Vitamin D and the racial difference in the genotype 1 chronic hepatitis C treatment response

Steven J Weintraub, Jacquelyn F Fleckenstein, Tony N Marion, Margaret A Madey, Tahar M Mahmoudi, and Kenneth B Schechtmann

ABSTRACT

Background: African Americans with genotype 1 chronic hepatitis C attain a sustained virologic response (SVR) at only approximately one-half the rate of whites after peginterferon and ribavirin treatment. The serum concentration of 25-hydroxyvitamin D [25(OH)D] has recently been established as a predictor of treatment response. Therefore, the low serum concentrations of 25(OH)D found among African Americans may contribute to the low response rate; however, to our knowledge, none of the studies of vitamin D in chronic hepatitis C treatment have included a significant number of black patients.

Objective: The objective was to compare the relation between the 25(OH)D concentration and genotype 1 chronic hepatitis C treatment response in African Americans with that in whites.

Design: This cross-sectional analysis included 106 African American and 65 white patients with genotype 1 chronic hepatitis C.

Results: Consistent with previous studies, we found that the SVR rate in the white patients increased significantly with an increasing serum concentration of 25(OH)D [SVR rates were 20%, 46%, and 70% for 25(OH)D serum concentrations <20, 20–35, and >35 ng/mL, respectively; P-trend = 0.008]; however, there was no relation between the SVR rate and 25(OH)D serum concentration in the African American patients [SVR rates were 32%, 28%, and 33% for 25(OH)D serum concentrations <20, 20–35, and >35 ng/mL, respectively; P-trend = 0.832]. We also found an analogous racial difference in the relation between the extent of liver fibrosis and the 25(OH)D concentration.

Conclusion: Racial differences in vitamin D physiology or race-specific factors that modify the effects of vitamin D may affect the immune response to genotype 1 hepatitis C virus. Am J Clin Nutr 2012;96:1025–31.

INTRODUCTION

When chronically infected with the most common hepatitis C virus (HCV)\(^4\), genotype 1 HCV, and treated with peginterferon and ribavirin, ~50% of whites but only ~25% of African Americans attain a sustained virologic response (SVR); the absence of detectable virus from the bloodstream 6 mo after the end of treatment, considered a cure (1–3). African Americans also have lower rates of SVR than do whites when treated with regimens in which a direct-acting antiviral agent is added to peginterferon and ribavirin (4, 5).

It is well established that the racial difference in allelic frequencies of IL-28B rs12979860 C/T single-nucleotide polymorphism (SNP) contributes significantly to the racial difference in the rate of SVR. Individuals with the CC genotype attain an SVR at ~2- to 3-fold the rate of individuals with either the CT or TT genotype, and whereas ~39% of whites have the IL-28B rs12979860 CC genotype, only 16% of African Americans have the IL-28B rs12979860 CC genotype (6). The IL-28 gene codes for the protein interferon-α3, which is a member of a family of interferons that induce the expression of genes that inhibit HCV replication; however, the rs12979860 SNP is thought to not be causal but solely a tag for an unidentified functional variant (7). Most importantly, the IL-28B rs12979860 genotype contributes to only approximately one-half of the racial difference in treatment outcome (6). Therefore, there must be other race-specific factors that contribute to the difference in outcome.

The serum concentration of 25-hydroxyvitamin D [25(OH)D] has recently been established as another predictor of the rate of SVR. Petta et al (8) found that low 25(OH)D serum concentrations correlate with a failure to attain an SVR in patients with genotype 1 chronic hepatitis C. In a second study, it was again found that low serum 25(OH)D concentrations predict a poor response to treatment, and it was demonstrated that the 25(OH)D

1 From the Department of Medicine, St Louis Veterans Affairs Medical Center—John Cochran Division, St Louis, MO (SJW and TMM); the Department of Medicine, Washington University School of Medicine, St Louis, MO (SJW and KBS); the Department of Medicine, Division of Hepatology (JFF, TNM, and MAM), the Hepatitis C Cooperative Research Center (JFF, TNM, and MAM), and the Department of Microbiology, Immunology and Biochemistry (TNM), University of Tennessee Health Science Center, Memphis, TN; the Division of Biostatistics, Washington University, St Louis, MO (KBS); and the Department of Radiological Sciences, St Jude Children’s Research Hospital, Memphis, TN (MAM).

