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ORIGINAL ARTICLE

Direct-acting antivirals in East Asian hepatitis C patients: real-world experience from the REAL-C Consortium

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Abstract

Background and aims One-third of the global hepatitis C virus (HCV) burden is found in Asia. Real-world data from diverse East Asian cohorts remain limited. This study addressed the real-world status of direct-acting antiviral (DAA) therapy among patients from East Asia.

Methods Chronic hepatitis C (CHC) patients from clinical sites in Japan, Taiwan, South Korea, and Hong Kong were recruited in the REAL-C registry, an observational chart review registry. The primary outcome was sustained virologic response (SVR12, HCV RNA PCR < 25 IU/mL 12 week post-therapy).

Results A total of 6287 CHC patients were enrolled. Compared to other East Asian patients, patients from Japan were older (66.3 vs. 61.5 years, $p < 0.0001$), had lower body mass indices (22.9 kg/m^2 vs. 24.6 kg/m^2, $p < 0.001$), and were more likely to have non-liver malignancy history (12.2% vs. 5.0%, $p < 0.001$).The overall SVR12 rate was 96.4%, similar to patients both inside and outside Japan (96.6% vs. 96%, $p = 0.21$). The SVR12 rate ranged from 91.1 to 99.4% except treatment-experienced cirrhotic HCV genotype-1 patients who received daclatasvir/asunaprevir (85.9%) and the treatment-experienced cirrhotic HCV genotype-2 patients treated with sofosbuvir/ribavirin (87%). The overall rate of drug discontinuation was 1.9%, also similar across regions. On multivariate regression analyses, there was no significant association between geographic region and SVR outcomes.

Conclusions In this large multinational CHC cohort from the East Asia, oral DAAs were highly effective and well tolerated across the region. Policies should encourage treatment for all CHC patients with DAAs in Asia with its heavy burden of HCV.

Keywords DAA · CHC · Korea · Taiwan · Japan · Hong Kong

Abbreviations

HCV	Hepatitis C virus
CHC	Chronic hepatitis C
HCC	Hepatocellular carcinoma
DAAs	Direct-acting antivirals
SVR	Sustained virologic response
GT	Genotype
ORs	Odds ratios
CI	Confidence interval
LDV	Ledipasvir
SOF	Sofosbuvir
RBV	Ribavirin
DCV	Daclatasvir
ASV	Asunaprevir
PrOD	Paritaprevir/ritonavir/ombitasvir/dasabuvir
EBR	Elbasvir
GZR	Grazoprevir
GLE	Glecaprevir

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PIB Pibrentasvir
VEL Velpatasvir

Introduction

In 2015, an estimated 71 million people were infected with hepatitis C virus (HCV) globally, half of whom resided in Asia [1]. While chronic hepatitis C (CHC) is well known to cause premature death from liver cirrhosis and hepatocellular carcinoma (HCC), these complications are of even higher importance in Asia, because HCV-infected persons from this region are more likely to be older and have had a longer duration of infection from earlier iatrogenic exposure [2, 3]. While HCV cure by means of antiviral therapy can greatly reduce such liver-related consequences, only 2.9 million persons worldwide have received antiviral therapy as of 2016, bringing the global coverage of hepatitis C curative treatment to only 13%, significantly less than the World Health Organization's goal of treating at least 80% of those infected with HCV by 2030.

Unfortunately, treatment with direct-acting antivirals (DAAs) lags further behind in Asia [4], even in high-income East Asian countries [5, 6]. The reasons for this are multiple, but mainly are a result of different reimbursement criteria and treatment policies established by local governments and agencies leading to differential patient selection and potentially different treatment outcomes for patients from the individual Asian countries/regions, especially with various restrictions when DAAs were first made available in Asia in 2014 [7–10].

Our knowledge on HCV treatment and treatment outcomes in routine practice in East Asia is also limited due to the lack of data. Recent meta-analyses pooling single-center and/or single-country-based studies have shown high treatment effectiveness and tolerability with DAAs in Asia, but the overall pooled estimates are limited by high heterogeneity and subgroup analyses that are limited by a lack of individual patient-level data [11–13]. In addition, a favorable reimbursement policy and early accessibility to DAAs in Japan has led to the majority of reported real-world DAA data from East Asia being from Japan, limiting the generalizability of these results to other East Asian countries.

Therefore, using data from a large multicenter, multinational real-world registry of CHC patients who received interferon (IFN)-free DAAs in East Asia, we characterized and compared the baseline characteristics and treatment outcomes of CHC patients treated in an area with a favorable reimbursement policy for DAAs (Japan) to areas with later DAA adoption, including neighboring South Korea, Taiwan, and Hong Kong.

Methods

Study design and study patients

The multicenter multinational registry cohort (Real-world Evidence from the Asia Liver consortium for HCV; REAL-C) enrolled CHC patients who received IFN-free DAAs from July 1, 2014 to November 1, 2018 from several East Asian study centers (Hong Kong, Japan, South Korea, and Taiwan). Eligible patients were ≥ 18 years old and identified from the hospital and/or clinic registries. Individual patient records were reviewed and data were extracted at each participating study center using a standardized Case Report Form and a unified data variable dictionary. Patients were excluded if they had a history of solid organ transplantation, were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), had significant use of immunosuppression within 3 months of DAA treatment initiation, or if patients were terminally ill (expected life expectancy less than 1 year), or moribund. HCC patients were reported to have lower treatment response [14]. Therefore, we elected to exclude patients who had HCC prior to DAA initiation from all sustained virologic response (SVR) analyses.

Completely de-identified data were sent to the central data coordinating center (Stanford University, Stanford, California, USA) for data management and data analysis.

Study assessment

Liver cirrhosis was defined by one or more of the following: liver histology of cirrhosis, transient elastography (FibroScan®; Echosens, Paris, France) score > 12.5 kPa or magnetic resonance elastography score > 7 kPa, the presence of clinical, radiologic, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension (nodular contour on imaging, thrombocytopenia with platelets less than 120×10^3 K/μL, splenomegaly, and presence of varices), or signs of clinical hepatic decompensation (ascites, hepatic encephalopathy, jaundice, and variceal hemorrhage). HCC was defined by cytology, histology, or noninvasive imaging criteria based on the guidelines of the American Association for the Study of Liver Diseases (AASLD) or the Asian Pacific Association for the Study of the Liver (APASL) [15, 16].

