HCV Triple Therapy is Equally effective in African-Americans and Non-African-Americans

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Abstract Real-world experience with HCV medications differs from original the index studies. African-Americans (AA) are commonly underrepresented in clinical trials. Therefore, we hypothesized that postmarketing experience with the first generation HCV protease inhibitors (PI) (telaprevir and boceprevir) differs from premarket reports in clinically meaningful ways regarding patient race. We conducted a single-center, retrospective, observational analysis to evaluate the efficacy of HCV triple therapy in a nontrial setting. Clinical response and quantitative laboratory values were compared between AA and non-AA patients throughout the duration of treatment. Patients were included if they started triple therapy treatment after July 2011 and are not a part of any other clinical/pharmaceutical trials. Thirty-five patients with HCV genotype 1 were included in this study—22 non-AA and 13 AAs. AAs had a higher BMI compared to non-AA (33.6 vs 28.8, $p=0.046$). “High” baseline HCV RNA values (above 800,000 copies) were more prevalent in AA (69.2 %) vs non-AA (63.6 %). AA had less favorable IL28B genotypes; only 7.7 % had type CC compared to 40.9 % of non-AA. SVR12 was achieved 82 % of the time with each PI but there was no significance in type of PI used ($p=1.00$). Patients with cirrhosis were less likely to achieve SVR12 (40 %) compared to those without cirrhosis (88 %, $p=0.013$). Thirty-three percent of the patients who received blood transfusions did not achieve SVR12 while every patient who did not require

transfusion achieved SVR12 ($p=0.001$). All patients with IL28B genotype CC achieved SVR12 ($p=0.007$). SVR12 did not differ among AA (77 %) and non-AA (86.4 %) ($p=0.528$).

Keywords Hepatitis C · Hepatitis treatment · Triple therapy · Real-world experience · HCV treatment

Introduction

The prevalence of hepatitis C is higher in African-Americans compared to other races in the USA. According to NHANES III data, African-Americans had a prevalence of 3.2 % in the reported population compared to 1.5 % in the general US population [1–3]. Historically, African-Americans have been underrepresented in HCV trials. Mehliia et al. [4] concluded that African-Americans were 65 % less likely to be eligible for treatment given comorbidities such as cytopenia, diabetes mellitus, and chronic kidney disease.

Given the prevalence of disease, especially in African-American men born between 1945 and 1965, HCV related complications such as cirrhosis, decompensation, and HCC are a growing health concern [5]. A study from the National Center for Health Statistics suggests that racial disparities exist in HCV infection, with African-Americans having a twofold higher rate of death than expected [6]. Such trends are expected to continue, with the number of HCV cases and decompensation events peaking between 2020 and 2022.

Enrollment of African-Americans in therapeutic trials for HCV has been disproportionate. According to 2011, US Census data estimated that 13.6 % of the population was African-American. The most recent major trials analyzing triple therapy treatment in HCV were able to enroll 7–27 % of the study participants as African-Americans [7–14]. Although improvements have been made in recruitment

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diversity, the reality is that these are sponsored trials, with inclusion and exclusion criteria. A large percentage of African-Americans have not been eligible. There are no studies that describe this population of patients who do not qualify or do not choose to participate in drug trials. Furthermore, no single center has published real-world experiences that clinicians may expect to see from their diverse set of patients undergoing triple therapy for HCV. The goal of this study was to offer the largest cohort of triple therapy patients, with a specific focus on comparing the treatment experiences of African-Americans to non-African-Americans.

Methods

Study Design

This approved study is a retrospective, observational design conducted in a single center (Tulane Medical Center, Hepatology Clinic, New Orleans, LA, USA). Eligible candidates were patients with chronic HCV, genotype 1 as identified by detectable levels of serum HCV RNA (Roche COBAS TaqMan HCV assay), and HCV Genotype analysis (LabCorp, Burlington NC). IL28B genotype polymorphism (RT-PCR) was determined by a serum sample (LabCorp, Burlington NC). Severity of fibrosis was determined by liver biopsy, (FibroSure LabCorp, Burlington NC), or radiographic evidence. Additionally, eligibility required that subjects initiate and complete HCV triple therapy after July 2011, could not be a part of any other clinical/pharmaceutical trials, receive at least one dose of HCV protease inhibitor, and be at least 17 years of age. Patients were excluded if they received triple therapy treatment as part of an industry-sponsored clinical trial. Also, patients could not have concurrent HIV infection, hepatocellular carcinoma. Individual treatment regimens were based on the clinical judgment of his/her treating hepatologist. Data including labs, medications, clinic notes, nursing visits, and hospitalization records were extracted by hand from individual patient charts.