2 Supported by a grant from the Washington University School of Medicine Institute for Clinical and Translational Studies (to SJW), the NIH (grants AB048216, AI066316, RR0211; to JFF, TNM, and MAM) and the University of Tennessee Health Science Center Clinical and Translational Science Institute (to JFF, TNM, and MAM). The Institute for Clinical and Translational Studies is supported by the NIH (grant RR024992). The University of Tennessee Cooperative Hepatitis C Center is a National Institute of Allergy and Infectious Diseases–sponsored cooperative center.

3 Address correspondence to SJ Weintraub, Department of Internal Medicine, St Louis VA Medical Center—John Cochran Division, 915 North Grand Boulevard, St Louis, MO 63105. E-mail: sjweintraub@gmail.com.

4 Abbreviations used: HCV, hepatitis C virus; PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism; SVR, sustained virologic response; 25(OH)D, 25-hydroxyvitamin D.
concentration complements the IL-28B rs12979860 SNP to enhance the correct prediction of SVR (9). Finally, it was found that the 25(OH)D concentration correlates with the rate of SVR in patients treated for recurrent chronic hepatitis C after a liver transplant for hepatitis C–related cirrhosis (10).

These findings suggested that the serum 25(OH)D concentration could have an important role in the racial difference in the response to genotype 1 hepatitis C treatment because African Americans are more likely to have an insufficient serum concentration of 25(OH)D in comparison with whites (11) and, in addition to the findings of the studies previously outlined, there is genetic evidence of a functional role for vitamin D in the treatment response (12, 13) and evidence that vitamin D supplementation improves the treatment response (10, 14). However, to our knowledge, all of the studies of 25(OH)D in chronic hepatitis C treatment have been European or Israeli, and none of these have included a significant number of black patients (8–10, 12–14; S Pettia and P Toniutto, personal communication, November 2011).

Therefore, the aim of the current study was to compare the relation between the serum 25(OH)D concentration and rate of SVR in response to peginterferon and ribavirin therapy in African Americans and whites with genotype 1 chronic hepatitis C. Although we confirmed that there is a correlation between an increasing 25(OH)D concentration and improvement in the rate of attaining an SVR in whites, there was no relation between the 25(OH)D concentration and rate of attaining an SVR in the African American cohort in this study. These findings, along with those of other published studies that we discuss, suggest that there are racial differences in the vitamin D physiology or race-specific factors that modify the effects of vitamin D that affect the immune response to genotype 1 HCV.

SUBJECTS AND METHODS

Patients

Serum samples and corresponding patient records were obtained from the University of Tennessee Cooperative Hepatitis C Center Tissue Repository, which is a repository of previously collected tissue and serum samples from 227 genotype 1 chronic hepatitis C patients from Memphis, Tennessee, and the surrounding area who participated in a previous chronic hepatitis C treatment study for which patients were enrolled from March 2001 through March 2009. All patients had genotype 1a or 1b chronic hepatitis C. Liver biopsies were staged according to the METAVIR model. Exclusion criteria were previous interferon treatment, decompensated cirrhosis, hepatocellular carcinoma, chronic liver disease other than hepatitis C, co-infection with HIV, neutrophil count <1500/mm$^3$, platelet count <85,000/mm$^3$, hemolytic anemia, serum albumin concentration <3.0 g/dL, or serum creatinine concentration >1.4 mg/dL. Patients with other conditions that could interfere with treatment, including psychiatric disease, were excluded. Race was self-identified; however, subjects with ancestry <50% concordant with their self-identified race were excluded from the repository. The study was conducted according to the principles of the Declaration of Helsinki and all procedures received necessary approvals by the institutional review boards at participating institutions. All patients gave written informed consent to participate in the repository. There was a sufficient volume of serum to assess the 25(OH)D concentration remaining in individual samples in the repository from 197 of the of the original 227 patients, and 171 of these patients had been treated for ≥12 wk; these patients were included in the current study. In this group, 106 subjects were African American, and 65 subjects were white. The demographic and clinical characteristics of this group are reported in Table 1.

