevation during 3-D therapy is 9.7% and 1.6%, respectively^[1], but it might be higher in HCC patients, so careful clinical and laboratory evaluations are required. This is also the first report for an elevation of the level of serum total bile acids during treatment with DAAs.

In our cases the above-described adverse events were transient and spontaneously resolved without an interruption of the 3-D regimen and without concomitant medications. Both patients remained in a good clinical condition and with persistently compensated liver disease. There were no signs of ascites, encephalopathy or GI bleeding.

We did not observe re-occurrence of HCC and newly developed liver nodules during the 3-D therapy or in a post-treatment follow-up of 24 wk. In addition, a recently published case report described a regression of HCC after sofosbuvir-based IFN-free therapy in a 53-year-old male with metastatic HCC, who failed sorafenib treatment^[9]. Together all these data clearly suggest that patients with HCC may benefit from IFN-free therapies.

The results of several studies and meta-analyses indicated that the risk of HCC is reduced among patients with HCV who achieved SVR with IFN/RBV dual therapy^[7]. Once cirrhosis is established, there is no conclusive evidence that antiviral therapy can prevent or delay the occurrence of HCC^[7]. Additional studies are needed to test the potential preventive effect of a combination with new DAAs in cirrhotic

patients and particularly in those who have cured early HCC.

COMMENTS

Case characteristics

Both cases had compensated hepatitis C virus (HCV) cirrhosis, were previous non responders or relapsers to interferon-alpha/ribavirin (IFN/RBV) and had a history of completely destroyed early hepatocellular carcinoma (HCC) by radiofrequency ablation (RFA) and/or transarterial chemoembolization (TACE) procedures.

Clinical diagnosis

Physical signs suggested compensated liver cirrhosis.

Differential diagnosis

There were no differential diagnostic dilemmas.

Laboratory diagnosis

HCV genotype 1b was found in both cases. The serum HCV RNA was above 100000 IU/mL. Alanine aminotransferase levels were elevated up to 2.5 × upper limit of normal. Serum albumin, bilirubin and prothrombin levels were normal. Both patients were hepatitis B surface antigen negative, anti-HBc total positive and anti-HIV negative.

Imaging diagnosis

Ultrasound showed liver cirrhosis without ascites. Esophageal varices grade I / II were found by upper endoscopy. Contrast-enhanced computed tomography scans confirmed the complete destruction of early HCC prior to initiation of the IFN-free therapy.

Pathological diagnosis

Liver cirrhosis and HCC were morphologically confirmed prior to local treatment of HCC with RFA and/or TACE.

Treatment

Both patients received a fixed dose combination of ombitasvir, paritaprevir boosted by ritonavir plus dasabuvir and RBV for 12 wk and were followed up for an additional 24 wk after the completion of the therapy.

Related reports

No reports on the safety and efficacy of the treatment regimen in patients with HCV cirrhosis and completely destroyed HCC described above are available to date.

Term explanation

Three drug (3-D) regimen is a spectacular treatment advance for genotype 1 patients with compensated HCV cirrhosis. The sustained viral response (SVR) rate in genotype 1b is 99% irrespective of the presence of cirrhosis. This new therapy provides the opportunity to achieve favourable results in a more difficult to treat subgroup of cirrhotic patients with completely destroyed early HCC.

Experiences and lessons

The authors observed a rapid suppression of serum HCV RNA to undetectable levels within the first two weeks of antiviral therapy. SVR was achieved even after a marked reduction of the RBV dose to only 200 mg daily in the first case. Treatment was well tolerated, but both subjects experienced signs of worsening of liver disease during therapy, so careful clinical and laboratory evaluation is required. Adverse events were transient and spontaneously resolved. Both

patients remained in a good clinical condition and with compensated liver disease.

Peer-review

The authors have described the first two cases in the literature with HCV-related cirrhosis and completely destroyed early HCC, treated with IFN-free therapy. The article highlights the obtained clinical data regarding efficacy, safety and tolerability of a 3-D regimen. Results suggest that IFN-free therapy might be a suitable treatment option for this specific patient subgroup.

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