Patient baseline demographic and clinical characteristics were evaluated at the time of DAA initiation and stratified by country/region. The primary treatment outcomes were SVR12 (defined as HCV RNA PCR < 25 IU/mL 12 weeks after the end of therapy) and treatment tolerability, including laboratory results, treatment-emergent

adverse events, and early treatment discontinuation (discontinuation prior to reaching the end of the intended treatment duration).

Statistical analyses

Descriptive and comparative statistics were performed for patient baseline characteristics and treatment outcomes. Frequency was compared between groups using the Chi-square test with the Yates correction or Fisher's exact test. Group means (presented as the mean ± standard deviation) were compared using the Student's *t* test and analysis of variance test if the data followed a normal distribution or the nonparametric Mann–Whitney test if not. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation [17].

Logistic regression analysis was performed to evaluate factors associated with SVR12. We first conducted univariable analyses to determine the association between selected variables and SVR. Variables were selected for a multivariable model using a stepwise backward selection approach. Measured values were expressed as odds ratios (ORs) and 95% confidence interval (CI). Model adequacy was evaluated using the Hosmer–Lemeshow goodness-of-fit test [18]. Multicollinearity was explored by estimating the variance inflation factor. We also assessed the discrimination of the logistic regression model using the receiver-operating characteristic (ROC) curve. We plotted standardized Pearson residuals to determine the existence of outlying and influential points. In addition, we estimated the *E* value to demonstrate the magnitude of an unmeasured confounder's minimum strength to calculate potential confounding effects between predictors and SVR [19].

All analyses were performed using STATA version 14 statistical package (College Station, USA). Statistical significance was defined as a two-tailed p value of < 0.05.

Results

Patient characteristics and treatment regimens

A total of 6287 patients were enrolled in the current study (Hong Kong, $n = 43$; Japan, $n = 4552$; South Korea, $n = 719$: Taiwan, $n = 973$). Patients' baseline demographic and clinical characteristics as well as their respective DAA regimens are shown in Table 1 and Supplemental Table 1. The mean age was 64.9 years for the total cohort, and male patients accounted for 43.6% of the cohort. The most common genotype was HCV genotype 1 (GT-1) (71.8%) followed by HCV genotype 2 (GT-2) (27.2%). Approximately one-third of the total cohort ($n = 1917$, 30.4%) had liver cirrhosis, of whom the vast majority had compensated liver disease (93.1%). A total of 482 patients (7.7%) had pre-existing HCC at the time of DAA initiation. About two-thirds of the cohort ($n = 4212$, 67.3%) were treatment-naïve. Among the 2051 patients with a history of prior treatment failure, the large majority ($n = 1781$, 86.8%) had been treated with IFN-based therapy (Table 1).

Patients from Japan were on an average 5 years older than patients from other study areas (66.3 years vs. 61.5 years, $p < 0.001$) with about 60% of patients from Japan being 65 years or older compared to about 39% for non-Japan regions. Patients from Japan were also more likely to have a history of non-liver malignancy than those from other countries/regions (12.2% vs. 5.0%, $p < 0.001$), and to have a lower body mass index (BMI, 22.9 kg/m^2 vs. 24.6 kg/m^2, $p < 0.001$) (Table 1).

By specific country/region, there were differences in most patient characteristics except for sex distribution, with higher BMIs in the Korea and Taiwan cohorts (about 24%), higher rates of diabetes (about 28%), and poorer renal function (about 24% with eGFR < 60 ml/min/1.73 m^2) in the Taiwan cohort and, most notably, higher rates of cirrhosis (about 48%) as well as HCC (about 11%) in the Taiwan and Hong Kong cohorts ($p < 0.001$) (Supplemental Table 1).

Regarding HCV GT distribution, patients from Taiwan had the highest proportion of HCV GT-1 (78.6%), with 71.9% in Japan, and 63.7% in Korea, whereas patients from Korea had the highest proportion of HCV GT-2 compared to other regions (35.5%), with 28.9% in Japan, and 18.9% in Taiwan. In Hong Kong, the most common HCV genotype was HCV-1 (55.8%), followed by HCV-6 (32.6%). HCV GT-2 accounted for only 7% ($n = 3$) of the Hong Kong cohort, but the sample size of patients from Hong Kong was very small ($n = 43$) (Supplemental Table 1).

Overall response to therapy

The overall SVR12 rate was 96.4% (95% CI 95.9%–96.9%) among the 5800 patients without HCC who had SVR12 data (SVR12 data were not available in 5 patients). The SVR12 rates were 97.6% (97.0%–98.1%) for treatment-naive non-cirrhotic patients, 96.7% (95.3%–97.7%) for treatment-naïve cirrhotics, 96.7% (95.6%–97.6%) for treatment-experienced non-cirrhotics, and 89.8% (87.1%–92.1%) for treatment-experienced cirrhotic patients (Supplemental Fig. 1A).

