Sustained virological response rates with direct-acting antivirals in black subjects with HCV genotype 1 infection: systematic analysis of clinical trials

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Abstract

Objectives: Under representation of black subjects in trials of hepatitis C virus (HCV) direct-acting antivirals (DAAs) complicates assessment of differential outcomes for black individuals *vs* non-black individuals. HCV trials submitted to the Food and Drug Administration (2013–2017) to support approval or to expand an indication of 12-week interferon-free DAA regimens with or without ribavirin to treat HCV genotype 1 (GT1) infection were pooled to explore efficacy comparisons by ethnicity.

Methods: Twenty-six trials were pooled and included 2869 individuals with HCV GT1 alone and 742 individuals with both HCV GT1 and HIV.

Results: Of the 2869 HCV GT1-mono-infected subjects, 408 (14.2%) were black. Sustained virological response assessed 12 weeks following cessation of treatment (SVR12) was 92%–100% in black individuals and 87.5%–100.0% in non-black individuals. In pooled analyses, SVR12 was numerically similar between black and non-black subjects (97.1% *vs* 97.3%). Baseline characteristics did not affect SVR12 for the two groups. Of the 742 subjects with both HCV GT1 and HIV, 243 (32.7%) were black: SVR12 was 89.5%–100% in black individuals and 94.4%–100% in non-black individuals. In pooled analyses for HCV GT1/HIV co-infection, black individuals had a 4% (95% confidence interval −7.7% to 0.3%) lower SVR12 than non-black individuals (93.4% *vs* 97.0%). This difference was driven by ION-4 in which study SVR12 was approximately 10% lower for black than for non-black individuals (89.5% *vs* 99.1%). Baseline characteristics did not affect SVR12 for the two groups.

Conclusion: No notable SVR12 differences were seen in between black and non-black individuals with HCV GT1 alone. Although a numerical difference was observed between black and non-black individuals with both HCV GT1 and HIV, this finding was driven by results from a single trial and may be due to reasons other than ethnicity: 19 subgroup analyses showed baseline characteristics did not affect SVR12 for black and non-black individuals with both HCV GT1 and HIV.

Keywords: hepatitis C, clinical trial, Food and Drug Administration

Introduction

Chronic hepatitis C virus (HCV) infection is a serious and life-threatening condition that can lead to cirrhosis and hepatocellular carcinoma, and affects approximately 71 million people worldwide and approximately 3.5 million people in the USA [1–4]. Black subjects are disproportionately affected by HCV [2]. In the USA, approximately 23% of the population with HCV infection are black [2,3]. Additionally, co-infection with HCV and HIV is common in the USA. Of the estimated 1.2 million individuals living with HIV in the USA, about a quarter (approximately 300,000) are also infected with HCV [3].

Recent studies have shown that achievement of sustained virological response (SVR) is associated with halting the progression of liver disease and decreasing chronic hepatitis C-related complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma and liver-related mortality [5,6].

Black subjects are often under represented in clinical trials of HCV direct-acting antivirals (DAAs), resulting in small sample sizes for the subset of black subjects [7]. This makes the assessment of differential outcomes for black *vs* non-black subjects challenging.

In the interferon (IFN) era, SVR rates were lower among black subjects and likely to be due to the high prevalence of interleukin (IL)-28B CT/TT genotype in black individuals. This genotype is associated with a reduced response to IFN [8,9]. Also IFN-based regimens, including those using the DAA protease inhibitors telaprevir and boceprevir, resulted in lower SVR rates among black subjects even when controlling for IL-28B status [10,11]. DAAs are safer, better tolerated and more effective than IFN-based regimens. If IL-28B genotype status was the main predictor of decreased SVR rates among black individuals, then ethnicity differences with non-IFN DAA regimens may not be apparent. However, the Food and Drug Administration (FDA) noted differences in SVR rates during the review of the ION-4 trial in which SVR rates were lower in black than in non-black individuals with both HCV genotype 1 (GT1) and HIV receiving ledipasvir/sofosbuvir (LDV/SOF) for 12 weeks. Some cohort analyses have found comparable SVR rates between black and non-black subjects, whereas other cohort analyses have found lower SVR rates in black compared with non-black subjects [12–27]. These observations focused on specific regimens, and not all FDA-approved 12-week products for the treatment of HCV GT1 were included. This has prompted the US FDA to pool data from clinical trials approved for 12-week IFN-free DAA regimens for the treatment of HCV GT1 infection to assess if SVR rates differed between

black and non-black individuals with HCV GT1 alone and with both HCV GT1 and HIV [27–34].

Methods

Definitions

Treatment outcomes were defined as described in current FDA guidance for HCV DAA development [35]. Antiviral treatment efficacy referred to sustained virological response assessed 12 weeks following cessation of treatment (SVR12). On-treatment virological failure was defined as HCV RNA ≥ lower limit of quantification (LLOQ) at the end of treatment (e.g. virological breakthrough or non-response). Virological relapse was defined as HCV RNA <LLOQ at the end of treatment but HCV RNA quantifiable (≥LLOQ) during follow-up. Non-virological failure referred to subjects who did not achieve SVR and did not meet any virological failure criteria (e.g. discontinued due to adverse event, lost to follow-up or subject withdrawal). The assays used to assess SVR included COBAS TaqMan HCV test (version 2.0, Roche, Branchburg, USA) for use with the High Pure System, COBAS AmpliPrep/COBAS TaqMan HCV test (version 2.0, Roche, Branchburg, USA).

Clinical trials

HCV trials to support approval or to expand an indication of 12-week IFN-free DAA regimens with or without ribavirin (RBV) in the treatment of HCV GT1 infection submitted to the FDA between 2013 and 2017 were pooled (Supplemental Table S1). The intent of these analyses was to explore efficacy comparisons by ethnicity, not to compare SVR across different regimens.