Antiviral therapy schedule and outcomes

All patients received a subcutaneous injection of 1.5 μg peg-interferon α-2b · kg$^{-1} · wk^{-1}$ (Peg-Intron; Schering-Plough) plus either 13 mg ribavirin · kg$^{-1} · d^{-1}$ (n = 163) or 800 mg ribavirin/d (n = 8). Patients were scheduled for therapy for 48 wk. SVR was defined as negative serum HCV RNA as assessed by using polymerase chain reaction (PCR) 24 wk after the end of therapy.

25(OH)D assay

Serum samples obtained within the first 2 wk of treatment that had been stored at −80°C in the University of Tennessee Cooperative Hepatitis C Center Tissue Repository were assessed for the 25(OH)D concentration by using the DiaSorin 25(OH)D$^{125}$I RIA (DiaSorin) as per the manufacturer’s instructions at the

<p>| TABLE 1 |</p>
<table>
<thead>
<tr>
<th>Patient baseline characteristics by race$^1$</th>
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<tr>
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<tr>
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<tr>
<td>Sex $[n (%)]$</td>
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<td>M</td>
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<td>F</td>
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<td>Age (y)</td>
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<td>Median</td>
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<td>IQR</td>
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<td>Range</td>
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<td>Men</td>
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<tr>
<td>IQR</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>rs12979860 genotype $[n (%)]$$^2$</td>
</tr>
<tr>
<td>CC</td>
</tr>
<tr>
<td>CT or TT</td>
</tr>
<tr>
<td>Viral load $[n (%)]$</td>
</tr>
<tr>
<td>&lt;800,000 IU/mL</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL</td>
</tr>
<tr>
<td>Fibrosis stage $[n (%)]$$^2$</td>
</tr>
<tr>
<td>0–2</td>
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<td>3–4</td>
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</tbody>
</table>

$^1$ Fisher’s exact test was used to compare categorical values, and the Mann-Whitney-Wilcoxon rank-sum test was used to compare continuous values.

$^2$ IL-28B rs12979860 genotype and fibrosis staging were available for the indicated number of patients.
VITAMIN D, RACE, AND CHRONIC HEPATITIS C

Washington University School of Medicine Institute for Clinical and Translational Studies Core Laboratory for Clinical Studies.

IL-28B SNP sequence analysis

PCR was used to amplify a 184-bp genomic DNA fragment that included the 19q13 rs12979860 SNP. The PCR oligonucleotide primers were forward 5’-CTGCCAGTCTGGGATTCC-3’ and reverse 5’-TCACAGAAGGGAGGCGCTGC-3’. PCR products were sequenced with an ABI Model 3130XL Gene Analyzer (Applied Biosystems, Life Technologies) in the University of Tennessee Health Science Center Molecular Resource Center. The nucleotide sequence at position 92 of the PCR fragment that corresponds to rs12979860 was determined with Sequence Scanner v1.0 software (Applied Biosystems).

Statistical analyses

Statistical analyses of the data were performed with GraphPad Prism 5 for Macintosh software (GraphPad Software) and SPSS 19 for Macintosh software (SPSS Inc). Categorical variables are presented with frequencies (percentages). Associations between categorical variables were evaluated by using Fisher’s exact test or a chi-square test for a linear trend. Continuous variables are presented as the median with the 25th and 75th percentile values and the range of values with P values calculated by using the Mann-Whitney-Wilcoxon rank-sum test. Logistic regression was used to analyze the interaction of race and 25(OH)D concentrations in the prediction of the rate of SVR.

RESULTS

Baseline characteristics

There were no significant differences regarding sex, weight, pretreatment viral load, or pretreatment hepatic fibrosis stage between African American and white groups in this study (Table 1). The 2 groups differed significantly in age, but it is unlikely that the difference was of clinical significance (medians differed by 2.5 y) and, as expected, the 2 groups differed significantly in the frequency of IL-28B rs12979860 SNP genotypes (Table 1). The following treatment-response rates for each IL-28B rs12979860 genotype were similar to those of previous studies (6, 15): 55.6% (n = 5 of 9) of African Americans and 68.8% (n = 11 of 16) of whites with the CC genotype and 27.7% (n = 23 of 83) of African Americans and 38.9% (n = 14 of 36) of whites with the CT or TT genotype attained an SVR.