By HCV genotype and treatment regimen, the SVR12 rate was 98.3% (97.7%–98.8%) for HCV GT-1 patients treated with LDV/SOF ± RBV, 93.2% (91.6%–94.5%) for DCV/ASV, and 94.9% (92.4%–96.8%) for PrOD + RBV (Supplemental Fig. 1B). Among HCV GT-1 patients treated with LDV/SOF ± RBV, 128 had cirrhosis (109 Child–Pugh class A and 19 class B). The SVR12 rate was significantly higher in Child–Pugh A compared to Child–Pugh B patients (100% vs. 89.5%, $p = 0.001$) and appeared consistent in both

Table 1 Patient characteristics and direct-acting antiviral (DAA) regimens by regions

	All patients ($n=6287$)	Japan ($n=4552$)	All non-Japan ($n=1735$)[a]	p value
Age (year)	64.9 ± 12.4	66.3 ± 12.4	61.5 ± 11.9	< 0.0001
Age > 65 years	3427 (54.5)	2749 (60.4)	678 (39.1)	< 0.001
Male	2741 (43.6)	1996 (43.9)	745 (43.6)	0.69
Body mass index (kg/m^2) (n=5454, 3920, 1534)	23.4 ± 3.7	22.9 ± 3.6	24.6 ± 3.9	< 0.0001
Comorbidity				
Diabetes (n=5033, 3664, 1369)	920 (18.3)	611 (16.7)	309 (22.6)	< 0.001
Renal function				
Creatinine > 1.5 (n=6059, 4356, 1703)	177 (2.9)	91 (2.1)	86 (5.1)	< 0.001
eGFR < 60 (n=6021, 4356, 1665)	545 (9.1)	260 (6.0)	285 (17.1)	< 0.001
eGFR < 30 (n=6021, 4356, 1665)	139 (2.3)	74 (1.7)	65 (3.9)	< 0.001
History of non-liver cancer (n=2865, 1506, 1359)	251 (8.8)	183 (12.2)	68 (5.0)	< 0.001
Breast cancer	17 (0.6)	12 (0.8)	5 (0.4)	
Colorectal cancer	18 (0.6)	13 (0.9)	5 (0.4)	
Gastric cancer	16 (0.6)	12 (0.8)	4 (0.3)	
Lung cancer	6 (0.2)	3 (0.2)	3 (0.2)	
Prostate cancer	9 (0.3)	4 (0.3)	5 (0.4)	
Thyroid cancer	9 (0.3)	1 (0.1)	8 (0.6)	
Cervical cancer	7 (0.2)	2 (0.1)	5 (0.4)	
Uterine cancer	7 (0.2)	5 (0.3)	2 (0.2)	
Lymphoma	6 (0.2)	2 (0.1)	4 (0.3)	
Other/unknown	156 (5.5)	129 (8.6)	27 (2.0)	
Virology, n (%)				< 0.001
Genotype (GT) 1 total	4138 (71.8)	3274 (71.9)	1241 (71.5)	
GT1 untyped	312 (5.0)	307 (6.7)	5 (0.3)	
GT1a	89 (1.4)	18 (0.4)	71 (4.1)	
G1b	4100 (65.2)	2949 (64.8)	1151 (66.3)	
G1a + 1b	14 (0.2)	0 (0)	14 (0.8)	
G2	1710 (27.2)	1268 (28.9)	442 (25.5)	
G3	8 (0.1)	0 (0)	8 (0.5)	
G4	3 (0.05)	2 (0.04)	1 (0.1)	
G6	38 (0.6)	0 (0)	38 (2.2)	
Mixed GTs 1 + 2	8 (0.1)	3 (0.1)	5 (0.3)	
Unclassified	5 (0.1)	5 (0.1)	0 (0)	
HCV RNA, log IU/mL	5.9 ± 0.9	5.9 ± 0.8	5.9 ± 1.0	0.03
HCV RNA > 80,000 IU/mL	5467 (87.2)	4007 (88.2)	1460 (84.7)	< 0.001
HCV RNA > 6,000,000 IU/mL	722 (11.5)	501 (11.0)	221 (12.8)	0.05
Liver-related disease				
Liver cirrhosis (n=6285, 4550, 1735)	1913 (30.4)	1223 (26.9)	690 (39.8)	< 0.001
Child–Turcotte–Pugh class (n=946, 342, 604)				0.20
Compensated-Child A	881 (93.1)	324 (94.7)	557 (92.2)	
Decompensation	65 (6.9)	18 (5.3)	47 (7.8)	
Child B	62 (6.6)	18 (5.3)	44 (7.3)	
Child C	3 (0.3)	0 (0)	3 (0.5)	
Prior HCC	482 (7.7)	343 (7.5)	139 (8.0)	0.53
Treatment history (n=6263, 4552, 1711)				< 0.001
Naive	4212 (67.3)	3059 (67.2)	1153 (67.4)	
Experience	2051 (32.8)	1493 (32.8)	558 (32.6)	
IFN-based/no DAA	1781 (28.4)	1241 (27.3)	540 (31.6)	
DAA with PEG IFN/RBV				

Table 1 (continued)

	All patients ($n=6287$)	Japan ($n=4552$)	All non-Japan ($n=1735$)[a]	p value
BOC/TVR	21 (0.3)	19 (0.4)	2 (0.1)	
SMV	131 (2.1)	131 (2.9)	0	
IFN-free DAA				
DCV + ASV only	45 (0.7)	44 (1.0)	1 (0.1)	
Other DAA regimen	17 (0.3)	11 (0.2)	6 (0.4)	
Multiple prior DAA courses	24 (0.4)	24 (0.5)	0	
Unknown treatment type	32 (0.5)	23 (0.5)	9 (0.5)	
Current DAA regimen				< 0.001
SOF + RBV	1583 (25.2)	1240 (27.2)	343 (19.8)	
LDV/SOF + RBV	2435 (38.7)	2206 (48.5)	229 (13.2)	
PrOD + RBV	496 (7.9)	12 (0.3)	484 (27.9)	
DCV + ASV	1397 (22.2)	908 (20.0)	489 (28.2)	
EBR/GZR	75 (1.2)	40 (0.9)	35 (2.0)	
GLE/PIB	12 (0.2)	0 (0)	12 (0.7)	
SOF/VEL	3 (0.1)	0 (0)	3 (0.2)	
SOF + DCV	111 (1.8)	0 (0)	111 (6.4)	
Others	175 (2.8)	146 (3.2)	29 (1.7)	

Values expressed as mean ± standard deviation or sample size and proportion (%)

eGFR estimated glomerular filtration rate (mL/min/1.73 m^2), *HCC* hepatocellular carcinoma, *BOC* boceprevir, *TVR* telaprevir, *SMV* simeprevir, *PrOD* paritaprevir/ritonavir/ombitasvir/dasabuvir, *DCV* daclatasvir, *ASV* asunaprevir, *SOF* sofosbuvir, *LDV* ledipasvir, *EBR* elbasvir, *GZR* grazoprevir, *GLE* glecaprevir, *PIB* pibrentasvir, *VEL* velpatasvir

[a]All Non-Japan regions include S. Korea, Taiwan, and Hong Kong

treatment-naïve (100% [67/67] vs. 83.3% [5/6], $p=0.001$) and treatment-experienced patients (100% [42/42] vs. 92.3% [12/13], $p=0.07$), though the difference between the Child–Pugh classes among treatment-experienced patients was less pronounced and did not reach conventional level of statistical significance. For HCV GT-2 patients, the SVR12 was 96.3% (95.2%–97.2%) for SOF/RBV and 98.6% (92.6%–99.9%) for SOF/DCV + RBV.