Data analyses included trials of daclatasvir (DCV), elbasvir (EBR)/grazoprevir (GZR), LDV/SOF, glecaprevir (GLE)/pibrentasvir (PIB), ombitasvir/paritaprevir/ritonavir plus dasabuvir (OBV/PTV-r+DSV, OPrD), simeprevir (SMV), SOF/velpatasvir (VEL) and SOF/VEL/voxilaprevir (VOX).

Study determinants

The following determinants were evaluated: age, gender, ethnicity (black *vs* non-black ethnicity), body mass index (BMI), country (USA *vs* non-USA), cirrhosis, treatment experience, baseline HCV RNA, IL-28B genotype and HIV-1 status. In our analyses, we do not make the assumption that black subjects in non-US sites are genetically similar to black subjects in the USA.

Statistical analysis

Descriptive statistics including the point estimate and corresponding exact confidence intervals (CIs) based on inverting a two-sided test for difference in SVR12 rates between black and non-black subjects are presented in each study; the overall subjects with HCV GT1 alone and both HCV GT1 and HIV and subgroups defined by baseline characteristics include age, gender, country, BMI, cirrhotic status, GT1 subtype, HCV treatment history, baseline HCV RNA and IL-28B status.

There were 19 subgroup analyses conducted in those with HCV GT1 alone and those with both HCV GT1 and HIV, respectively. Although the analyses were exploratory, Bonferroni's method was used to address multiple comparisons.

Results

Demographics and baseline characteristics

Overall, 26 clinical trials (20 trials with subjects with HCV GT1 alone, five trials with subjects with both HCV GT1 and HIV and

one trial with both mono-infected and co-infected subjects) were pooled and included 2869 indivudals with HCV GT1 alone and 742 individuals with both HCV GT1 and HIV. Eleven trials enrolled both treatment-naive (TN) and treatment-experienced (TE) subjects; the remaining 15 trials were conducted in either TN subjects only (*n*=7) or TE subjects only (*n*=8). Only five trials (19%) included the use of RBV. All FDA-approved 12-week IFN-free DAA regimens were represented in this analysis, and most subjects received an OPrD-based regimen (27%), an LDV/SOF-based regimen (25%) or an EBR/GZR-based regimen (20%).

Table 1 summarises the overall baseline characteristics by ethnicity for the 12-week regimens for both individuals with HCV GT1alone and both HCV GT1 and HIV. Most subjects included in our analyses were male (65%), and 18% were black. A higher proportion of black subjects with HCV GT1 alone or both HCV GT1 and HIV were from US sites. Additionally, fewer black subjects with both HCV GT1 and HIV compared with non-black subjects had HCV GT1a. A higher proportion of IL-28B CT/TT genotype was seen among black subjects with HCV GT1 alone and those with both HCV GT1 and HIV compared with non-black subjects. However, there were similar proportions of black and non-black subjects with cirrhosis at baseline among those with HCV GT1 alone and those with both HCV GT1 and HIV. Cirrhosis is generally considered to be the most clinically relevant baseline covariate to predict SVR12 rate even for DAA regimens.

SVR12 rates in HCV GT1-mono-infected black *vs* non-black subjects

Of the 2869 HCV GT1-mono-infected subjects, 408 (14.2%) were black. Across 21 clinical trials, SVR12 rates were between 92% and 100% in black individuals and between 87.5% and 100.0% in non-black individuals. In pooled analyses of each DAA regimen, the difference in SVR12 rates was numerically similar for black and non-black subjects (97.1% *vs* 97.3%, Figure 1). Baseline characteristics did not appear to affect SVR12 rates for the two groups (Figure 2). SVR12 rates were also numerically similar for black and non-black subjects with cirrhosis (95.2% *vs* 97.6%, Figure 2). As shown in Table 2, for mono-infected subjects, the proportions of on-treatment virological failure and relapse were similar between black and non-black subjects.

SVR12 rates in black and non-black subjects with both HCV GT1 and HIV

Of the 742 subjects with HCV GT1 and HIV, 243 (32.7%) were black. Across six clinical trials, SVR12 rates were between 89.5% and 100% in black individuals and between 94.4% and 100.0% in non-black subjects. In pooled analyses for HCV GT1/HIV co-infection, black subjects had a 4% lower SVR12 rate than non-black subjects (93.4% *vs* 97.0%, 95% CI −7.7% to −0.3%).

As illustrated in Figure 1, this difference was driven by ION-4 in which the SVR12 rate for black subjects was approximately 10% lower than that for non-blacks (89.5% *vs* 99.1%). Baseline characteristics did not appear to affect SVR12 rates for the two ethnicity groups (Figure 3). Of note, SVR12 rates were numerically higher for non-black subjects with cirrhosis (*n*=91) than for black subjects (*n*=43) (97.8% *vs* 90.7%, Figure 3). This finding is limited by the number of individuals in this subgroup. For individuals with both HCV GT1 and HIV who did not take part in ION-4, SVR12 rates for black subjects (96.9%) were numerically comparable with that of non-black subjects (95.5%). Additionally, the proportion of on-treatment virological failure was similar between black and non-black subjects (Table 2). There was a numerical difference in the proportion of black and non-black subjects who experienced virological relapse (5.3% *vs* 1.0%).