End Points

The primary end points were the comparative SVR12 of African-Americans versus White patients. Secondary end-points included medication dosing, side effects, transfusion requirements, BMI, gender, previous treatment outcome, genotype, IL28B polymorphism, and final outcome (SVR12). Chen et al. recently demonstrated that the positive predictive value of SVR12 for SVR24 was 98 % and negative predictive value was 99 % [15]. As SVR12 was a treatment endpoint for this study, final treatment outcomes could vary slightly.

Statistical Analysis

Descriptive statistics for patients were reported in Table 1. A chi-squared test was used to compare categorical variables between White Americans and African-Americans. Continuous variables were summarized as means with standard deviation. ANOVA was performed to compare treatment outcomes relative to SVR12, ethnicity, and protease inhibitor. Significance was chosen to be <0.05 . All statistical analysis was performed using SPSS.

Results

A total of 35 patients were included in this study—22 White Americans and 13 African-Americans. Demographic details were compared between African-Americans and White Americans and are shown in Table 1. Significant differences between the two groups included BMI, baseline HCV RNA, IL28B polymorphism, history/response to previous HCV treatment, and platelet count at baseline. African-Americans were more likely to have a higher BMI compared to White Americans (33.6 vs 28.8, $p=0.046$). Baseline HCV RNA values considered high (above 800,000 copies) were more prevalent in African-Americans (69.2 %) vs White Americans (63.6 %). African-Americans had less favorable IL28B genotypes; only 7.7 % had type CC compared to 40.9 % of White Americans. African-Americans were more likely to be treatment naïve (76.9 %) compared to White Americans (40.9 %). In six cases, IL28B was not collected and was therefore unknown. Finally, the baseline blood counts, specifically platelet count, were significantly higher prior to treatment initiation in African-Americans (224,000) compared to White Americans (177,000).

Table 2 shows which variables were significantly associated with virus negativity 12 weeks after completion of treatment (SVR12). Patients with cirrhosis were less likely to achieve SVR12 (50 %) compared to those without cirrhosis (87 %, $p=0.013$). Approximately 33 % of the patients who received blood transfusions did not achieve SVR12 yet 100 % of the patients who achieved SVR12 did not require blood transfusion ($p=0.001$). All patients with IL28B genotype CC achieved SVR12 compared to only 40 % with Type TT ($p=0.007$). While blood transfusion was significant for SVR12, neither ribavirin dose reduction ($p=0.384$) nor erythropoietin injection ($p=0.686$) requirement were found to be significant. Despite these observations, race (African-Americans—37 % of study population, White Americans—63 % of study population) was not found to be significant ($p=0.528$) in this study in predicting SVR12. Thirty-three percent of non-SVR patients and 25 % of SVR patients were hospitalized, most commonly for weakness (Supplemental Table 2).

