Genetic Variation in IL28B and Treatment-induced Clearance of Hepatitis C Virus in HIV-Positive Patients With Acute and Chronic Hepatitis C

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Recently, a IL28B (rs 12979860) gene polymorphism was identified as a predictor for response to hepatits C virus–specific treatment in human immunodeficiency virus (HIV)–uninfected and –infected patients with chronic hepatitis C. In an analysis of HIV-infected patients with acute hepatitis C, we found that the IL28B genotype was associated with serum levels of hepatitis C virus RNA, g-GT, and CD4 cell count. In contrast to HIV-infected patients with chronic hepatitis C, the IL28B genotype was not significantly associated with treatment response rates in patients with acute hepatitis C. Thus, effects of the IL28B single-nucleotide polymorphism may differ in HIV-infected patients with chronic and acute hepatitis C.

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In Europe and the United States, up to ~30% of human immunodeficiency virus (HIV)–infected individuals are coinfected with the hepatitis C virus (HCV) [1], and currently, outbreaks of acute hepatitis C in HIV-infected men have been reported. HCV-HIV coinfection is characterized by more rapid progression toward severe liver disease and has become a major health problem in HIV-infected patients [1].

Pegylated interferon (IFN)–α, in combination with ribavirin, represents the backbone of HCV-specific therapy. However, in clinical studies IFN-based combination therapy sustained virologic response (SVR) is achieved in only 50% of HCV-mono-infected patients and in a maximum of 40% of HCV-HIV–coinfected patients with chronic hepatitis C [1]; SVR may be even lower in clinical practice [2].

Although epidemiological, viral, and host factors have been associated with outcomes of HCV-specific treatment, most variability in SVR versus nonresponse remained incompletely understood.

Recently, several independent studies identified a single nucleotide polymorphism (SNP) on chromosome 19q13 (rs12979860) to be strongly associated with response to treatment in HIV-uninfected [3–7] and HIV-infected [7, 8] patients with chronic hepatitis C. This SNP is located ~3 kilobases upstream of the IL28B gene, which encodes for the type III IFN-3λ.

In the present study, we analyzed the impact of the IL28B-polymorphism in HIV-infected patients with acute hepatitis C.

Patients And Methods

Study Population

A total of 254 HIV-HCV–coinfected white patients were enrolled in the present study, including 157 patients with chronic and 97 patients with acute hepatitis C. Acute hepatitis C was diagnosed when at least 2 of the following 3 criteria were fulfilled within the 4 months prior to the diagnosis of HCV infection: (1) HCV seroconversion; (2) alanine aminotransferase level >350 IU, with prior normal aminotransferase levels; and (3) risk exposure to HCV (modified to reference [9]).

As a control, 418 HIV-uninfected, HCV-infected; 262 HIV-infected, HCV-uninfected; and 144 HIV-uninfected, HCV-uninfected healthy individuals were included.

The study received ethics approval from the local ethics committee.

IL28B Genotyping

IL28B genotyping was performed using the LightSNiP Typing Assay (TIB MOLBIOL). In brief, each 10-μL reaction contained

1 μL LightCycler-FastStart Reaction Mix Hybridization Probes (Roche), 3.0 mmol/L magnesium chloride, and .5 μL of the primers and probes containing LightSNiP reagent. The amplification conditions on the LightCycler Instrument (Roche) consisted of 1 denaturation/activation cycle of 10 min at 95°C and 45 cycles of amplification. Each amplification cycle consisted of 95°C for 10 s, 60°C for 10 s, and 72°C for 15 s, with a single fluorescent acquisition step at the 60°C hold. This was followed by a melting curve analysis of 95°C for 20 s, 40°C for 20 s, and a slow ramp (.2°C/s) to 85°C with continuous fluorescence acquisition.

Statistics

Allele and genotype frequencies were analyzed and tested for consistency with use of Hardy-Weinberg equilibrium with software designed by Strom and Wienker (http://ihg.gsf.de/ihg/snps.html). For the association (case-control) study, we selected patients with SVR as case patients. Allele and genotype frequencies were compared between case patients (SVR) and control subjects (patients with nonresponse) with use of 2×2 contingency tables and Armitage's trend test, respectively.