Table 1. Baseline characteristics by ethnicity (black *vs* non-black subjects) for 12-week regimens

	Mono-infection			Co-infection		
	Overall (*N*=2869)	Black (*n*=408)	Non-black (*n*=2461)	Overall (*N*=742)	Black (*n*=243)	Non-black (*n*=499)
Age (years)						
Mean (SD)	53.6 (10.7)	57.5 (7.8)	53.0 (11.0)	51.5 (8.8)	54.8 (7.9)	49.9 (8.7)
Median (Q1, Q3)	56.0 (48.0, 61.0)	59.0 (54.0, 62.0)	55.0 (47.0, 60.0)	52.0 (47, 58)	56.0 (51.0, 60.0)	51.0 (45.0, 56.0)
Male	60.5% (1737)	67.6% (408)	59.4% (1461)	84.8% (629)	75.7% (184)	89.2% (445)
USA	56.2% (1612)	94.6% (386)	49.8% (1226)	80.1% (594)	97.9% (238)	71.3% (356)
BMI (kg/m²)						
Mean (SD)	27.1 (5.0)	29.5 (4.8)	26.7 (4.9)	26.6 (4.8)	28.7 (6.0)	25.6 (3.8)
Median (Q1, Q3)	26.5 (23.6, 30.0)	28.7 (26.1, 32.6)	26.1 (23.3, 29.4)	25.9 (23.5, 28.7)	27.7 (24.6, 31.3)	25.3 (23.1, 27.7)
Cirrhosis						
Yes	16.6% (475)	15.4% (63)	16.7% (412)	18.1% (134)	17.7% (43)	18.2% (91)
No	83.3% (2391)	84.6% (345)	83.1% (2046)	81.3% (603)	80.7% (196)	81.6% (407)
Missing	0.1% (3)	0%	0.1% (3)	0.7% (5)	1.6% (4)	0.2% (1)
Subtype						
GT1a	63.4% (1820)	68.6% (280)	62.6% (1540)	77.9% (578)	70.0% (170)	81.8% (408)
GT1b	36.1% (1036)	29.9% (122)	37.1% (914)	21.8% (162)	29.6% (72)	18.0% (90)
Other*	0.5% (13)	1.5% (6)	0.3% (7)	0.3% (2)	0.4% (1)	0.2% (1)
HCV treatment experienced	34.1% (979)	37.3% (152)	33.6% (827)	59.3% (440)	54.3% (132)	61.7% (308)
IL-28B						
CC	23.3% (668)	12.3% (50)	25.1% (618)	25.9% (192)	11.1% (27)	33.1% (165)
CT	57.5% (1650)	49.3% (201)	58.9% (1449)	53.5% (397)	50.2% (122)	55.1% (275)
TT	19.0% (544)	37.5% (153)	15.9% (391)	20.6% (153)	38.7% (94)	11.8% (59)
Missing	0.2% (7)	1.0% (4)	0.1% (3)	0%	0%	0%
Baseline HCV RNA ≥ 800,000 IU/mL	77.6% (2227)	78.7% (321)	77.4% (1906)	79.2% (588)	81.5% (198)	78.2% (390)

BMI: body mass index; HCV: hepatitis C virus; IL: interleukin.
*Including subjects with other subtypes, undetermined subtype and missing information on subtype.

This result was driven by ION-4, where there was relapse in 8.8% of black subjects but 0% in non-black subjects.

Of the 43 black subjects with HCV GT1, HIV and cirrhosis, the SVR12 rate was 90.7%. Of 200 black subjects without cirrhosis and both HCV GT1 and HIV, SVR12 rates were 94%. These differences were not statistically significant.

Discussion

Prior to the advent of IFN-free DAA regimens, HCV GT1 was considered difficult-to-treat [36]. Since 2013, several IFN-free DAA regimens have been approved with SVR12 rates that exceed 90% for the overall GT1 population and 95% for certain GT1 subpopulations [27–34]. Additional data to further characterise SVR12 rates in various subgroups are helpful in establishing outcomes. The pooled analysis population comprises a substantially larger dataset compared with individual clinical development programmes for black subjects with HCV GT1 infection and allows for several observations, including among a multitude of baseline characteristics (age, gender, country, BMI, cirrhosis, treatment experience, HCV RNA and IL-28B genotype), as well as for HIV co-infection. A sizeable proportion of the overall study population is from the USA, including a high proportion of black subjects from the USA (386 out of 408 subjects with HCV GT1 alone and 238 out of 243 subjects with both HCV GT1 and HIV). As

there were few black subjects who were not from the USA (22 [5.4%] out of 408 of those with HCV GT1 alone and five [2.1%] of 243 with both HCV GT1 and HIV), we grouped them together for simplicity although we do not make the assumption that these subgroups are genetically similar, and acknowledge that the overall number of black non-US subjects is limited and separate analyses of this subgroup would not generate meaningful data.

To our knowledge, our analyses represent the most systematic review of 12-week IFN-free DAA SVR12 clinical trial data in black subjects to date and provide another data source regarding SVR12 rates among black and non-black subjects with HCV GT1 alone and with both HCV GT1 and HIV [27–34].

