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Twelve-week ravidasvir plus ritonavir-boosted danoprevir and ribavirin for non-cirrhotic HCV genotype 1 patients: A phase 2 study

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Abstract

Background and Aim: The need for all-oral hepatitis C virus (HCV) treatments with higher response rates, improved tolerability, and lower pill burden compared with interferon-inclusive regimen has led to the development of new direct-acting antiviral agents. Ravidasvir (RDV) is a second-generation, pan-genotypic NS5A inhibitor with high barrier to resistance. The aim of this phase 2 study (EVEREST study) was to assess the efficacy and safety of interferon-free, 12-week RDV plus ritonavir-boosted danoprevir (DNVr) and ribavirin (RBV) regimen for treatment-naïve Asian HCV genotype 1 (GT1) patients without cirrhosis.
Methods: A total of 38 treatment-naïve, non-cirrhotic adult HCV GT1 patients were enrolled in this multicenter, open-label, single-arm phase 2 study (NCT03020095). All patients received a combination of RDV 200 mg once daily (q.d.) plus DNVr 100 mg/100 mg twice daily (b.i.d.) and oral RBV 1000/1200 mg/day (body weight $< 75/\geq 75$ kg) for 12 weeks. The primary endpoint was the rate of sustained virologic response 12 weeks after the end of treatment (SVR12).
Results: Of 38 patients, all (100%) achieved SVR12. During the study, no treatment-related serious adverse events, no patients discontinued treatment due to adverse events, and no deaths were reported. Six of 37 (16%) patients with available sequences had HCV NS5A resistance-associated variants at baseline. All patients (6/6) with baseline NS5A resistance-associated variants achieved SVR12.
Conclusions: Twelve-week RDV and DNVr in combination with RBV for 12 weeks achieves the SVR12 rate of 100% in treatment-naïve non-cirrhotic Asian patients with HCV GT1 infection. This interferon-free regimen is also safe and well tolerated.

Introduction

In the Asia–Pacific region, the estimated viremic hepatitis C virus (HCV) prevalence range from 0.6% in Caribbean to 2.3% in Central Asia.[1] Approximately one-fifth of patients who are chronically infected with HCV eventually develop cirrhosis, which can lead to liver failure and hepatocellular carcinoma.[2] Many patients are intolerant or ineligible for interferon-based therapies.[3] The efficacy of interferon-based therapies can be affected by factors such as cirrhosis status, HCV genotype (GT), and IL28B GT.[4] All-oral, interferon-free regimens of direct-acting antivirals are better tolerated than interferon-based regimens with improved sustained virologic response (SVR) rates and shorter treatment duration.[4]

Ravidasvir (RDV, ASC16) is a second-generation, pan-genotypic non-structural (NS) 5A inhibitor, which inhibits viral replication and assembly.[5,6] RDV exhibits high antiviral potency with EC_{50} 0.04–1.14 nM for HCV GT1–GT6. The pharmacokinetics results indicated that steady status achieved quickly after the

first dose. Metabolism studies utilizing human clinical samples showed that RDV was very stable, with only modest (~2%) metabolite formation. Biliary excretion of RDV appears to be the primary route of elimination of the absorbed dose, while renal excretion of intact drug appears to be negligible. High virologic response rate was achieved in phase 3 Egyptian HCV GT4 patients treated with RDV and sofosbuvir.[7]

Danoprevir is a macrocyclic non-covalent reversible NS protein 3 inhibitor with antiviral activity against HCV GTs 1, 2, 4, and 6 *in vitro*.[8,9] The ritonavir-boosted danoprevir (DNVr) and plus peginterferon alpha and ribavirin (RBV) triple therapy produced SVR12 rates > 90% after 12-week treatment in non-cirrhotic Taiwanese patients with HCV GT1 infection.[10]

In this phase 2 study (NCT03020095), the efficacy and safety of all oral IFN-free direct-acting antiviral combination therapy in treatment-naïve non-cirrhotic Asian HCV GT1 patients were evaluated.

Methods

Study design. This phase II, single-arm, non-comparative trial, multicenter study (EVEREST) evaluated the efficacy and safety of RDV and DNVr plus RBV in treatment-naïve, non-cirrhotic patients with HCV GT1 infection. The study was conducted in full conformance to the principles of the Declaration of Helsinki and the laws and regulations of the country in which the research is conducted. The institutional review boards of all participating institutions approved the study. Written informed consents were obtained from all participants according to the local regulations.