Table 1 Selected baseline characteristics by race

	White American (<i>n</i> =22) ^a	African-American (<i>n</i> =13) ^a	Significance
Age (SD)	49.3 (12.1)	49.9 (10.0)	0.887
BMI (SD) ^b	28.8 (5.2)	33.6 (8.6)	0.046
Male sex (%)	12 (54.5)	4 (30.8)	0.183
Married (%)	11 (50)	7 (53.9)	0.832
Job (%)	15 (68.2)	6 (46.2)	0.210
Insurance (%)			0.125
Private	18 (81.8)	8 (61.5)	
Medicare or Medicaid	4 (18.2)	4 (30.8)	
Uninsured	0 (0)	1 (7.7)	
HCV RNA baseline >800,000 (%)	14 (63.6)	9 (69.2)	0.040
Genotype			0.772
1a (%)	19 (86.2)	10 (76.9)	
1a/1b (%)	1 (4.5)	0 (0)	
1b (%)	2 (9.1)	3 (23.1)	
IL28B			0.008
CC (%)	9 (40.9)	1 (7.7)	
CT (%)	10 (45.5)	4 (30.8)	
TT (%)	1 (4.5)	4 (30.8)	
Unknown (%)	2 (9.1)	4 (30.8)	
Previous HCV treatment			0.022
Stopped due to side effects (%)	2 (9.1)	0 (0)	
Naïve (%)	9 (40.9)	10 (76.9)	
Nonresponder (%)	4 (18.2)	2 (15.4)	
Relapse (%)	4 (18.2)	1 (7.7)	
Platelet count (baseline)			
Mean baseline—100 K (SD)	177 (61)	224 (67)	0.045
100 to 150 K (SD)	8 (36.4)	2 (15.4)	
>150 K (SD)	14 (63.6)	11 (84.6)	
Cirrhosis ^c			0.951
No (%)	16 (72.7)	9 (69.2)	
Yes (%)	3 (13.6)	3 (23.1)	
Unknown (%)	3 (13.6)	1 (7.7)	
Protease inhibitor treatment			0.251
Boceprevir (%)	9 (40.9)	8 (61.5)	
Telaprevir (%)	13 (59.1)	5 (34.5)	

^a Race was self-reported. No Hispanic, Latino, or Asian patients were included in this consecutive patient analysis

^b BMI was according to height and weight at initiation of triple therapy

^c Cirrhosis was determined according to radiographic, histologic, or serologic criteria

Table 3 shows treatment outcomes stratified by race: African-Americans to White Americans. The only significantly disparate variables related to BMI ($p=0.046$) and initial ribavirin dose ($p=0.024$). African-Americans had higher BMI at treatment initiation compared to White Americans (33.6 and 28.8, respectively), resulting in higher mean starting ribavirin doses in African-Americans (1,092 and 900 mg, respectively). There was no significant effect of race on cytopenia that required erythropoietin injection ($p=0.831$), neupogen injection ($p=0.891$), or blood transfusion ($p=0.282$) noted between the two groups. Additionally, there was not a significant trend ($p=0.528$) in SVR12 rates between White Americans (81.0 %) and African-Americans (77 %).

Finally, there was no significant difference between races of pegylated interferon dosing at treatment initiation ($p=0.206$) or lowest reduced dose ($p=0.213$).

Table 4 compares the outcomes-based protease inhibitor used, boceprevir or telaprevir. Only viral negativity at week 4 ($p=0.000$) differed between the two groups—29 % of the patients achieve rapid viral response (RVR) on boceprevir, while 89 % of patients achieved RVR on telaprevir. This reflects the use of the “lead” in phase with boceprevir. However, SVR12 was ultimately achieved 79.4 % of the time in both groups and was not significant ($p=1.00$). Finally, there was no significant difference in cytopenia and blood product transfusion requirements between the two groups.

Table 2 Treatment outcomes by SVR12

	No SVR ^a (n=7)	SVR ^a (n=27)	Significance
BMI (SD)	28.7 (5.9)	31 (7.3)	0.471
Lowest RBV dose in mg (SD)	667 (372)	785 (357)	0.467
Lowest PEG dose in mcg (SD)	147.5 (38)	155 (41)	0.698
Starting RBV dose in mg (SD)	866.7 (301)	1,000 (237)	0.241
Starting PEG dose in mcg (SD)	155 (40)	169 (27)	0.292
RBV reduced to <600 mg daily	57 %	43 %	0.421
Age in years (SD)	48 (8.9)	49.7 (12.0)	0.749
Married	83 %	46 %	0.106
Needed RBV reduction	67 %	46 %	0.384
Needed PEG reduction	33 %	21 %	0.547
Job	50 %	64 %	0.528
Men	22 %	78 %	0.473
Women	13 %	88 %	
White American (n=22)	19 %	81 %	0.528
African-American (n=13)	23 %	77 %	
Cirrhosis ^b	50 %	13 %	0.013
Needed epogen injection	33 %	25 %	0.686
Needed neupogen	0 %	18 %	0.276
Needed blood transfusion	33 %	0 %	0.001
Hospitalized ^c	33 %	25 %	0.686
IL28B genotype ^d (CC) (n=9)	0 %	100 %	0.007
IL28B genotype (CT) (n=14)	14 %	86 %	
IL28B genotype (TT) (n=5)	60 %	40 %	
Tx naïve (n=19)	11 %	89 %	0.589
Prev nonresponder (n=5)	40 %	60 %	
Prev relapser (n=8)	25 %	75 %	
Boceprevir	18 %	82 %	1.000
Telaprevir	18 %	82 %	

