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Pharmacodynamics of PEG-IFN alpha-2a and HCV response as a function of IL28B polymorphism in HIV/HCV co-infected patients

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Abstract

We examined the association between IL28B single-nucleotide-polymorphism rs12979860, hepatitis C virus (HCV) kinetic and pegylated-interferon-alpha-2a pharmacodynamic parameters in HIV/HCV-co-infected patients from South America. Twenty-six subjects received PEG-IFN-alpha-2a+ribavirin. Serum HCV-RNA and interferon concentrations were measured frequently during the first 12-weeks of therapy and analyzed using mathematical models. African Americans and Whites had a similar distribution of IL28B genotypes (p=0.5). The CC genotype was overrepresented (p=0.015) in patients infected with HCV genotype-3 compared to genotype-1. In both genotype-1 and genotype-3, the first-phase-viral decline and the average PEG-IFN-alpha-2a effectiveness during the first week of therapy were larger (trend P≤0.12) in genotype-CC compared with genotypes-TC/TT. In genotype-1 patients, the second-slower phase of viral decline (days 2–29) and infected-cells-loss rate, δ, were larger (p=0.02 and 0.11, respectively) in genotype-CC than in genotypes-TC/TT. These associations were not observed in genotype-3 patients.

Introduction

Coinfection with human immunodeficiency virus (HIV) and HCV affects approximately 10 million people worldwide[1] and up to 100,000 persons in Brazil[2]. Antiviral therapy for hepatitis C virus (HCV) consisting of pegylated-interferon-α (PEG-IFN) and ribavirin (standard of care, SOC) has potential adverse effects, and response rates are lower in HCV/HIV co-infected than in HCV-monoinfected patients[3–9]. Consequently, there is considerable interest in identifying better predictors of treatment response. A seminal study showed that single nucleotide polymorphisms (SNPs) in the IL28B gene region were associated with race/ethnicity and correlated with response to pegylated interferon-alpha (PEG-IFN) and ribavirin therapy in HCV mono-infected patients[10–13].

Recently, early HCV kinetics (e.g., first and second phases of viral decline) have been evaluated as a function of IL28B SNPs in HCV mono-infected patients, although pharmacodynamic parameters are lacking in these analyses[14, 15]. To the best of our

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Conflict of Interest

ESAA and AAB have received support for travel to international conferences, honoraria for scientific activities and research support from Roche Brazil. HD has had a paid consulting relation with Genentech.

knowledge, there is no such information in HIV/HCV co-infected individuals. To determine the relationship between IL28B polymorphisms and viral/host parameters in HIV/HCV co-infected patients, we compared IL28B genotypes with recent results of viral response[16] and estimates of viral kinetic and pharmacodynamic parameters[17] in 26 patients with HIV and HCV who were treated with PEG-IFN-α-2a and ribavirin.

Patients and Methods

Data form twenty six HIV/HCV co-infected patients who were treated with PEG-IFN-α-2a (180 μg/week) plus weight based ribavirin (11 mg/kg/day) and provided informed written consent for DNA and HCV RNA kinetic testing are included here. Detailed baseline characteristics, viral response and viral kinetic and pharmacodynamic parameters, estimated via mathematical modeling, were recently studied[16, 17]. The SNP near the IL28B gene, rs12979860, was examined using the 5' nuclease assay with allele specific PCR probes as recently described[10]. Genotyping was conducted in a blinded fashion. We used nonparametric methods analyses to compare parameters with IL28B genotype-CC vs genotype-TC/TT. To compare categorical variables, we used the two-tailed Fisher Exact and Pearson Chi-Square Tests. The level of statistical significance was set at ($p \leq 0.05$). All tests were performed by SPSS v.17 Chicago, IL. Parameters are presented as median and interquartile (IQR) [Table 1 and Table S1 in Supplementary Material File].

Results

Baseline characteristics and IL28B polymorphism

There were no differences in the distribution of IL28B genotypes by age, gender or race/ethnicity (Table S1). Notably, the distribution of IL28B genotypes was similar between Whites and African Americans in this sample of patients from Brazil. Patients with genotype-CC were significantly heavier (mean 71 kg) than patients with genotype-TC/TT (mean 65 kg) [p=0.012]. Baseline virus levels were similar across IL28B genotypes. A higher proportion (p=0.015) of HCV genotype-3 patients had IL28B genotype-CC (8 out of 11) compared to those with HCV genotype-1 (3 out of 15) [Table S1].