Patients and treatment. This open-label, phase 2 study included 38 adult patients in five centers from Taiwan between December 2015 and March 2016. Eligibility criteria were provided in the study registration information (NCT03020095). In brief, eligible patients (aged ≥ 20 years) had confirmed chronic HCV GT1 infection for more than 6 months, screening plasma HCV-RNA concentration > 10 000 IU/mL, and no prior treatment for HCV with interferon, RBV, and other direct-acting or host-targeting antivirals for HCV. Chronic liver disease consistent with chronic hepatitis C infection without cirrhosis as determined by biopsy obtained within the past calendar 36 months using one of the liver biopsy methods in the protocol. Non-cirrhosis is defined as METAVIR score < 4, or as determined by Fibroscan defined as < 14.6 kPa. Patients who have not obtained a liver biopsy or Fibroscan in the last 3 years will have a study-related Fibroscan performed in order to confirm the diagnosis. Liver biopsy will be performed by investigator's judgment.

Patients were excluded if they had positive hepatitis B surface antigen or human immunodeficiency virus antibody at screening and a history or presence of decompensated liver disease or non-hepatitis C chronic liver disease, including but not limited to history of ascites, hepatic encephalopathy, hepatocellular carcinoma, bleeding esophageal varices, or autoimmune hepatitis.

All patients received an all-oral combination of RDV 200-mg tablets once daily, DNVr 100 mg/100 mg twice daily, and weight-based RBV 500 mg (< 75 kg) or 600 mg (≥ 75 kg) twice daily for 12 weeks and were followed up for 24 weeks after stopping the regimen. Study drug should be taken within 15 min before or within 30 min after the meal.

Study assessment. Hepatitis C virus RNA was quantified using the Abbott Real Time HCV quantification assay with a lower limit of quantitation (LLOQ) of 12 IU/mL. Virologic response was defined as HCV-RNA below the LLOQ, rapid virologic response (RVR) was defined as a virologic response at week 4, and SVR was defined as a virologic response at week 4 (SVR4) or 12 (SVR12) after the end of treatment. Plasma HCV-RNA was quantified at screening and at each visiting time thereafter to assess the virologic response to treatment.

Blood samples will be collected throughout the study to monitor for the development of drug resistance. In the event of failure, post-baseline viral sequences will be compared with the baseline viral sequence, and sequence variations will be analyzed and reported.

Safety outcomes included adverse events (AEs), serious AEs, and laboratory abnormalities.

The primary efficacy endpoint was the proportion of patients achieving SVR12. Secondary endpoints included SVR24, safety, tolerability, and virologic response over time.

Statistics. The percentage of patients achieving undetectable HCV-RNA during treatment and follow-up period will be reported. All data were analyzed by SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Study population. A total of 38 patients were enrolled: 37/38 (97.4%) were infected with HCV GT1b, and 1/38 (2.6%) was infected with HCV GT1a. Among them, 31/38 (81.6%) had IL28B (a single-nucleotide polymorphism on chromosome 19, rs12979860) CC GT, which is favorable for interferon-inclusive treatment. The mean (SD) age was 57.6 (12.7) years (Table 1). In total, all patients completed the 12-week treatment and achieved SVR12.

Table 1 Demographics and disease characteristics of 38 patients

	n = 38
Age (years), median (range)	59.5 (29–85)
≥ 65 years, *n* (%)	11 (28.9)
Gender (M/F), *n*	12/26
HCV genotype, *n* (%)	
1a	1 (2.6)
1b	37 (97.4)
Baseline HCV-RNA (log_{10} IU/mL), mean (SD)	6.45 (6.41)
> 800 000 IU/mL, *n* (%)	26 (68)
IL28B genotype, *n* (%)	
CC	31 (81.6)
Non-CC	7 (18.4)
ALT (U/L), mean (SD)	66.8 (72.0)
Platelet (mm^3), mean (SD)	221.6 (58.6)

ALT, alanine transaminase; HCV, hepatitis C virus; HCV-RNA, hepatitis C virus RNA.

Efficacy endpoints. All (38/38, 100%) patients achieved SVR12. No virologic breakthrough was found during the treatment. One patient failed to complete 24 weeks of follow-up, and the remaining 37/37 (100%) achieved SVR24 without relapses at the end of follow-up. All patients receiving RDV and DNVr plus RBV had rapid decline of serum HCV-RNA levels (Fig. 1). By week 2 of treatment, 42.1% (16/38) of patients had HCV-RNA level of less than LLOQ. By week 8, 100% (38/38) of patients achieved virologic response, and the response rate was maintained till the end of treatment. The profile of virologic response from baseline to the end of follow-up is shown in Table 2.