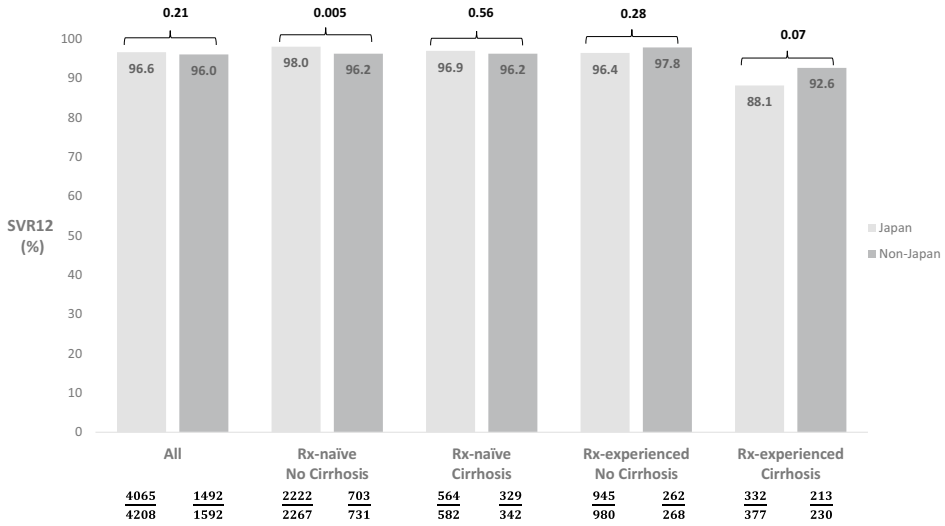
Of the patients who failed DAA therapy ($n=208$), 71.2% had HCV GT-1 and 28.4% had HCV GT-2 infection (one patient [0.5%] had mixed infection with HCV GTs 1 and 3). The majority of treatment failure were due to relapse (58.7%, $n=122$), followed by on-treatment virological breakthrough (28.4%, $n=59$) with only a small percentage of patients with primary nonresponse (4.8%, $n=10$) or early treatment termination due to various reasons (8.2%, $n=17$).

Response to treatment by country/region

The largest group in the study was from Japan. Therefore, our primary analyses were performed comparing patients from Japan to those not from Japan. Figure 1 displays the SVR12 rates comparing the rates for patients from Japan vs. non-Japan regions. Overall, there was no significant difference in SVR12 rates for those from Japan (96.6%) and not from Japan (96.0%, $p=0.21$). However, for those who were treatment-naïve without cirrhosis, patients from Japan had a higher SVR12 rate compared to those not from Japan (SVR12: 98.0% vs. 96.2%, $p=0.005$). There were no significant differences in SVR12 rates for those from Japan and those not from Japan for the treatment-naïve with cirrhosis population (SVR 12: 96.9% vs 96.2%, $p=0.56$), treatment-experienced without cirrhosis (SVR-12 96.4% vs 97.8%, $p=0.28$), or treatment-experienced with cirrhosis (SVR-12 88.1% vs 92.6%, $p=0.07$) (Fig. 1).

We further explored the treatment effectiveness of different regimens according to patients' prior treatment experience and cirrhosis status. As shown in Fig. 2a, the SVR12 rate was > 90% (91.1–99.4%) among all subgroups except the treatment-experienced cirrhotic HCV GT-1 patients who received DCV/ASV (85.9%, $n=158/184$), and the treatment-experienced cirrhotic HCV GT-2 patients who received SOF/RBV (87.0%, $n=80/92$).

Overall, treatment was well tolerated and appeared similar by region and country. Only 1.9% ($n=109$) of the overall cohort had to stop treatment early, which was also similar by country. The majority of the reasons for early termination of DAA treatment appeared to be unrelated to treatment or liver disease. For those who received RBV, the prevalence of severe anemia overall was only 0.8% ($n=10$) among those receiving RBV-containing regimens (Table 2 and Supplemental Table 2).



*All SVR analyses were performed in non-HCC patients only.

Fig. 1 Treatment responses stratified by cirrhosis, prior treatment, and patients from Japan and patients from non-Japanese regions. Asterisk indicates all SVR analyses were performed in non-HCC patients only