^a SVR12 unknown for one of the cases as patient was lost to follow-up. SVR12 was defined as undetectable HCV RNA level at least 12 weeks after completion of treatment duration, which varies according to protease inhibitor, presence of cirrhosis, and dose modifications as per management decisions of hepatologist

^b Cirrhosis was determined according to radiographic, histologic, or serologic criteria

^c Hospitalization includes ER visits or inpatient admission

^d Not all participants had known IL28B

Discussion

Contrary to results from several large, sponsored trials, this study of real-world outcomes with HCV triple therapy failed to confirm the SVR disparity between African-American and White-American patients seen in previous PEG/RBV-based treatment trials. SVR12 with triple therapy was 81 % in White Americans vs 77 % in African-Americans ($p=0.528$). In addition, real-world overall SVR rates were higher than observed in index trials by Poordad et al. [7] and Jacobson et al. [8]. Patients with IL28B polymorphism subtype CT/TT or cirrhosis were less likely to achieve SVR12, but this was regardless of race. Patients with severe anemia, requiring blood transfusions, were also less likely to achieve SVR12; however, this did not negatively alter treatment efficacy when stratified by race.

Prior to triple therapy, previous treatment regimens with PEG/RBV demonstrated a significant difference in SVR in African-Americans compared to non-African-Americans [16–19]. Despite the overall increase in SVR with first generation protease inhibitors, the SVR gap between White and African-Americans did not appear to be completely resolved.

In the index trial (SPRINT-2) for triple therapy using boceprevir by Poordad et al. (SPRINT-2), the SVR (modified ITT population) of group 2 (boceprevir + PEG/RBV for 24 weeks) and group 3 (boceprevir + PEG/RBV for 44 weeks) combined were 50 % for African Americans and 70.4 % for White Americans [7]. The odds ratio of SVR between black and non-Black cohorts was 0.5 ($p<0.001$). Similarly, a difference was also seen in the index trial of telaprevir (ADVANCE—T12PR arm) by Jacobson et al [8]; SVR was achieved in 62 % of African-Americans and 75 % of White Americans. In our study, overall SVR was higher than published in the index trials, but SVR did not differ significantly between our African-American (77 %) and White American (81 %) ($p=0.53$) cohorts. As seen in McCombs et al.'s recent report on Veterans Affairs' experience where overall SVR with telaprevir-based therapy where only 4 % of treated subjects achieved a negative viral load, real-world success can often lag behind that seen in strictly conducted clinical trials [20]. It is reassuring to find these expensive medications can yield very favorable results in a nonstudy setting even in historically difficult to treat populations.

Table 3 Treatment outcomes by race

	White American (<i>n</i> =22)	African-American (<i>n</i> =13)	Significance
BMI (SD)	28.8 (5.2)	33.6 (8.6)	0.046
VN week 4 ^a	68 %	46 %	0.21
VN week 8	95 %	85 %	0.303
VN week 12	91 %	85 %	0.585
Starting mean RBV dose in mg (SD)	900 (244)	1,092 (210)	0.024
Starting mean PEG dose in mcg (SD)	162 (34)	175 (16)	0.206
Lowest mean RBV dose in mg (SD)	709 (347)	800 (424)	0.496
Lowest mean PEG dose in mcg (SD)	147 (43)	165 (30)	0.219
RBV dose <600 mg daily (%)	45	46	0.969
Required blood transfusion (%)	1 (4.5)	2 (15.3)	0.282
Required neupogen (%)	3 (13.6)	2 (15.3)	0.891
Required epogen (%)	6 (27.2)	4 (30.8)	0.831
Protease inhibitor held ^b (%)	1 (4.5)	3 (23.1)	0.101
ANC decrease week 0 to 24 (SD)	2,210 (1395)	2,820 (2081)	0.328
Hgb decrease (SD)	3.37 (1.4)	2.38 (2.0)	0.114
Plt decrease 100 K (SD)	62.4 (52.8)	71.3 (49.0)	0.187
SVR12 ^c (%)	17 (80.9)	10 (76.9)	0.528