HCV NS3/4A and NS5A gene sequences were available in 37 patients (Table 3 and Table S1). Baseline amino acid polymorphisms showed 6/37 (16.2%) patients had at least one resistance-associated variants (RAVs) in the NS5A gene. All patients with NS5A RAVs achieved SVR12. Consistent virologic responses were found in patients with or without NS3/4A RAVs (Fig. 1). SVR12 was achieved across all subgroups, regardless GT, host IL28B GT, viral load, and age (Fig. 2).

Safety and tolerability. Ravidasvir and DNVr plus RBV for treatment-naïve, non-cirrhotic HCV GT1 patients was safe and well tolerated. There was no death, treatment-related serious AE, and discontinued cases due to AE.

All AEs were mild or moderate severity (grades 1 and 2), and no grade 3 or 4 AEs occurred during the treatment. The most common treatment-related AEs were anemia (26.3%), diarrhea (15.8%), rash (13.2%), upper respiratory tract infection (10.5%), fatigue (10.5%), and cough (10.5%) (Table 4); 3 patients had AEs that led to dose reductions of RBV. All laboratory abnormalities that occurred on-treatment were grade 1 or 2. Grade 1 laboratory abnormalities that occurred were hemoglobin decrease or anemia (26.3%) and reticulocyte count increase (2.6%). Grade 2 laboratory abnormalities (≥ 1 patient) were direct and total bilirubin increase (2.6%). Given the additional ease of clinical monitoring, these treatment-emergent laboratory abnormalities can be safely managed in this patient population (Table 4).

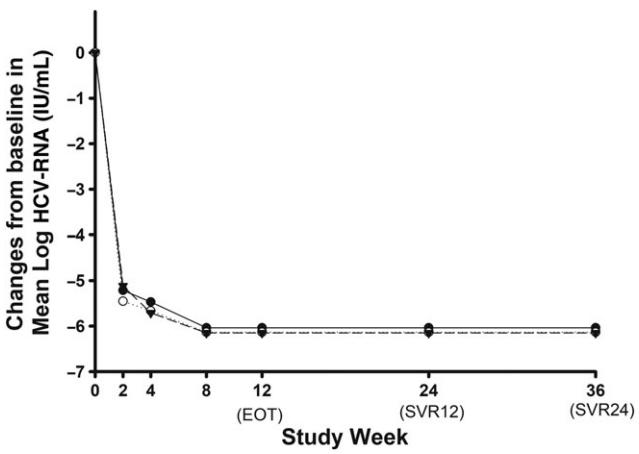

Figure 1 Mean change of hepatitis C virus RNA (HCV-RNA) level from baseline to the end of follow-up. —●—, five patients with both NS5A and NS3/4A resistance-associated variants (RAVs) at baseline; ···o···, six patients with NS5A RAVs at baseline; −▼−, 31 patients without RAVs at baseline; EOT, end of treatment; SVR, sustained virologic response.

Table 2 Virologic response (HCV-RNA < LLOQ) during and after treatment with RDV, DNVr, and RBV

Response	FAS (n = 38)	PPS (n = 37)[†]
During treatment, n (%)		
At week 2	16 (42.1)	15 (40.5)
At week 4 (RVR)	28 (73.7)	27 (73.0)
At week 8	38 (100)	37 (100)
At week 12 (EOT)	38 (100)	37 (100)
Post-treatment, n (%)	38 (100)	37 (100)
SVR12	38 (100)	37 (100)
SVR24	37[†] (97.4)	37 (100)

[†]One patient failed to complete 24-week follow-up.
DNVr, ritonavir-boosted danoprevir; EOT, end of treatment; FAS, full analysis set; HCV-RNA, hepatitis C virus RNA; LLOQ, lower limit of quantitation; PPS, per-protocol set; RBV, ribavirin; RDV, ravidasvir; RVR, rapid virologic response; SVR, sustained virologic response.

Table 3 Baseline resistance-associated variants analysis of HCV NS5A gene

Amino acid and position at HCV NS5A protein	Resistance-associated substitutions	Cases
L31	L31M	2
Y93	Y93H	1
	Y93Y/C	1
	Y93Y/H	2

HCV, hepatitis C virus.