SVR12 rates in black and non-black individuals with HCV GT1 alone

Despite varying SVR12 rates among black and non-black individualss reported from real-world observational cohorts, our pooled analysis showed consistently high SVR12 rates of at least 94% (range 94%–99.5%) in all 19 subgroups evaluated. Notably, ethnicity did not affect SVR12 rates. Our results provide data on all the approved 12-week DAAs for the treatment of HCV GT1 infection, and our SVR 12 findings are comparable with those findings reported in observational cohorts, retrospective subgroup analyses for a given DAA and meta-analyses of published literature [12–17].
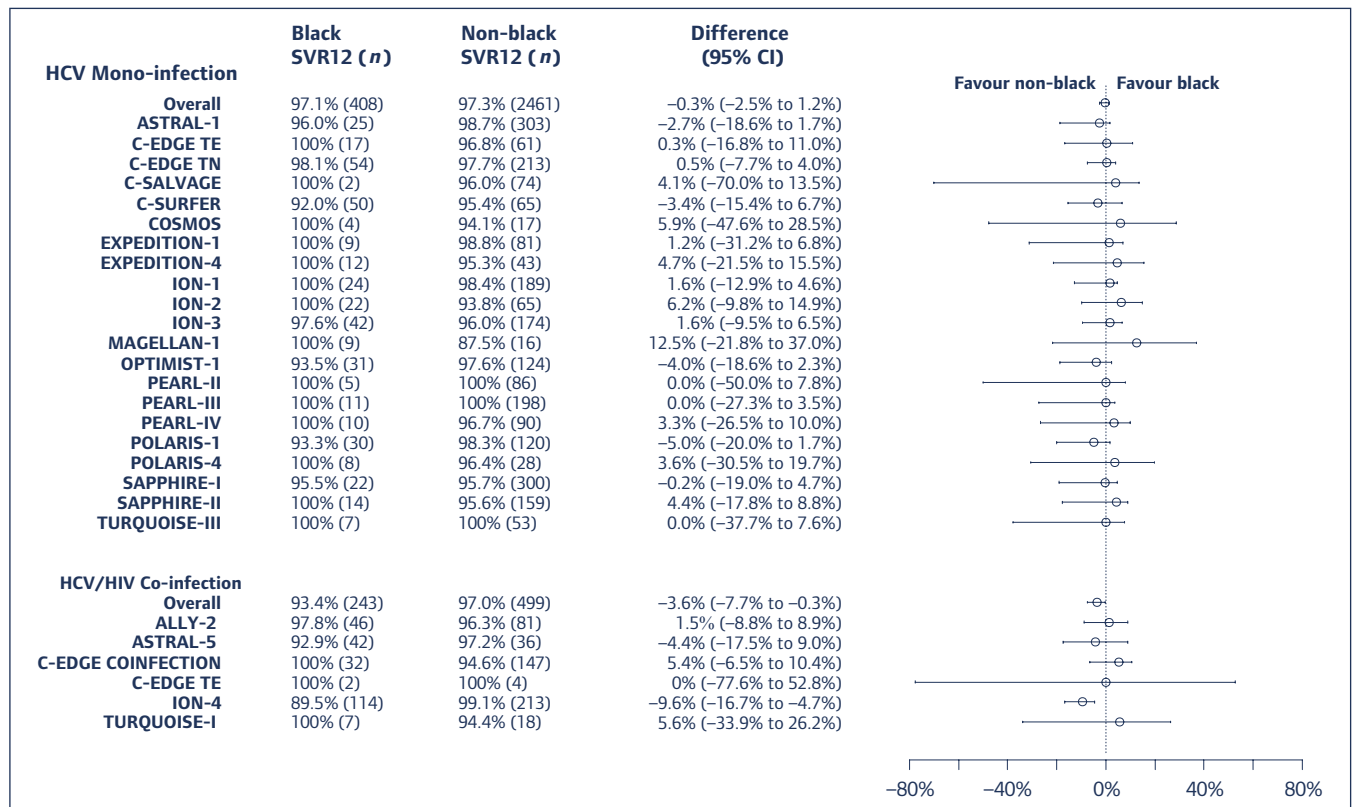
HCV Mono-infection	Black SVR12 (*n*)	Non-black SVR12 (*n*)	Difference (95% CI)
Overall	97.1% (408)	97.3% (2461)	−0.3% (−2.5% to 1.2%)
ASTRAL-1	96.0% (25)	98.7% (303)	−2.7% (−18.6% to 1.7%)
C-EDGE TE	100% (17)	96.8% (61)	0.3% (−16.8% to 11.0%)
C-EDGE TN	98.1% (54)	97.7% (213)	0.5% (−7.7% to 4.0%)
C-SALVAGE	100% (2)	96.0% (74)	4.1% (−70.0% to 13.5%)
C-SURFER	92.0% (50)	95.4% (65)	−3.4% (−15.4% to 6.7%)
COSMOS	100% (4)	94.1% (17)	5.9% (−47.6% to 28.5%)
EXPEDITION-1	100% (9)	98.8% (81)	1.2% (−31.2% to 6.8%)
EXPEDITION-4	100% (12)	95.3% (43)	4.7% (−21.5% to 15.5%)
ION-1	100% (24)	98.4% (189)	1.6% (−12.9% to 4.6%)
ION-2	100% (22)	93.8% (65)	6.2% (−9.8% to 14.9%)
ION-3	97.6% (42)	96.0% (174)	1.6% (−9.5% to 6.5%)
MAGELLAN-1	100% (9)	87.5% (16)	12.5% (−21.8% to 37.0%)
OPTIMIST-1	93.5% (31)	97.6% (124)	−4.0% (−18.6% to 2.3%)
PEARL-II	100% (5)	100% (86)	0.0% (−50.0% to 7.8%)
PEARL-III	100% (11)	100% (198)	0.0% (−27.3% to 3.5%)
PEARL-IV	100% (10)	96.7% (90)	3.3% (−26.5% to 10.0%)
POLARIS-1	93.3% (30)	98.3% (120)	−5.0% (−20.0% to 1.7%)
POLARIS-4	100% (8)	96.4% (28)	3.6% (−30.5% to 19.7%)
SAPPHIRE-I	95.5% (22)	95.7% (300)	−0.2% (−19.0% to 4.7%)
SAPPHIRE-II	100% (14)	95.6% (159)	4.4% (−17.8% to 8.8%)
TURQUOISE-III	100% (7)	100% (53)	0.0% (−37.7% to 7.6%)
HCV/HIV Co-infection			
Overall	93.4% (243)	97.0% (499)	−3.6% (−7.7% to −0.3%)
ALLY-2	97.8% (46)	96.3% (81)	1.5% (−8.8% to 8.9%)
ASTRAL-5	92.9% (42)	97.2% (36)	−4.4% (−17.5% to 9.0%)
C-EDGE COINFECTION	100% (32)	94.6% (147)	5.4% (−6.5% to 10.4%)
C-EDGE TE	100% (2)	100% (4)	0% (−77.6% to 52.8%)
ION-4	89.5% (114)	99.1% (213)	−9.6% (−16.7% to −4.7%)
TURQUOISE-I	100% (7)	94.4% (18)	5.6% (−33.9% to 26.2%)