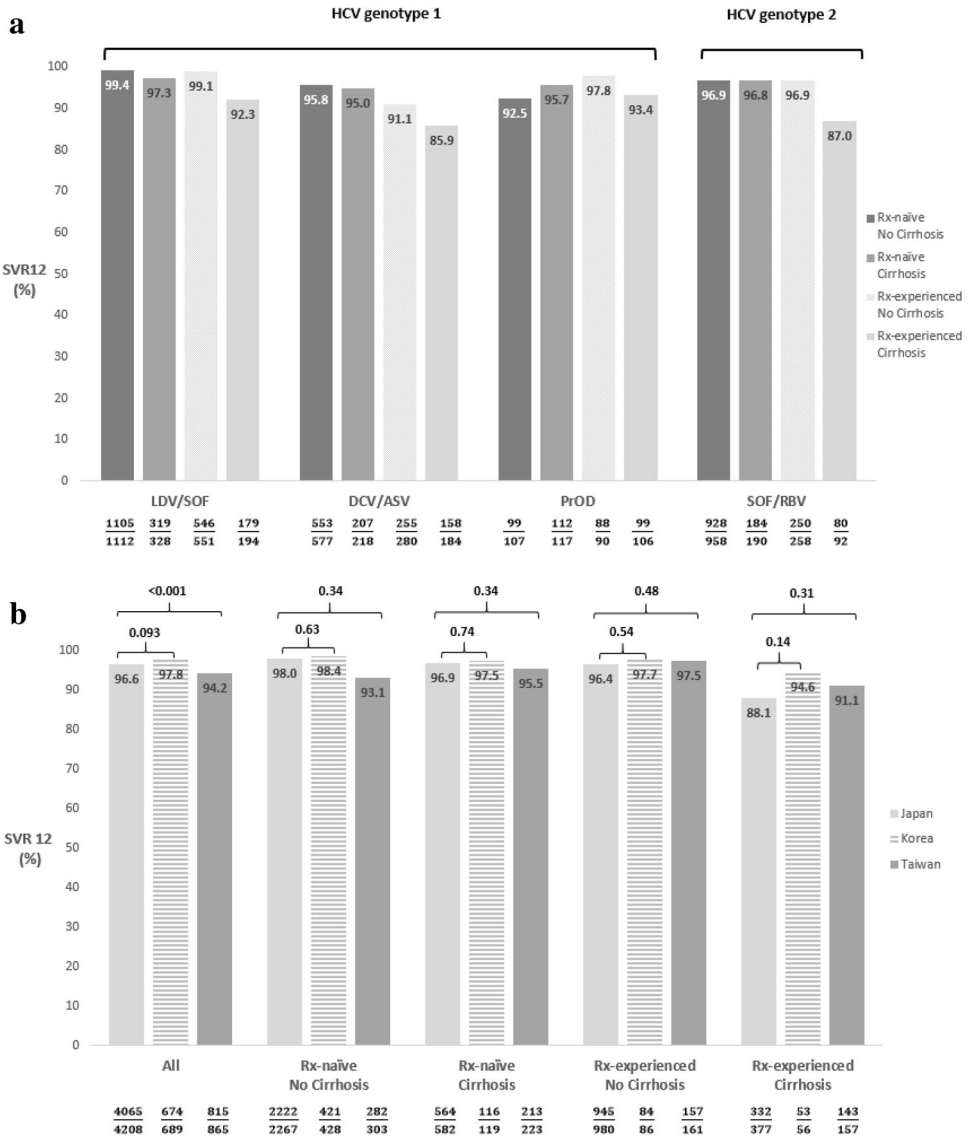


Fig. 2 **a** Treatment responses stratified by genotype, treatment regimen, prior treatment experience, and cirrhosis status. **b** Treatment response stratified by cirrhosis, prior treatment experience, and country. *PrOD* paritaprevir/ritonavir/ombitasvir/dasabuvir, *DCV* daclatasvir, *ASV* asunaprevir, *SOF* sofosbuvir, *LDV* ledipasvir. All the regimens were with or without ribavirin combination except DCV/ASV. Asterisk indicates that all SVR analyses were performed in non-HCC patients only. No analyses were performed for Hong Kong due to small sample size

Table 2 Treatment tolerability by regions

	All patients ($n=6287$)	Japan ($n=4552$)	All non-Japan ($n=1735$)[a]
Anemia[†] (n=3904, 2904, 1000)	1222 (31.3)	901 (31.0)	321 (32.1)
RBV-containing regimens (n=1253, 968, 285)			
Mild	412 (32.9)	332 (34.3)	80 (28.1)
Moderate	318 (25.4)	225 (23.2)	93 (32.6)
Severe	10 (0.8)	5 (0.5)	5 (1.8)
Early treatment discontinuation rates (n=5800, 1592, 1592)	109 (1.9)	76 (1.8)	33 (2.1)
Reason for early discontinuation			
Patient refusal	7 (0.1)	4 (0.1)	3 (0.2)
Non-compliance	8 (0.1)	0 (0.1)	8 (0.5)
Anemia	7 (0.1)	5 (0.1)	2 (0.1)
Psychological side effects[b]	2 (0.03)	0	2 (0.1)
Other[+]	85 (1.5)	67 (1.6)	18 (1.1)

Values expressed as sample size and proportion (%)

[a]All Non-Japan regions include S. Korea, Taiwan, and Hong Kong

[b]Psychological side effects: suicidal ideology, depression, sleep disturbances, etc

[†]WHO definition: hemoglobin levels < 12.0 g/dL in women and < 13.0 g/dL in men (mild anemia: hemoglobin levels > 11.0 g/dL. Moderate anemia: hemoglobin levels 8.0-11.0 g/dL. Severe anemia: hemoglobin levels < 8.0 g/dL)

[+]Other: hepatic injury, viral breakthrough, other extrahepatic disease (rash, cerebral hemorrhage, pneumonia, hyperamylasemia, aortic dissection, rheumatoid arthritis, kidney dysfunction, urosepsis, gastric ulcer bleeding, mediastinal tumor, and gastric cancer), death

As shown in Fig. 2a (data combined for all genotypes and DAA regimens), the SVR12 rates were > 90% (94.2%–97.8%) overall in all regions. The SVR rates were also over 90% for all subgroups by prior treatment experience and cirrhosis status for all regions except the treatment-experienced cirrhotic subgroup from Japan (88.1%). Of note, subanalysis was not performed for patients from Hong Kong due to the small sample size for this region ($n=43$).

Figure 3a–d describes SVR12 rates for HCV GT-1 patients from Japan vs. non-Japan regions by treatment regimens with further stratification by prior treatment experience and cirrhosis status. For the LDV/SOF ± RBV group, SVR12 rates were slightly lower in patients from outside Japan, and the difference was statistically significant. We observed this mainly in the treatment-naïve non-cirrhotic subgroups ($p=0.001$), but the rates were overall high, ranging 95–99% (Fig. 3a). Similar findings were found but in the reverse direction, with patients from Japan having lower SVR12 for the DCV/ASV cohort, particularly in the treatment-experienced cirrhotic subpopulation (81.8% vs. 94.7%, $p=0.02$) (Fig. 3c). SVR12 rates were similar in all subgroups between those from Japan and those not from Japan for PrOD ± RBV and SOF/RBV regimens (Fig. 3b, d).