For statistical comparisons between the groups, the χ^2 test, Fisher's exact test, and the Mann-Whitney *U* test were used as appropriate. All calculations were performed using SPSS, version 17.0 (SPSS).

Results

Genotype Distribution

IL-28B rs12979860 genotype distribution did not differ significantly between HIV-infected patients with acute (C/C 49 [50.5%], C/T 41 [42.3%], T/T 7 [7.2%]) and chronic hepatitis C (C/C 72 [45.9%], C/T 75 [47.8%], T/T 10 [6.4%]). Moreover, distribution of IL-28B genotypes in both cohorts of coinfected patients was similar to that seen in healthy individuals (C/C 58 [40.3%], C/T 69 [47.9%], T/T 17 [11.8%]) but differed significantly to that found in individuals with HCV infection (C/C 144 [34.4%], C/T 209 [50%], T/T 65 [15.6]; $P = .001$ vs. HIV/acute HCV; $P = .001$ vs. HIV/chronic HCV) or HIV mono-infection (C/C 100 [40.3%], C/T 126 [48%], T/T 36 [13.7]; $P = .02$ vs. HIV/acute HCV; $P = .02$ vs. HIV/chronic HCV).

All distributions were in accordance with the Hardy Weinberg equilibrium.

IL-28B rs12979860 and HCV-Related Parameters

No statistically significant differences could be detected in demographic variables, route of infection, or distribution of HCV genotypes between carriers of different IL-28B genotypes in HCV-HIV coinfection (data not shown).

However, in HIV-infected patients with acute or chronic hepatitis C, carriage of a C/C genotype was associated with significantly lower mean g-GT levels, compared with patients with a non-C/C genotype (acute HCV: 258 IU/mL [range, 77–476 IU/mL] vs. 526 IU/mL [range, 92–962 IU/mL] IU/mL; $P = .05$; chronic HCV: 76 IU/mL [range, 11–193 IU/mL] vs. 145 IU/mL [range, 12–916 IU/mL]; $P = .03$). Of note, this association could not be confirmed in patients with HIV and HCV mono-infection (Table 1).

Moreover, in HIV-infected patients with acute hepatitis C, we found that carriers of the C/C genotype had significantly higher mean HCV loads (1.6×10^6 IU/mL; range, <.01 to 12.4 IU/mL) than did patients with another genotype ($.5 \times 10^6$ IU/mL ; range, <.01 to 4.6 IU/mL; $P = .023$). A similar effect was also seen in patients with chronic HCV mono-infection (2.8×10^6 IU/mL [range, <.01 to 133 IU/mL] vs. 1.6 IU/mL [range, <.01–61 IU/mL]; $P < .001$) but could not be confirmed in the group of HIV-infected individuals with chronic hepatitis C (Table 1).

Finally, the IL28B genotype was significantly associated with alanine aminotransferase serum levels in patients with HCV mono-infection (CC: mean level, 109 [range, 14–748 IU/mL]; non-C/C: mean level, 69 [range, 11–405 IU/mL]; $P < .001$) but not in individuals with HCV-HIV coinfection (Table 1).

IL-28B rs12979860 and HIV-Related Parameters

Among HIV-infected patients with chronic hepatitis C, carriers with a non-C/C genotype displayed significantly higher mean HIV RNA serum levels, compared with C/C carriers (38.6×10^3 copies/mL [range, <.01 to 500×10^3 copies/mL] vs. 13.8×10^3 copies/mL [range, <.01–100×10^3 copies/mL; $P = .03$). Of interest, the opposite was true in patients with acute HCV coinfection, although this difference did not reach statistical significance ($P = .09$).

Regarding CD4 cell count, we found that C/C carriers with acute HCV coinfection had significantly lower mean CD4 cell count (457 cells/μl; range, 148–1074 cells/μl) than did patients with a non-C/C genotype (573 cells/μl; range, 162–1074 cells/μl; $P = .01$). No such association was observed in patients with chronic coinfection (Table 1).