^a VN—HCV RNA viral level was undetectable at weeks 4, 8, and 12

^b Protease inhibitor held due to side effects with continuation of PEG/RBV or discontinuation of all medications

^c SVR12 unknown for one of the cases as patient was lost to follow-up. SVR12 was defined as undetectable HCV RNA level at least 12 weeks after completion of treatment duration, which varies according to protease inhibitor, presence of cirrhosis, and dose modifications as per management decisions of hepatologist

Table 4 Treatment outcomes by protease inhibitor

	Bocepr (<i>n</i> =17)	Tela (<i>n</i> =18)	Significance
BMI	31.2 (8.2)	30.1 (5.8)	0.655
VN week 4 ^a	29 %	89 %	0.000
VN week 8	88 %	94 %	0.491
EVR—week 12	82 %	94 %	0.274
Lowest RBV dose in mg (SD)	718 (367)	767 (390)	0.705
Lowest PEG dose in mcg (SD)	145 (46)	163 (31)	0.205
RBV dose <600 mg daily (%)	41	50	0.613
Required blood transfusion (%)	6	11	0.594
Required neupogen (%)	18	11	0.594
Required epogen (%)	29	28	0.918
PI held (%) ^b	6	17	0.331
ANC decrease week 0 to 24 (SD)	2723 (1974)	2154 (1325)	0.346
Hgb decrease (SD)	2.9 (1.8)	3.1 (1.6)	0.731
Plt decrease 100 K (SD)	6.8 (54.2)	71.2 (48.9)	0.609
SVR12 (%) ^c	14 (82)	14 (82) ^d	1.000

^a VN—HCV RNA viral level was undetectable at weeks 4 and 8

^b Protease inhibitor held due to side effects with continuation of PEG/RBV or discontinuation of all medications

^c SVR12 unknown for one of the cases as patient was lost to follow-up. SVR12 was defined as undetectable HCV RNA level at least 12 weeks after completion of treatment duration, which varies according to protease inhibitor, presence of cirrhosis, and dose modifications as per management decisions of hepatologist

^d Unknown SVR12 in one patient

Several characteristics of our cohort, such as baseline HCV RNA, genotype, and fibrosis score may help to explain the differences seen in overall SVR between our study and the index trials for boceprevir (groups 2 and 3) and telaprevir (T12PR)—See Supplemental Table 1. Baseline HCV RNA >800,000 were higher in the boceprevir trial (85 % of non-Blacks, 91 % of Blacks) as well as the telaprevir trial (overall 77 %). In our study, 69 % of African-Americans and 64 % of White Americans had a baseline HCV RNA >800,000. Also, patients with genotype 1a tend to be more responsive to PEG/RBV dual therapy [21]. Our study had slightly higher percentage of subtype 1a (76.9—African-American, 91 %—White American) compared to the boceprevir trial (75 %—Black, 65 %—non-Black) and the telaprevir trial (59 % overall). An enrichment of genotype 1a patients may partially explain the high SVR rate we observed.

We feel our findings have external validity given that we were able to confirm several factors reported in the large sponsored trials. For example, the distribution of IL-28B genotypes was consistent with previous trials as was the relative influence of advanced liver fibrosis on SVR rates. In telaprevir trial (ADVANCE-T12PR arm), 20 % of included subjects were Metavir fibrosis stage 3 or 4 [8]. Patients with cirrhosis were 2.5 times less likely to achieve SVR in that trial. In the boceprevir trial (SPRINT-2), as expected, SVR rates were also higher in patients without cirrhosis (i.e., Metavir stage 0, 1, or 2). Based on clinical judgment regarding radiographic, serologic, and pathologic evidence, approximately 15 % of African-Americans and 14 % of White Americans had cirrhosis in our cohort. As with these original studies, cirrhosis was a significant predictor of treatment failure in our real-world data as well, where only 40 % of cirrhotic patients obtained SVR12 compared to 88 % of patients without evidence of advanced fibrosis obtained SVR12.