25(OH)D concentrations

Serum 25(OH)D concentrations were significantly lower in African American patients than in white patients [median: 18.8 ng/mL (IQR: 15.1–25.0 ng/mL); range: 5.0–40.4 ng/mL] compared with 28.6 ng/mL (IQR: 21.6–37.2 ng/mL; range: 10.1–64.8 ng/mL), respectively; P < 0.0001] (Figure 1). The Institute of Medicine recently designated a serum 25(OH)D concentration of 20 ng/mL as the cutoff for sufficiency (16). On the basis of this value, 84.6% of white patients and 46.2% of African American patients in this study had sufficient concentrations of 25(OH)D (Table 2). However, more recently, the Endocrine Society presented evidence that the cutoff for sufficiency should be 30 ng/mL (17). With the use of 30 ng/mL as a cutoff, 43.1% of whites and only 14.2% of African Americans in this study had sufficient concentrations of 25(OH)D (Table 2).

Although 49.2% of white patients attained an SVR, only 30.2% of the African American patients attained an SVR (Table 3). The 25(OH)D concentrations of whites who attained an SVR were significantly higher than the 25(OH)D concentrations of whites who did not attain an SVR [median: 31.8 ng/mL (IQR: 27.3–38.9 ng/mL; range: 16.3–64.8 ng/mL) compared with 26.4 ng/mL (IQR: 19.8–32.3 ng/mL; range: 10.1–53.0 ng/mL), respectively; P = 0.017] (Figure 2A). Notably, the rate of SVR in white patients continued to improve at 25(OH)D concentrations that are considered above the threshold for sufficiency [SVR rates were 20%, 46%, and 70% for 25(OH)D serum concentrations <20, 20–35, and >35 ng/mL, respectively; P-trend = 0.008] (Figure 2B); in contrast, there was no relation between 25(OH)D concentrations and the rate of SVR in African Americans, regardless of whether 25(OH)D concentrations were examined as a group [median: 18.20 ng/mL (IQR: 11.5–23.7 ng/mL; range: 5.0–37.6 ng/mL) compared with 19.0 ng/mL (IQR: 15.5–25.4 ng/mL; range: 5.5–40.4 ng/mL) for subjects who attained an SVR compared with subjects who did not, respectively; P = 0.228] (Figure 2C) or in discrete ranges [SVR rates were 32%, 28%, and 33% for 25(OH)D serum concentrations <20, 20–35, and >35 ng/mL, respectively; P-trend = 0.832] (Figure 2D).

TABLE 2

Vitamin D sufficiency by race

<table>
<thead>
<tr>
<th>25-hydroxyvitamin D</th>
<th>White (n = 65)</th>
<th>African American (n = 106)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20 ng/mL±</td>
<td>84.6% (n = 55)</td>
<td>46.2% (n = 49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥30 ng/mL±</td>
<td>43.1% (n = 28)</td>
<td>14.2% (n = 15)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 Fisher’s exact test was used to compare the frequency of vitamin D sufficiency between races.

2 Vitamin D sufficiency as defined by the Institute of Medicine.

3 Vitamin D sufficiency as defined by the Endocrine Society.

FIGURE 1. Dot plots of the comparison of 25(OH)D concentrations in AA (n = 106) and W (n = 65) with genotype 1 chronic hepatitis C. The difference in 25(OH)D concentrations between races was significant (P < 0.0001) when analyzed by using the Mann-Whitney-Wilcoxon rank-sum test. Arrowheads denote medians and IQRs. AA, African Americans; W, whites; 25(OH)D, 25-hydroxyvitamin D.
We performed logistic regression to determine whether there was a significant effect of race on the relation between the 25(OH)D concentration and rate of SVR. In whites, the OR of attaining an SVR increased significantly by a factor of 1.061 for each 1-ng/mL increase in 25(OH)D concentration ($P = 0.026$) (Table 4); however, as expected, there was no relation between the 25(OH)D concentration and rate of SVR in African Americans when analyzed by using logistic regression ($P = 0.256$) (Table 4). Most importantly, the relation between the 25(OH)D concentration and rate of SVR was significantly different in whites and African Americans ($P = 0.019$) when analyzed by logistic regression as an interaction term (Table 4), which suggests that there are racial differences in vitamin D physiology or race-specific factors that modify the effects of vitamin D that affect the immune response to genotype 1 HCV.