Figure 1. Difference in SVR12 rate between black and non-black subjects for those with HCV GT1 alone and those with both HCV GT1 and HIV for 12-week regimens. CI: confidence interval; GT1: genotype 1; HCV: hepatitis C virus; SVR12: sustained virological response assessed 12 weeks following cessation of treatment; TE: treatment experienced; TN: treatment naive
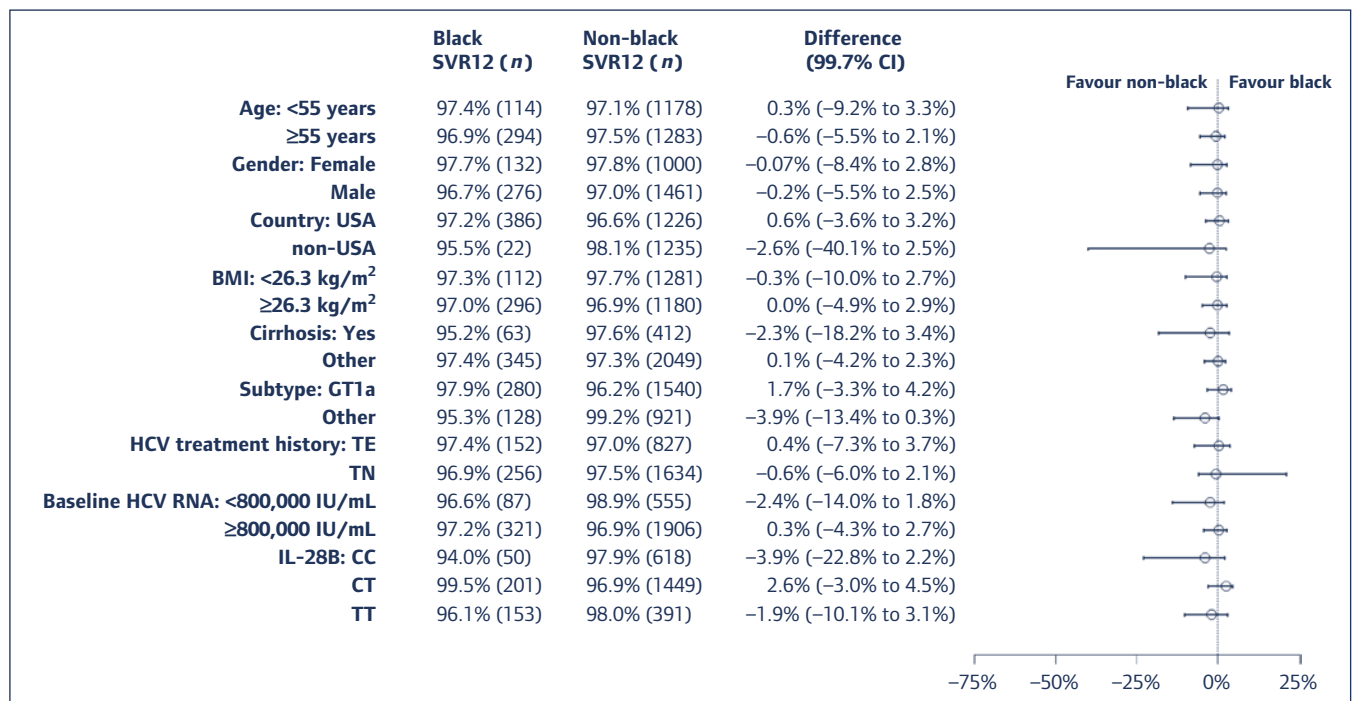
	Black SVR12 (*n*)	Non-black SVR12 (*n*)	Difference (99.7% CI)
Age: <55 years	97.4% (114)	97.1% (1178)	0.3% (−9.2% to 3.3%)
≥55 years	96.9% (294)	97.5% (1283)	−0.6% (−5.5% to 2.1%)
Gender: Female	97.7% (132)	97.8% (1000)	−0.07% (−8.4% to 2.8%)
Male	96.7% (276)	97.0% (1461)	−0.2% (−5.5% to 2.5%)
Country: USA	97.2% (386)	96.6% (1226)	0.6% (−3.6% to 3.2%)
non-USA	95.5% (22)	98.1% (1235)	−2.6% (−40.1% to 2.5%)
BMI: <26.3 kg/m^2	97.3% (112)	97.7% (1281)	−0.3% (−10.0% to 2.7%)
≥26.3 kg/m^2	97.0% (296)	96.9% (1180)	0.0% (−4.9% to 2.9%)
Cirrhosis: Yes	95.2% (63)	97.6% (412)	−2.3% (−18.2% to 3.4%)
Other	97.4% (345)	97.3% (2049)	0.1% (−4.2% to 2.3%)
Subtype: GT1a	97.9% (280)	96.2% (1540)	1.7% (−3.3% to 4.2%)
Other	95.3% (128)	99.2% (921)	−3.9% (−13.4% to 0.3%)
HCV treatment history: TE	97.4% (152)	97.0% (827)	0.4% (−7.3% to 3.7%)
TN	96.9% (256)	97.5% (1634)	−0.6% (−6.0% to 2.1%)
Baseline HCV RNA: <800,000 IU/mL	96.6% (87)	98.9% (555)	−2.4% (−14.0% to 1.8%)
≥800,000 IU/mL	97.2% (321)	96.9% (1906)	0.3% (−4.3% to 2.7%)
IL-28B: CC	94.0% (50)	97.9% (618)	−3.9% (−22.8% to 2.2%)
CT	99.5% (201)	96.9% (1449)	2.6% (−3.0% to 4.5%)
TT	96.1% (153)	98.0% (391)	−1.9% (−10.1% to 3.1%)