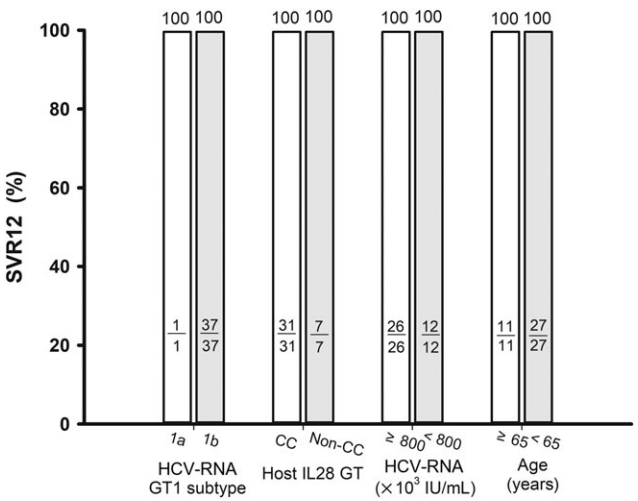

Figure 2 Sustained virologic response (SVR)12 stratified by subgroups. GT, genotype; HCV-RNA, hepatitis C virus RNA.

Table 4 Adverse events and laboratory abnormalities

Patients, *n* (%)	Total (*n* = 38)
Discontinuation of any study drug due to AE	0 (0)
Serious adverse events	1 (2.6)[†]
Treatment-related SAE	0 (0)
AE led to dose reductions of RBV	3 (7.9)
Common adverse events (≥ 10%)	
Anemia	10 (26.3)
Hb < 10 g/dL	4 (11.0)
Hb < 8.5 g/dL	0 (0)
Diarrhea	6 (15.8)
Rash	5 (13.2)
Upper respiratory tract infection	4 (10.5)
Fatigue	4 (10.5)
Cough	4 (10.5)
Laboratory abnormalities, *n* (%)	
Total bilirubin increase	1 (2.6)
Direct bilirubin increase	1 (2.6)
Reduced Hb	10 (26.3)
Reticulocyte count increase	1 (2.6)

[†]One patient experienced unexpected sudden fall at 6 months after end of treatment and achieved SVR12 and SVR24.
AE, adverse event; Hb, hemoglobin; RBV, ribavirin; SAE, serious adverse event; SVR, sustained virologic response.

Discussion

The results of phase 2 EVEREST study showed that a 12-week all-oral combination regimen of RDV and DNVr plus RBV achieved high SVR12 and SVR24 rates (100%) in treatment-naïve non-cirrhotic HCV GT1 Asian patients. The SVR12 rate was not affected by patient's IL28B status, age, and viral load. No virologic breakthrough or relapse occurred during and after the treatment, implying the high genetic barrier of RDV and DNVr regimen to drug resistance. Baseline NS5A RAVs were found in 16% (6/37) of patients, but all of them still achieved SVR12. In a recent study, NS5A RAVs were found in 29.9% of Chinese HCV GT1 patients.[11] In the phase 3 daclatasvir plus asunaprevir studies, NS5A (L31M or Y93H) RAVs were present in 11.9% of HCV GT1b Asian patients. However, only 42% (8/19) of patients with baseline NS5A RAVs achieved SVR12, whereas it was even lower in Chinese patients (2/10, 20%). Virologic failure tended to coincide with the presence of baseline NS5A (L31M or Y93H) RAVs in daclatasvir and asunaprevir regimen.[12] In contrast, RDV and DNVr plus RBV regimen exhibited a high SVR12 in patients with baseline NS5A polymorphisms.

The treatment regimen was safe and well tolerated. Compared with studies of interferon-based regimens, the incidence of AEs and laboratory abnormalities was much lower.[3] Only grade 1 or 2 treatment-related AEs occurred during the treatment. There was no death, treatment-related serious AE, and discontinued cases due to AE. The treatment-emergent AEs and laboratory abnormalities can be safely managed in this patient population.

The inclusion criteria only defined the lowest age limit; thus, patients enrolled covering a wide range of age from 29 to 85. Eleven (28.9%) patients were above 65 years, suggesting this all-oral regimen was highly effective, safe, and well tolerated for elderly patients.

In conclusion, RDV and DNVr plus RBV for 12 weeks achieved 100% of SVR12 and was well tolerated in treatment-naïve non-cirrhotic Asian HCV GT1 patients. Further phase 3 clinical trials will be conducted soon.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.