In our subanalysis stratified by age (< 65 vs ≥ 65), HCV genotype, and DAA treatment regimen (Supplemental Fig. 2A), there was no significant difference among treatments and age groups with HCV GT1. However, in the HCV GT 2 group, those 65 years and older had a significantly lower SVR12 compared to those younger than 65 (94.9% vs 97.2%, $p=0.02$) (Supplemental Fig. 2A).

In our next subanalysis stratified by non-liver cancer status, HCV genotype, and DAA treatment, there were no significant differences between all groups (Supplemental Fig. 2B).

Our final subanalysis data, shown in Supplemental Tables 3 and 4, were differentiated by renal function. There were no significant differences in SVR 12 rates across renal function status and country/region, with SVR 12 rates ranging about 95–99% across subgroups (Supplemental Table 3). Treatment was also well tolerated, with early discontinuation ranging from 1.6 to 3.2% among all subgroups. Among the group with eGFR < 30 ml/min/1.73 m^2 ($n=127$, Supplemental Table 4), about half were treated with DCV/ASV (54.3%) and about one-quarter were treated with PrOD + RBV (24.4%). The most common adverse events were fatigue (11.5%), followed by insomnia (10.3%) and pruritus (10.1%). Two patients had decompensated liver cirrhosis (one treated with PrOD + RBV and one with LDV/SOF + RBV), and both completed the full treatment course without any serious adverse event.

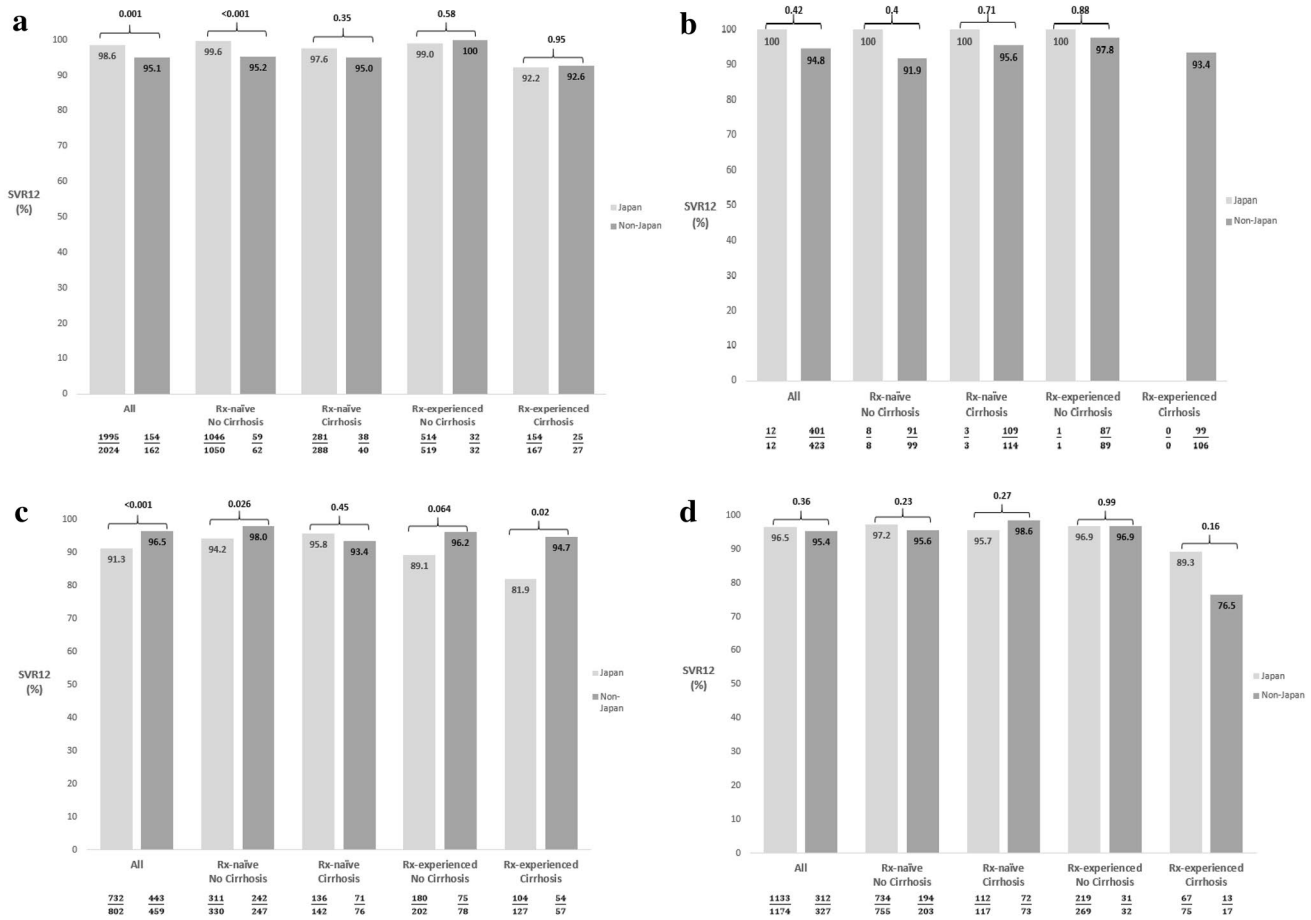


Fig. 3 **a** Treatment response HCV genotype 1 patients treated with LDV/SOF (ledipasvir/sofosbuvir) stratified by cirrhosis, prior treatment experience, and patients from Japan versus patients from non-Japan regions. **b** Treatment responses by HCV genotype 1 patients treated with PrOD (paritaprevir/ritonavir/ombitasvir/dasabuvir) stratified by cirrhosis, prior treatment experience, and patients from Japan versus patients from non-Japan regions. **c** Treatment responses by HCV genotype 1 patients treated with DCV/ASV (daclatasvir/asunaprevir) stratified by cirrhosis, prior treatment experience, and patients from Japan versus patients from non-Japan regions. **d** Treatment responses by HCV genotype 2 patients treated with SOF/RBV (sofosbuvir/ribavirin) stratified by cirrhosis, prior treatment experience, and patients from Japan versus patients from non-Japan regions. *SVR* sustained virological response. Asterisk indicates that all SVR analyses were done in non-HCC patients only