Figure 2. Difference in SVR12 rates between black and non-black subjects by subgroups for those with HCV GT1 alone in 12-week regimens. *: Including non-cirrhotic subjects and subjects with missing cirrhosis status; **: including GT1b subjects and subjects with other or undetermined subtype; ***: excluding subjects with missing IL-28B status. BMI: body mass index; CI: confidence interval; HCV: hepatitis C virus; SVR12: sustained virological response assessed 12 weeks following cessation of treatment; TE: treatment experienced; TN: treatment naive

SVR12 rates in black and non-black individuals with both HCV GT1 and HIV

Individuals with both HCV GT1 and HIV have increased liver-related morbidity and mortality, non-hepatic organ dysfunction, and overall mortality than those with HCV alone [36–40]. Efforts are ongoing to ensure that treatment of HCV infection in individuals living with HIV is a priority. Additional advances related to IFN-free DAA regimens include improved HCV treatment uptake and high SVR rates that are independent of HIV co-infection [36,40]. Although a numerical difference in SVR12 rates between black and non-black subjects with both HCV GT1 and HIV was seen in our analyses, it is noteworthy that this difference was driven by a single trial (ION-4) with its associated uncertainty. In ION-4, relapse was

Table 2. Virological outcome at post-treatment week 12 for 12-week regimens

Study	Black	Non-black
Mono-infection		
n	408	2461
SVR12 rate	97.1% (396)	97.3% (2395)
Not achieving SVR12		
On-treatment virological failure	0.2% (1)	0.1% (2)
Relapse	1.0% (4)	1.4% (34)
Other	1.7% (7)	1.2% (30)
Co-infection (including ION-4)		
n	243	499
SVR12 rate	93.4% (227)	97.0% (484)
Not achieving SVR12		
On-treatment virological failure	0.8% (2)	0.2% (1)
Relapse	5.3% (13)	1.0% (5)
Other	0.4% (1)	1.8% (9)
Co-infection (excluding ION-4)		
n	129	286
SVR12 rate	96.9% (125)	95.5% (273)
Not achieving SVR12		
On-treatment virological failure	0% (0)	0.3% (1)
Relapse	2.3% (3)	1.7% (5)
Other	0.8% (1)	2.4% (7)
ION-4		
n	114	213
SVR12 rate	89.5% (102)	99.1% (211)
Not achieving SVR12		
On-treatment virological failure	1.8% (2)	0% (0)
Relapse	8.8% (10)	0% (0)
Other	0% (0)	0.9% (2)

SVR12: sustained virological response assessed 12 weeks following cessation of treatment.

observed only in black subjects (relapse rate 9%), all of whom were IL-28B non-CC genotype. This difference in relapse rate between ION-4 black and non-black subjects is not explained by differences in LDV/SOF exposure, concomitant antiretroviral regimen or adherence, or pharmacogenomic markers; thus, there remains a degree of uncertainty in understanding why this difference in relapse rate was observed [18,29]. Given the overall sample size in ION-4 and the overall high SVR in this study, it is unclear if clinically meaningful differences exist. In the ION-1, ION-2 and ION-3 HCV mono-infection trials submitted with the original LDV/SOF new drug application (NDA), relapse rates were 3% (10/305) in black subjects and 2% (26/1637) in non-black subjects [29]. Overall, our pooled findings of high SVR12 rates between black and non-black individuals differ from the single ION-4 trial and from the Veterans Affairs observational cohort data, which lower SVR12 rates in black compared with non-black individuals [15,18].

Aside from the ION-4 trial, our extensive subgroup analyses of baseline characteristics (age, gender, country, BMI, cirrhosis, treatment experience, HCV RNA and IL-28B status) showed no

differences between SVR12 rates for black and non-black individuals with both HCV GT1 and HIV.

Given the degree of uncertainty regarding the relapse rate difference in ION-4, we believe our findings overall support the treatment guidelines as well as the published literature (primarily derived from observational cohorts or from retrospective subgroup analysis of a given individual DAA regimen) that DAAs have similar SVR12 rates among those with both HCV GT1 and HIV, and those with HCV alone [19–26].

Limitations of the FDA's HCV GT1 database

We do acknowledge that treatment durations could impact SVR and have differential outcomes for black *vs* non-black subjects; however, the small numbers of GT1 subjects from clinical trials with other treatment durations (i.e. 8, 16 and 24 weeks) precluded the ability to conduct the analyses described earlier. Only 24 (4.7%) black subjects with HCV alone were enrolled in clinical trials with other treatment durations. No black subjects with both HCV GT1 and HIV were enrolled in clinical trials with other treatment durations [27–34]. As a result, the assessment of differential outcomes for black *vs* non-black subjects in clinical trials with other treatment durations is not a part of this work. Additionally, we acknowledge that other factors may affect SVR rates. Real-world cohorts such as the Veterans Cohort study may differ from clinical trial participants and may include those with more advanced disease and other factors not otherwise represented in clinical trials that could affect SVR rates.