Viral response and IL28B polymorphism

The rapid virologic response rate (RVR, HCV RNA undetectable at week 4) was greater in patients with genotype-CC compared to those with genotype-TC/TT (p=0.04). The CC genotype was even more strongly associated (p=0.004 in Table S1) with the complete early virologic response rate, cEVR (HCV RNA undetectable at week 12). End treatment response and sustained virological response (SVR) rates were higher in patients with genotype-CC but did not reach significance (p=0.5 and 0.2, respectively) probably due to the discontinuation of 5 patients by week 12 of therapy (Table S1). The response rates among HCV genotype (1 vs 3) and IL28B genotype (CC vs CT/TT) are shown in Table S1.

Viral kinetics and IL28B polymorphism

Overall, the first phase viral decline from baseline to nadir viral load (see V_{min} in Table 1) was significantly (p=0.005) higher in patients with genotype-CC (median (IQR) 1.7 (0.6)) than in patients with genotype-TC/TT (0.92 (0.8), Table 1 and Fig. 1A). The slower-second-phase slopes calculated from day 7 to day 15 or from day 2 to day 29 also were significantly faster (p=0.046 and p=0.01, respectively) in patients with genotype-CC (median (IQR) 1.1 (1.1) and 0.7(0.6) log/wk, respectively) than in patients with genotype-TC/TT (0.4(0.5) and 0.3(0.4) log/wk, respectively, Table 1 and Figs. 1 A&B). Confining the analysis to HCV genotype-1 patients confirmed the associations between IL28B genotype-CC and higher first phase (p=0.08) viral decline and second phase calculated between d2-d29 (p=0.02) viral

decline slope (Table 1 and Figs. 1 C&D). Interestingly, in HCV genotype-3 subjects, while there was a trend toward a higher first phase viral decline (p=0.1) with genotype-CC, the second-slower phase of viral decline was not associated (p=0.7 for both d7-d15 and d2-d29) with IL28B genotype-CC (Table 1 and Figs. 1 E&F).

Viral kinetic and pharmacodynamic parameters and IL28B polymorphism

The maximum PEG-IFN effectiveness during the first week of therapy, ε_{7max}, the average PEG-IFN effectiveness during the first week of therapy, $\varepsilon_{7average}$, and the maximum PEG-IFN effectiveness from week 4 to week 12 of therapy, ε_{max}, were significantly (p=0.008, 0.008 and 0.044, respectively) higher in genotype-CC (median (IQR) 94% (11%), 92%(13%) and 96%(6%), respectively) than in patients with genotype-TC/TT (81% (45%), 77%(45%) and 87%(33%), respectively; Table 1). The PEG-IFN concentration at which the PEG-IFN-α-2a effectiveness in blocking viral production is half its maximum, EC_{50}, was significantly (p=0.02) lower in genotype-CC (median (IQR) 1.3(1.8)) than in genotype-TC or TT (3.3(11.5)). When the analysis was confined to HCV genotype-1 cases, EC_{50} was lower (but not significant p=0.6) in genotype-CC, but there was a trend toward a correlation between genotype-CC and both $\varepsilon_{7average}$ and δ (P=0.11, Table 1). In contrast, in HCV-genotype-3 patients, there were trends toward higher $\varepsilon_{7average}$ and lower EC_{50} (p=0.1) with genotype-CC, while an association was less evident for δ (P=0.7, Table 1) among IL28B genotypes.

Discussion

A detailed HCV kinetic analysis provided new and important information regarding the impact of IL28B genotype on response to PEG-IFN plus RBV in HIV/HCV co-infected patients. Overall, the CC-genotype was most strongly associated with a higher first phase viral decline and maximum PEG-IFN effectiveness during the first week of therapy, ε_{7max}. These findings indicate that PEG-IFN has greater efficacy in blocking HCV production/release in patients with the favorable IL28B CC-genotype. Our results are in agreement with recent findings in HCV-mono-infection patients[14, 15]. The PEG-IFN-α-2a EC_{50} was lower in genotype-CC compared with genotype-TC/TT, providing further evidence that the CC-genotype confers a higher sensitivity to IFN treatment. Thus far, the mechanism of action of the IL28B polymorphism has not been identified. The location of the genetic polymorphism upstream of the IFN-λ gene[18, 19] raises the possibility that the IL28B genotype mediates endogenous production of IFN-λ, which contributes to the first phase response by stimulating IFN signaling.