Predictors for SVR12

As displayed in Table 3 and per univariate analysis, patients with older age, baseline cirrhosis, higher baseline HCV RNA levels, lower albumin levels, lower platelet counts, prior treatment with IFN and DAAs other than boceprevir (BOC) and telaprevir (TVR), as well as not receiving LDV/SOF ± RBV or receiving ASV/DCV, were less likely to attain SVR12. On multivariate logistic regression, significant independent factors predictive of treatment failure were higher HCV RNA levels [odds ratio (OR), 95% CI 0.73, 0.59–0.90; $p = 0.004$], the presence of liver cirrhosis (0.68, 0.49–0.84, $p = 0.046$), prior treatment failure with IFN (0.57, 0.42-0.79, $p = 0.001$), and prior treatment failure with DAA other than BOC and TVR (0.04, 0.02–0.08, $p < 0.001$), but not geographic region (non-Japan versus Japan, 1.09, 0.74–1.60, $p = 0.68$). This model displayed a good fit with a Hosmer–Lemeshow p value of 0.84 and AUROC of 0.76. The E values for adjusted ORs for the observed significant associations were also acceptable (1.7 for cirrhosis, 1.6 for HCV RNA, 2.0 for albumin, 2.0 for prior IFN experience, and 9.8 for prior DAA other than BOC and TVR), indicating that in the current multivariable model, an unmeasured confounder would be unlikely, as the unmeasured confounder effect size (OR) would need to be at least the E values for factors of interest and SVR to fully explain any observed association between the factor and SVR.

Table 3 Factors associated with SVR12 (sustained virologic response at 12 weeks after treatment completion)

	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Age (years)	0.99 (0.98–0.999)	0.038	0.99 (0.97–1.002)	0.11
Male	1.26 (0.95–1.67)	0.12	1.16 (0.85–1.59)	0.34
Baseline cirrhosis	0.43 (0.33–0.57)	< 0.001	**0.68 (0.47–0.993)**	**0.046**
Baseline HCV RNA (log IU/mL)	0.80 (0.67–0.96)	0.018	**0.73 (0.59–0.90)**	**0.004**
Baseline total bilirubin (mg/dL)	0.88 (0.75–1.02)	0.089	0.88 (0.70–1.10)	0.25
Baseline albumin (g/dL)	1.89 (1.41–2.53)	< 0.001	**1.75 (1.24–2.47)**	**0.002**
Platelet count (10^3/μL)	1.01 (1.003–1.008)	< 0.001	1.002 (0.999–1.005)	0.21
Region				
Japan	Referent		Referent	
Non-Japan	0.83 (0.61–1.11)	0.21	1.09 (0.74–1.60)	0.68
Genotype				
1	Referent		Referent	
Non-1	1.01 (0.74–1.38)	0.94	0.85 (0.17–4.27)	0.85
Prior treatment				
Treatment-naïve	Referent		Referent	
IFN	0.52 (0.39–0.70)	< 0.001	**0.57 (0.42–0.79)**	**0.001**
DAA other than BOC and TVR	0.10 (0.056–0.18)	< 0.001	**0.04 (0.02–0.08)**	**< 0.001**
Unknown prior treatment type	0.74 (0.099–5.46)	0.76	0.62 (0.08–4.75)	0.65
Treatment regimen				
SOF + RBV	Referent		Referent	
LDV/SOF	2.25 (1.48–3.41)	< 0.001	3.85 (0.73–20.4)	0.11
2D or 3D	0.90 (0.55–1.46)	0.67	0.94 (0.18–4.87)	0.94
ASV + DCV	0.52 (0.37–0.73)	< 0.001	0.57 (0.11–2.96)	0.51
Other	3.88 (0.94–16.0)	0.06	12.5 (1.13–137.4)	0.04

Hosmer–Lemeshow *p* value: 0.5239. No collinearity found. All SVR analyses were done in non-HCC patients only

ALT alanine transaminase, *OR* odds ratio, *CI* confidence intervals, *SOF* sofosbuvir, *RBV* ribavirin, *LDV* ledipasvir, *2D* ombitasvir/paritaprevir/ritonavir, 3D ombitasvir/paritaprevir/ritonavir + dasabuvir, *ASV* asunaprevir, *DCV* daclatasvir

Discussion

In the current cohort of CHC patients from four countries/regions of East Asia, we identified several differences in the demographic and clinical characteristics of CHC patients who were treated with eight major interferon-free DAAs (± RBV). Despite these differences, DAA therapy was well tolerated and equally effective overall with a high SVR 12 rate of 96.4% and was consistently greater than 90% for all groups despite prior treatment failure history and cirrhosis status except for those with prior treatment failure experience and cirrhosis who experienced an SVR12 rate of 89.8% These data suggest that CHC patients in these East Asian countries/regions who receive the all-oral DAAs can expect a high cure rate regardless of treatment received. Such findings can help decision-makers when reviewing their HCV treatment policies.

As noted, this study reinforced the effectiveness of DAA in several subpopulations, such as patients with old age, non-liver malignancy, and renal insufficiency with data similarly favorable as previously reported in prior Western real-world studies [20]. Therefore, we suggest that HCV eradication with DAA therapy should not be withheld in these populations as all had excellent results.

In the current study, we also observed several notable differences in the demographic and clinical characteristics of patients in major regions of East Asia. Some of these differences may be related to local epidemiology, practice, and reimbursement policy as also noted by Lim et al. in their recent study on management of hepatitis C virus infection in several areas of South and Southeast Asia [4]. Notably, only about one-fourth of our Japan cohort (26.9%) had cirrhosis compared to 28.5% of the cohort from South Korea to almost one-half of the cohorts from Taiwan (47.7%) and Hong Kong (48.8%), a disparity that is most likely due to more restrictive reimbursement policy for DAA therapy in areas outside of Japan, especially in the earlier years when only patients with cirrhosis or advanced fibrosis could receive reimbursement for DAA therapy. Despite these differences, the SVR rates were consistently high and not different throughout East Asian countries/regions included in this study, except for a few caveats that are important to mention.