Conclusion

The balance of clinical trial data and real-world observational data can help inform treatment guideline decisions regarding regimen and duration for various subgroups such as ethnicity. Our pooled analyses included all 12-week approved DAA regimens; however, some regimens had a limited number of HCV GT1 black subjects. Although the small numbers of black subjects with HCV GT1from clinical trials precluded the ability to make definitive conclusions when evaluating efficacy by ethnicity the individual SVR12 rates for the trials included in our analyses ranged from 89.5% to 100% and did not substantially differ between HCV GT1-mono-infection and HCV GT1/HIV-co-infection.

Further evaluation from clinical trials and real-world observational cohorts will help inform possible underlying reasons that affect SVR12 rates based on ethnicity or other factors. At the time of initial approval, it is not possible to address all factors for varying response rates among subgroups in clinical trials. Post-approval trials and other sources of data, such as real-world observational cohorts, can help identify factors associated with treatment success or failure. More representation of minority subgroups is needed in clinical trials to better assess possible efficacy or safety differences at the time of initial approval.

FDA has a Drug Trials Snapshot database to provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. The information provided in these snapshots also highlights whether there were any differences in the benefits and side effects among gender, ethnicity and age groups. Drug Trials Snapshots is part of an overall FDA effort to make demographic data more available and transparent (www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm).

We hope these data help raise awareness of the need for widespread participation in clinical trials, including among black subjects in general, as well as those with both HCV and HIV, with the potential to address the issue of ethnicity differences throughout drug development and to have data available at the time of initial approval regarding any potential subgroup differences.
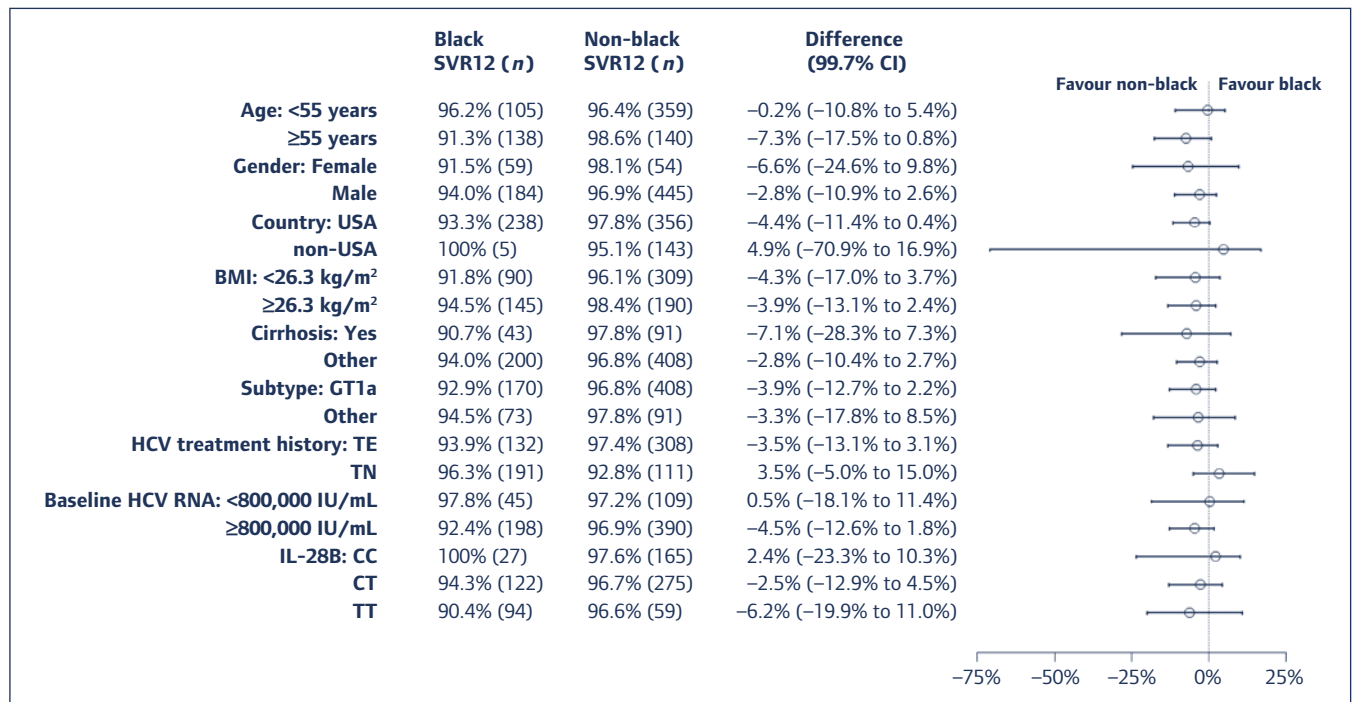
	Black SVR12 (*n*)	Non-black SVR12 (*n*)	Difference (99.7% CI)
Age: <55 years	96.2% (105)	96.4% (359)	−0.2% (−10.8% to 5.4%)
≥55 years	91.3% (138)	98.6% (140)	−7.3% (−17.5% to 0.8%)
Gender: Female	91.5% (59)	98.1% (54)	−6.6% (−24.6% to 9.8%)
Male	94.0% (184)	96.9% (445)	−2.8% (−10.9% to 2.6%)
Country: USA	93.3% (238)	97.8% (356)	−4.4% (−11.4% to 0.4%)
non-USA	100% (5)	95.1% (143)	4.9% (−70.9% to 16.9%)
BMI: <26.3 kg/m^2	91.8% (90)	96.1% (309)	−4.3% (−17.0% to 3.7%)
≥26.3 kg/m^2	94.5% (145)	98.4% (190)	−3.9% (−13.1% to 2.4%)
Cirrhosis: Yes	90.7% (43)	97.8% (91)	−7.1% (−28.3% to 7.3%)
Other	94.0% (200)	96.8% (408)	−2.8% (−10.4% to 2.7%)
Subtype: GT1a	92.9% (170)	96.8% (408)	−3.9% (−12.7% to 2.2%)
Other	94.5% (73)	97.8% (91)	−3.3% (−17.8% to 8.5%)
HCV treatment history: TE	93.9% (132)	97.4% (308)	−3.5% (−13.1% to 3.1%)
TN	96.3% (191)	92.8% (111)	3.5% (−5.0% to 15.0%)
Baseline HCV RNA: <800,000 IU/mL	97.8% (45)	97.2% (109)	0.5% (−18.1% to 11.4%)
≥800,000 IU/mL	92.4% (198)	96.9% (390)	−4.5% (−12.6% to 1.8%)
IL-28B: CC	100% (27)	97.6% (165)	2.4% (−23.3% to 10.3%)
CT	94.3% (122)	96.7% (275)	−2.5% (−12.9% to 4.5%)
TT	90.4% (94)	96.6% (59)	−6.2% (−19.9% to 11.0%)