25(OH)D concentrations and hepatic fibrosis
Consistent with a previous report (8), we found that higher 25(OH)D concentrations were associated with milder fibrosis in TABLE 3: Treatment response by race.

<table>
<thead>
<tr>
<th></th>
<th>−SVR</th>
<th>+SVR</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>White [n (%)]</td>
<td>33 (50.8)</td>
<td>32 (49.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>African American [n (%)]</td>
<td>74 (69.8)</td>
<td>32 (30.2)</td>
<td>0.256</td>
</tr>
</tbody>
</table>

$−SVR$, failed to attain a sustained virologic response; $+SVR$, attained a sustained virologic response. Fisher’s exact test was used to compare the treatment response between races.

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Table 4
Table 4 presents the racial difference in serum 25(OH)D concentration as a predictor of SVR.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>White</td>
<td>1.061 (1.007, 1.118)</td>
<td>0.026</td>
</tr>
<tr>
<td>African American</td>
<td>0.969 (0.917, 1.023)</td>
<td>0.256</td>
</tr>
<tr>
<td>Interaction of race and 25(OH)D serum concentration</td>
<td>1.095 (1.015, 1.181)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

1 SVR, sustained virologic response; 25(OH)D, 25-hydroxyvitamin D.
2 Simple logistic regression was used to analyze the relation between the serum 25(OH)D concentration and rate of SVR for each race.
3 Logistic regression with race × serum 25(OH)D concentration as an interaction term was used to analyze the effect of race on the relation between the serum 25(OH)D concentration and rate of SVR.

Discussion
We have compared the relationship between the serum concentration of 25(OH)D and rate of SVR in whites and African Americans with genotype 1 chronic hepatitis C. Consistent with previous reports (8, 9), we found a significant correlation between an increasing 25(OH)D serum concentration and increasing rate of SVR in whites with genotype 1 chronic hepatitis C; however, there was no relation between the 25(OH)D serum concentration and rate of SVR within our African American cohort. We also found an analogous racial difference in the relationship between 25(OH)D concentrations and liver fibrosis in our patient population. Notably, consistent with our results, another group (A Jazwinski, personal communication, June 2012) has recently found that there was no relation between the serum 25(OH)D concentration and treatment response in 82 African American patients with genotype 1 chronic hepatitis C.

It is well established that there are racial differences in the relations between the 25(OH)D concentrations, parathyroid hormone concentration, and calcium homeostasis (18–29). Our findings are consistent with the increasing evidence that there are also racial differences in the noncalcemic activities of vitamin D. For example, in a recent study of individuals in the third NHANES, it was found that there is a strong inverse relation between 25(OH)D serum concentration and both diabetes risk and insulin resistance in non-Hispanic whites and Mexican Americans, but there was no relation between the 25(OH)D serum concentration and diabetes risk or insulin resistance in African Americans (30). Likewise, in another study that used the third NHANES data, it was found that, although there was a correlation between an increasing serum 25(OH)D serum concentration and decreasing stroke risk in whites, there was no relation between the 25(OH)D serum concentration and stroke risk in African Americans (31). We report a similar racial difference in the relation between the 25(OH)D serum concentration and response to treatment in patients with genotype 1 chronic hepatitis C.

Such differences could be a manifestation of racial differences in vitamin D physiology. This possibility is supported by evidence that the efficiency with which vitamin D supports certain immune cell functions is lower in individuals who express a high-affinity variant of the vitamin D–binding protein (the Gc-1f protein isoform expressed from the rs7041T/rs4588C allele of the vitamin D–binding protein gene) (32) [ie, individuals who express the high-affinity variant may need higher concentrations of 25(OH)D for optimal immune function than do individuals who express the lower-affinity variants (the Gc-1s and Gc-2 isoforms expressed from the rs7041G/rs4588C and rs7041T/...
Americans have lower 25(OH)D concentrations than do whites. Americans with milder stages of fibrosis was the same as in the Americans in our study. Furthermore, the proportion of African between 25(OH)D concentrations and liver fibrosis in the African recently demonstrated that treatment with vitamin D lowered the mechanisms through which vitamin D could limit liver fibrosis in whites (34). There could be comparable racial differences in the activity of enzymes of the vitamin D metabolic pathway in the cells of the immune system. Differences such as these could be a consequence of differences in ancestral cutaneous vitamin D synthesis and vitamin D dietary intake or differences in ancestral infectious exposure.