The second phase viral decline slope also was associated with genotype-CC in genotype 1 patients (Table 1). The overall correlation between the CC-genotype and the infection death/loss rate, δ, was less prominent (trend, p=0.11). This discrepancy could be explained by the fact that 6 out of 21 of patients who finished 48 weeks of therapy in our study[17] had a triphasic viral decline pattern, consisting of a first phase (1–2 days) with a rapid virus load decline followed by a “shoulder phase” (8 – 28 days), in which virus levels decay slowly or remain constant, and a third phase of renewed viral decay[20, 21]. Calculating the slower phase slope from the measured data includes the “shoulder phase” in these triphasic patients. In contrast, by using a mathematical model that includes hepatocytes proliferation, estimated δ reflects the final slope and excludes the shoulder phase[22]. Interestingly, five of the six triphasic patients had genotype-TT/TC and only one had genotype-CC (not shown). In addition, we recently showed that drug effectiveness, ε, can significantly affect the serum second phase slope decline[22], and that when $\varepsilon \sim 1$ the slower phase slope is close to δ. Indeed, when the analysis was performed only in patients with first phase decline > 1 log (i.e., ε>90%), the association between IL28B genotype-CC and the slower phase slope was lost (p=0.5, not shown), in agreement with recent results in HCV mono-infection patients[15].

Thus, although the slower phase slope, and as a consequence RVR rates, are correlated with the IL28B genotype, the driving effect is the difference in the IFN anti-viral effectiveness in blocking virion production (first phase decline). The data suggest that the IL28B polymorphism has less of an effect on the infected-cell-loss rate that has been attributed to immune mediated clearance of infected cells[23].

Among viral response parameters, we found that RVR and cEVR rates are significantly associated with genotype-CC (Table S1), in agreement with recent results in HCV (genotypes 1/2/3) monoinfected patients[15, 24]. Among HCV genotype-1 subjects in our study, 10 subjects (out of 11) who had genotype CT/TT failed to achieve an SVR in agreement with the strong association recently shown in larger HIV/HCV co-infected cohorts by Rallon et al.[25] and Pineda et al[26]. However, the weak association between genotype-CC and SVR (p=0.3; Table S1) in HCV genotype-1 infected subjects in our study may be related to the small sample size and due the discontinuation of five patients at week 12 of therapy as previously explained[17]. The faster first and second phase viral declines observed in IL28B genotype-1-CC patients and the higher first phase viral decline in genotype-3-CC patients provide evidence that the IL28B genotype favorably impacts on viral kinetics.

Evaluation of baseline characteristics showed genotype-CC subjects had a higher body weight. Larger studies are needed to evaluate whether genotype CC might overcome the deleterious impact of higher body weight on SVR. In addition, there was a significantly higher proportion of IL28B genotype-CC in patients infected with HCV-genotype 3 than in patients infected with HCV-genotype 1 (Table S1), in agreement with recent studies that include HIV/HCV-coinfected[25], and HCV-monoinfected individuals[27]. We previously reported higher first and faster second phase viral declines in genotype-3 compared to genotype-1 HIV/HCV co-infected patients[16]. In the current study, we identified a higher prevalence of IL28B CC-genotype in HCV genotype-3 cases, but no association between IL28B genotype and the second phase viral decline or the loss rate of HCV-infected cells, δ. Since the second-slope phase and/or δ correlate with the outcome of therapy[23], these findings suggest that the relatively rapid second phase viral decline in genotype-3 patients is related to factors other than the genetic polymorphism. Our observations might explain the lack of association between IL28B genotype and SVR in genotype-3 patients recently reported by Rallon et al.[25] In contrast, higher $\varepsilon_{7average}$ and δ were associated (trend, p=0.1) with CC-genotype in HCV genotype-1 infected patients. The trends observed in genotype-1 patients may reflect the small sample size and is anticipated to be significant in larger studies.

Previous studies of HCV mono-infected patients conducted in the United States reported a higher proportion of IL28B genotype-TC/TT in African Americans than in non-Hispanic Caucasians[10, 14]. In contrast, we did not identify a significant (p=0.5) difference in IL28B genotype frequencies between African Americans and White patients from Brazil (Table 1). The lack of an association between race and IL28B genotype in our South American patient population might partly explain the lack of association between race/ethnicity and viral kinetic parameters or viral response patterns in our recent reports[16, 17]. Indeed, preliminary results indicate that ~80% (of 353) of HCV-mono-infected individuals in Brazil are TC or TT with a similar distribution of CC/TC/TT genotypes between African Americans and Whites (Araujo et al. manuscript in preparation). Larger studies are needed to provide a comprehensive evaluation of IL28B genotypes and viral kinetics by race/ethnicity in South America, where patient ancestry may differ from that in the United States.