It remains unclear as to why patients with severe anemia who received blood transfusions were less likely to achieve SVR12 in our study. Although there were differences in BMI and subsequently RBV dosing between the AA and the non-AA study groups, SVR12 was not statistically significant between these two groups. Erythropoietin injections and blood transfusions have been used historically in order to allow patients to maintain higher levels of RBV and in turn, optimize their chances at SVR. No randomized studies have evaluated erythropoietin use in achieving SVR. Similarly, no conclusive data exists about transfusion requirements predicting treatment outcomes. Recently, Poordad et al. [22] evaluated the management of anemia in patients on triple therapy (boceprevir) and concluded that RBV reduction was an effective primary management approach. Additionally, RBV dose reduction did not affect SVR. Our observation of a negative correlation between transfusion and SVR does nothing to refute Poordad et al.'s findings.

Consideration must also be given to the mechanisms of action of the individual medications comprising the regimens, and how newer, direct-acting anti-viral agents have improved outcomes. As the previous standard of care, IFN/RBV therapy had less than 50 % efficacy in the treatment of chronic HCV. Pegylated-interferon is an immunoregulatory cytokine with profound effects on immune system responses to viral antigens. This activation is not virus-specific, and genetic variants (both host and pathogen) allow for resistance and varied responses to treatment. Consensus opinion has suggested that the innate and adaptive immune responses, host genetic variables, genetic diversity of the virus, and clinical comorbidities (diabetes) may all account for the ineffectiveness of IFN/RBV in the treatment of HCV [23].

First generation direct-acting antiviral agents (DAA), specifically boceprevir and telaprevir, are specific inhibitors of viral proteases, leading to direct inhibition of the processing of viral proteins critical to viral replication. Although the addition of first-generation DAA's was a significant improvement to existing IFN/RBV regimens, there were still differences in treatment outcomes based upon race, genotype, IL28B polymorphism, and severity of fibrosis. The next generation of DAAs (combinations of sofosbuvir and ledipasvir, which inhibit multiple viral targets simultaneously) [24, 25] have demonstrated superior SVR12 rates as well as equivalent efficacy in challenging populations such as African-Americans, non-CC IL28B polymorphism, and cirrhotics. These results suggest that combination regimens of direct-acting antivirals may transcend patient factors (race, IL28B polymorphism, and genotype) that have previously limited treatment options for these more challenging cohorts.

There are several limitations inherent to this retrospective evaluation. Chiefly, there may be an element of selection bias in which patients to treat. While African-Americans have historically been less likely to be eligible for pharmaceutical studies compared to White Americans [4], it is possible that this group of nontrial patients was disproportionately represented in this study. This may yield patients with more complicated medical and socioeconomic cofactors that both positively or negatively influence outcomes. Thirdly, the strategies used for anemia—blood transfusions, erythropoietin injection, or ribavirin reduction—may not be consistent with recommended treatment protocols in study trials. This could place more emphasis on blood transfusion as an indicator of treatment outcome. Finally, as this was a retrospective analysis, there was some missing data (labs, biopsy) and inconsistent follow-up visits that could not be accounted for our secondary endpoint analyses, and could possibly influence these results

Conclusion

We studied the treatment outcomes of 35 consecutive nonstudy patients who represented a balanced panel based upon disease prevalence and racial demographics. Many risk factors for treatment outcome, such as IL28B genotype and presence of cirrhosis, were consistent with the index trials SPRINT-2 and ADVANCE. However, we found SVR may not be lower in AA as compared to non-AA treated with first generation protease inhibitors in combination with pegylated interferon and ribavirin. Real-world SVR rates may actually be consistent with or higher than the index trial results. Finally, the treatment of severe anemia with red cell transfusion is negatively associated with SVR.

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