It is also possible that race-specific factors that are not directly involved in vitamin D metabolism modify the relation between 25(OH)D concentration and the genotype 1 chronic hepatitis C treatment response in African Americans and whites. For example, the T allele of the IL-28B rs12979860 C/T SNP is more prevalent in African Americans than in whites, and patients with chronic hepatitis C who have the CT or TT genotype at the IL-28B rs12979860 C/T SNP attain an SVR at only one-third to one-half the rate of patients with CC genotype (6). Therefore, it is possible that the high prevalence of the T allele results in blunting of the effect of increasing 25(OH)D concentrations in African Americans as a group. This possibility is supported by the finding that a group of white patients with the IL-28B rs12979860 CC genotype who had 25(OH)D concentrations >20 ng/mL had an SVR rate of 85.7%, whereas whites with the CT and TT genotype who also had 25(OH)D concentrations >20 ng/mL had an SVR rate of only 36.8% (9). Similarly, the rate of SVR decreases with increasing insulin resistance, and African Americans have higher rates of insulin resistance than whites have (35, 36). Because of these and other factors, it is possible that African Americans as a group would need higher 25(OH)D concentrations than whites need to attain a significantly improved rate of SVR.

As has been observed previously (8), we found that decreasing 25(OH)D concentrations were correlated with worsening liver fibrosis in whites. The hepatic hydroxylation of vitamin D to 25(OH)D is robust and not impaired in patients with cirrhosis until there is terminal liver failure (37). Therefore, it is unlikely that the correlation between decreasing 25(OH)D and worsening liver fibrosis in our white patients was attributable to hepatic dysfunction. However, it has been noted that there are several mechanisms through which vitamin D could limit liver fibrosis in individuals with chronic hepatitis C (8, 38), and indeed, it was recently demonstrated that treatment with vitamin D lowered the fibrotic score in a rodent model of liver fibrosis (39). Thus increasing 25(OH)D may limit liver fibrosis in whites with chronic hepatitis C.

In contrast to the findings in whites, there was no correlation between 25(OH)D concentrations and liver fibrosis in the African Americans in our study. Furthermore, the proportion of African Americans with milder stages of fibrosis was the same as in the whites in this and a previous study (40), even though African Americans have lower 25(OH)D concentrations than do whites. These results suggest that African Americans with genotype 1 hepatitis C are less sensitive to the profibrotic mechanisms that occur at low 25(OH)D concentrations in whites with genotype 1 hepatitis C in the same manner that African Americans are less sensitive to the bone-resorptive effects of parathyroid hormone (22). Such traits may have been selected for as a consequence of the lower serum concentrations of 25(OH)D found in African Americans.

This study has limitations. The cross-sectional nature of the study precluded the conclusion that there is a causal influence of 25(OH)D concentration on response to treatment and liver fibrosis. In addition, pretreatment serum to assess vitamin D concentrations was not available for all patients—all other serum samples were obtained within the first 2 wk of treatment. However, in this context it is notable that Lange et al (13) found that the change in 25(OH)D serum concentration in a group of 50 genotype 1 chronic hepatitis C patients from pretreatment to 24 wk posttreatment was small and not significant [the median 25(OH)D concentration only changed from 16.2 to 18.2 ng/mL]. We also note that the clustering of the 25(OH)D concentrations in the lower range in the African Americans in our study may have obscured a correlation between the 25(OH)D concentration and the rate of SVR in African Americans. However, the logistic regression analysis presented in Table 4 argues that the relation between the 25(OH)D concentration and rate of SVR in whites and African Americans is in fact different within the range of 25(OH)D concentrations found among the patients in our study. Importantly, it is possible that African Americans require higher concentrations of 25(OH)D than do whites for an optimal treatment response, and that a readily detectable correlation between the 25(OH)D concentration and treatment response would occur in a group of African Americans with higher serum concentrations of 25(OH)D. Finally, a larger study would be required to examine the interaction of 25(OH)D serum concentrations and other host factors, such as the IL-28B genotype, in the genotype 1 chronic hepatitis C treatment response in African Americans.

In conclusion, this study provides preliminary evidence for a differential role for vitamin D in both the treatment response and development of liver fibrosis in whites and African Americans with genotype 1 chronic hepatitis C.

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