Figure 3. Difference in SVR12 rates between black and non-black subjects by subgroups for those with both HCV GT1 and HIV in 12-week regimens. *: Including non-cirrhotic subjects and subjects with missing cirrhosis status; **: including GT1b subjects and subjects with other or undetermined subtype. BMI: body mass index; CI: confidence interval; HCV: hepatitis C virus; SVR12: sustained virological response assessed 12 weeks following cessation of treatment; TE: treatment experienced; TN: treatment naïve

Acknowledgements

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Conflicts of interest

All authors have no potential conflicts of interest related to this article.

Funding

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Supplemental Table S1. Data included in analysis for 12-week regimens

Drugs	Study	Study population/subgroups	Number of subjects (*n*)	Approved 12-week regimen
DCV	ALLY-2	GT1, TN/TE, ±cirrhosis, HCV/HIV co-infection	127	DCV+SOF
EBR and GZR	C-EDGE co-infection	GT1a without baseline NS5A polymorphisms/GT1b, TN, ±cirrhosis, HCV/HIV co-infection	179	EBR/GZR
	C-EDGE TE	GT1a without baseline NS5A polymorphisms/GT1b, TE, ±cirrhosis, HCV mono-infection or HCV/HIV co-infection	86 (80 mono-infections, 6 co-infections)	EBR/GZR
	C-EDGE TN	GT1a without baseline NS5A polymorphisms/GT1b, TN, ±cirrhosis	267	EBR/GZR
	C-SALVAGE	GT1a without baseline NS5A polymorphisms/GT1b, TE, ±cirrhosis	76	EBR/GZR+ribavirin (RBV)
	C-SURFER	GT1a without baseline NS5A polymorphisms/GT1b, TN/TE, ±cirrhosis, severe renal impairment	115	EBR/GZR
LDV and SOF	ION-1	GT1, TN, ±cirrhosis	213	LDV/SOF
	ION-2	GT1, TE, without cirrhosis	87	LDV/SOF+RBV
	ION-3	GT1, TN, without cirrhosis	216	LDV/SOF
	ION-4	GT1, TN/TE, ±cirrhosis, HIV/HCV co-infection	327	Same as mono-infection
GLE and PIB	Expedition-1	GT1, TN/TE (PRS), with cirrhosis	90	GLE/PIB
	Expedition-4	GT1, TN/TE (PRS), ±cirrhosis, severe renal impairment	55	GLE/PIB
	Magellon-1	GT1, TE (NS3/4A PI), ±cirrhosis	25	GLE/PIB
OBV and PTV-r+DAS	PEARL-II	GT1b, TE, without cirrhosis	91	OBV/PTV-r+DAS
	PEARL-III	GT1b, TN, without cirrhosis	209	OBV/PTV-r+DAS
	PEARL-IV	GT1a, TN, without cirrhosis	100	OBV/PTV-r+DAS+RBV
	SAPPHIRE-I	GT1a, TN, without cirrhosis	322	OBV/PTV-r+DAS+RBV
	SAPPHIRE-II	GT1a, TE, without cirrhosis	173	OBV/PTV-r+DAS+RBV
	TURQUOISE I	GT1, TN/TE, ±cirrhosis, HCV/HIV co-infection	25	Same as mono-infection
	TURQUOISE III	GT1b, TN/TE, with cirrhosis	60	OBV/PTV-r+DAS
SMV	COSMOS	GT1, TN/TE, without cirrhosis	21	SMV+SOF
	OPTIMIST-1	GT1, TN/TE, without cirrhosis	155	SMV+SOF
SOF and VEL	ASTRAL-1	GT1, TN/TE, ±cirrhosis	328	SOF/VEL
	ASTRAL-5	GT1, TN/TE, ±cirrhosis, HIV co-infection	78	SOF/VEL
SOF, VEL and VOX	Polaris-1	GT1, TE, ±cirrhosis	150	SOF/VEL/VOX
	Polaris-4	GT1a, TE, ±cirrhosis	36	SOF/VEL/VOX

DAS: dasabuvir; DCV: daclatasvir; EBR: elbasvir; GLE: glecaprevir; GT1: genotype 1; GZR: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; NS3/4A PI: HCV NS3/4A protease inhibitor; NS: HCV nonstructural protein; OBV: ombitasvir; PIB: pibrentasvir; PRS: Prior treatment experience with regimens containing (peg) interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor; PTV-r: paritaprevir/ritonavir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TE: treatment experienced; TN: treatment naive; VEL: velpatasvir; VOX: voxilaprevir.