In conclusion, in HIV/HCV co-infected patients, the IL28B-CC genotype was most strongly associated with a higher first phase viral decline and greater average PEG-IFN effectiveness

during the first week of therapy, ε_{7max}. Pharmacodynamic analysis showed that genotype-CC conferred increased sensitivity to PEG-IFN, as shown by a lower PEG-IFN-α-2a EC_{50}. These kinetic findings raise the possibility that the IL28B CC-genotype favorably affects viral response by augmenting IFN-λ mediated activation of the IFN signaling cascade, leading to increased effectiveness in blocking virion production/release. Notably, as we approach a new era of combination therapy with PEG-IFN and direct antiviral agents, a better understanding of factors associated with PEG-IFN-related viral kinetics will provide the basis to develop optimal treatment strategies for HCV[28, 29]. Larger and more detailed studies are needed to confirm these new observations in HIV/HCV co-infected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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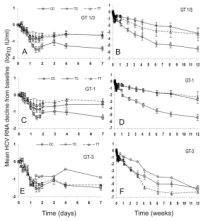

Figure 1. HCV kinetics per IL28B genotypes per HCV genotypes

(A) (C) and **(E)** early viral kinetics from initiation of therapy until day 7, in patients infected with HCV genotype-1/3 (GT-1/3), genotype-1 (GT-1) or genotype-3 (GT-3), respectively. **(B) (D)** and **(F)** viral kinetics from initiation of therapy until week 12, in patients infected with HCV genotype-1/3 (GT-1/3), genotype-1 (GT-1) or genotype-3 (GT-3), respectively. Statistical differences in the first and slower (second) phases of viral decline are shown in Table 1. Gray filled symbols represent undetectable HCV RNA (<10 IU/ml) in all patients at week 12. Vertical lines represent standard error of the mean (note that in **(E)** and **(F)** vertical lines in genotype-TC curve (circles) are missing since the curve represents one patient).

Table 1

Viral kinetic and pharmacodynamic parameters and IL28B polymorphism

Viral response parameter	All (n = 26 or 21**)		Genotype-1 (n=15)		Genotype-3 (n=11)		P value
	CC	TC/TT	CC	TC/TT	CC	TC/TT	All, Gen-1, Gen-3
1st phase viral decline, median [$log_{10}(V_0/V_{min})$] and (IQR)	1.7(0.6)	0.9(0.8)	1.5(0.3*)	0.7(0.9)	1.8(0.6)	1.4(0.1*)	**0.005**, **0.08**, 0.1
ε_{7max} [%], median (IQR)	94(11)	81(45)	91(6*)	76(44)	95(10)	86(14*)	**0.008**, 0.19, 0.10
$\varepsilon_{7average}$ [%], median (IQR)	92(13)	77(45)	87(9*)	73(45)	93(11)	84(13*)	**0.008**, 0.12, 0.10
ε_{max} [%], median (IQR)	96(6)	87(33)	95(3*)	84(35)	96(9)	91(14*)	**0.044**, 0.11, 0.6
EC_{50}, median (IQR)	1.3(1.8)	3.3(11.5)	2.9(2.4*)	3.6(11.4)	1.0(1.2)	3.0 (2.3*)	**0.02**, 0.6, 0.10
Viral rebound [V_{d7}/V_{min}], median (IQR)	1.6 (2.1)	1.7 (2.7)	1.1(0.4)	1.7(4.4)	1.7(1.0*)	2.1(5.7)	0.3, 0.11, 1.0
slower phase slope decline (d7–d15), median [log/wk] and (IQR)	1.13(1.12)	0.40(0.51)	1.13(0.55*)	0.32(0.61)	1.0 (1.3)	1.18 (0. 46*)	**0.046**, 0.11, 0.7
slower phase slope decline (d2–d29), median [log/wk] and (IQR)	0.67(0.64)	0.26(0.41)	0.54(0.25*)	0.22(0.20)	0.70(0.89)	0.98 (0.37*)	**0.01, 0.02**, 0.7
δ[1/day], median (IQR)	0.25(0.16)	0.13(0.10)	0.20(0.11*)	0.11(0.05)	0.25(0.13)	0.18(0.13*)	0.11, 0.11, 0.7

*One standard deviation; IQR, interquartile range; V_0, baseline HCV RNA level; V_{min}, the observed nadir HCV RNA in each patient[16] during the administration of the first dose of PEG-IFN; V_{7d}, HCV RNA level at day 7 of therapy; δ, death/loss rate of HCV-infected cells; EC_{50}, PEG-IFN concentration at which the drug's effectiveness in blocking viral production is half its maximum; ε_{7max}, maximum PEG-IFN effectiveness during the first week of therapy; $\varepsilon_{7average}$, average PEG-IFN effectiveness during the first week of therapy; ε_{max}, maximum PEG-IFN effectiveness from week 4 to week 12 of therapy;

**n=21 for δ, EC_{50}, ε_{7max}, $\varepsilon_{7average}$, ε_{max} parameters as recently estimated[17].