The first caveat is that patients who were HCV GT-2, treatment-experienced with cirrhosis and treated with SOF/RBV had a significantly lower SVR than all others. This is important, as SOF/RBV remains one of the recommended options for HCV GT-2 infection in the regional guideline [21]. Consequently, further study may be warranted to determine whether these guidelines need to be modified to better address treatment for those who are treatment-experienced and have cirrhosis, especially as the more recent American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) no longer recommend SOF/RBV as first-line therapy for HCV GT-2, due to the recent availability of more potent DAAs.

Second, as with HCV GT-2, we found that in HCV GT-1 patients who were treatment-experienced with cirrhosis and were treated with DCV/ASV, SVR12 results were significantly lower. In fact, when we examined SVR12 rates by treatment regimen, as well as those from Japan compared to those not from Japan, we found that those from Japan who received DCV/ASV had a significantly lower SVR12 than those not from Japan. This finding appears to be driven by those from Japan who were treatment-experienced whether they had cirrhosis or not, and this may be the result of the inclusion of patients with baseline non-structural 3 or 5A resistance-associated substitutions due to lack of pre-treatment testing prior to the administration for DCV/ASV in routine practice in the early years of the DAA era in Japan.

Ideally, patients without advanced liver disease should be treated to prevent disease progression, and all CHC patients should be treated to accomplish the goal of HCV elimination [22, 23]. The current survey emphasizes the gap between the need for treatment and treatment availability in the real-world setting; as those with cirrhosis universally experienced lower SVR12 rates, which was confirmed in our prediction models for failure to obtain SVR. Patients with cirrhosis had a 32% lower chance of obtaining SVR compared to those that did not have cirrhosis. Such findings suggest that if non-cirrhotic patients were treated to prevent cirrhosis, the SVR12 outcomes may improve, helping to achieve the WHO goal of viral hepatitis elimination by 2030. Furthermore, among the HCV GT-1 cirrhotic patients treated with LDV/SOF ± RBV, we also found that both treatment-naïve and treatment-experienced Child–Pugh A cirrhosis had higher SVR12 rates than those with Child–Pugh B cirrhosis, though additional studies with more Child–Pugh B patients are needed.

Our study observations were similar to prior reports in Western treatment-experienced cirrhotic HCV GT-2 patients [24, 25], but different from findings from a clinical trial of real-world data in Asia. It should be noted that previous Asian studies had either small sample sizes or a requirement for the extended 16-week regimen, which might have contributed to differences between our study results [26, 27].

The current study was limited to regional areas with selected HCV genotypes in East Asia, so these findings should not be generalized to the whole Asian population, such as HCV genotypes 3, 4, and 6 patients in South, Southeast and Southwest Asia [4]. In addition, though the study included several centers in the various regions of South Korea, Taiwan, Hong Kong, and Japan, the study is not a population-based registry, so the data may not be generalizable to all areas of each of these countries/regions. However, this is the first and largest multinational cohort that may have avoided the pitfall of previously non-registered, single-center, or single-country-based studies in East Asia. In addition, regarding the safety of the DAAs, we were only able to provide anemia and discontinuation rates as they can be assessed objectively and retrospectively which is true for the vast majority of real-world retrospective studies.

In conclusion, despite several regional differences in patient demographics, liver and non-liver disease severity, and highly different DAA reimbursement policy and usage, DAAs were highly effective and well tolerated in our large and diverse East Asian CHC cohort, including patients with advanced age, poor renal function, and those with a history of non-liver malignancy. Our study findings could assist policy makers in modifying DAA recommendations as these newer drugs become more accessible and less expensive in Asia. The future direction of this REAL-C study will include additional patient and genotype diversity, with patient enrollment from mainland China and long-term follow-up of all registered patients.

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Compliance with ethical standards

Conflict of interest HT: Speaker for AbbVie and MSD. YCH: Research support from Gilead; advisory board for Gilead; speaker for Abbvie, BMS, Gilead, and Merck Sharp & Dohme. GW: Research support from Gilead; advisory board/consulting for Gilead; speaker for Abbott, Abbvie, BMS, Echosens, Furui, and Gilead. CHL: Research support from Abbvie, Gilead, and MSD; advisory board/consulting for Abbvie, Gilead, and MSD; speaker for Abbvie, Gilead, MSD, and Abbott. WLC: Advisory board for Gilead, Abbvie, MSD, BMS, PharmaEssentia. RC: Research support from Gilead. CYD: Advisory board for Abbvie; speaker for Abbvie, Merck, and Gilead. JHK: Research support from Gilead and BMS; advisory board/consulting for Gilead, Abbvie, BMS, and MSD; speaker for Gilead, Abbvie, MSD, and BMS. YU: Research support from Abbvie, Gilead, and Bayer. NF: Research support from Janssen Pharmaceutical K.K., Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Abbvie GK; speaker for Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Torii Pharmaceutical Co., Ltd. and Roche Diagnostics K.K. MLY: Research support: Abbvie, BMS, Gilead, Torpedo and Merck; consultant for Abbvie, Abbott, Ascletis, BMS, Gilead, Merck, and PharmaEssentia; speaker for Abbvie, Abbott, Ascletis, BMS, Gilead, and Merck. YT: Research support from Chugai Pharmaceutical, Janssen, and the Japan Agency for Medical Research and Development (AMED); honoraria from Gilead. MHN: Research support from Janssen, Pfizer, Gilead, National Cancer Institute; BK Kee Foundation; advisory board/consulting for Novartis, Gilead, Janssen, Bayer, Eisai, Exact Sciences, Laboratory of Advanced Medicine. All other authors have no relevant conflict of interests to disclose.

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