IL-28B rs12979860 Genotype and Treatment Response

Data on treatment response were available from 74 HIV-infected patients with acute hepatitis C and 118 HIV-infected patients with chronic HCV infection. HCV-HIV–coinfected patients with chronic HCV infection were treated with pegylated IFN-α and body weight–adapted doses of ribavirin according to standard recommendations [10]. HCV-HIV–coinfected patients with acute HCV infection without spontaneous viral clearance 12 weeks after presumed date of infection or date of diagnosis were offered a pegylated IFN and ribavirin combination therapy over a 24-week course [11]. In addition, 156 patients with chronic hepatitis C mono-infection who received combination therapy were included.

In both HIV-uninfected and HIV-infected patients chronically infected with HCV, we found a significant association between IL28B genotype and treatment response, with carriers of

Table 1. IL28B rs12979860 genotype and clinical parameters

	IL-28B Genotype		
	C/C	non-C/C	P-value
HIV(+) acute HCV (n=97)			
Female sex[a]	1 (2%)	1 (2%)	n.s.
Age (years)[b]	45 (30 - 58)	43 (28 - 60)	n.s.
Risk Factors			
I.V. Drugs[a]	0	0	n.s.
Blood Transfusion[a]	0	0	
Heterosexual[a]	1 (2%)	1 (2%)	
Haemophilia[a]	0	0	
MSM[a,b]	48 (98%)	47 (98%)	
Endemic[a]	0	0	
Unknown[a]	0	0	
HCV status			
ALT (IU/mL) [b]	593 (28 - 2288)	585 (24 - 3089)	n.s.
AST (IU/mL) [b]	357 (138 - 479)	311 (199 - 424)	n.s.
g-GT (IU/mL)[b]	258 (77 - 476)	526 (92 - 962)	*.05*
HCV RNA level (x10^6 IU/mL) [b]	1.6 (<.01–12.4)	0.5 (<.01–4.6)	*.023*
HIV status			
HIV RNA level (x10^3 copies/μl) [b]	213 (<.01–2190)	115 (<.01–1371)	*.09*
CD4 cell count (cells/μl) [b]	457 (148 - 1074)	573 (162 - 1074)	*.01*
HIV(+) chronic HCV (n=157)			
Female sex[a]	15 (21%)	15 (18%)	n.s.
Age (years)[b]	47 (32 - 69)	46 (28 - 73)	n.s.
Risk Factors			
I.V. Drugs[a]	27 (39%)	30 (35%)	n.s.
Blood Transfusion[a]	0	1 (1%)	
Heterosexual[a]	2 (2%)	0	
Haemophilia[a]	37 (51%)	42 (49%)	
MSM[a,b]	5 (7%)	7 (8%)	
Endemic[a]	1 (1%)	1 (1%)	
Unknown[a]		5 (6%)	
HCV status			
ALT (IU/mL) [b]	94 (124 - 916)	84 (10 - 450)	n.s.
AST (IU/mL) [b]	79 (15-197)	71 (13 - 267)	n.s.
g-GT (IU/mL)[b]	76 (11 - 193)	145 (12 - 916)	*.03*
HCV RNA level (x10^6 IU/mL) [b]	0.9 (<.01–6.7)	0.9 (<.01–8)	n.s.
HIV status			
HIV RNA level (x10^3 copies/μl) [b]	13.8 (<.01–100)	38.6 (<.01–500)	*.03*
CD4 cell count (cells/μl) [b]	479 (44 - 1902)	462 (16 - 1170)	n.s.
HIV(+) chronic HCV (n=418)			
Female sex[a]	59 (41%)	118 (43%)	n.s.
Age (years)[b]	50 (25 - 85)	51 (28 - 81)	n.s.
Risk Factors			
I.V. Drugs[a]	34 (23%)	52 (19%)	n.s.
Blood Transfusion[a]	22 (15%)	38 (14%)	
Heterosexual[a]	1 (1%)	2 (1%)	
Haemophilia[a]	2 (2%)	1 (1%)	
MSM[a,b]	1 (1%)	0	
Endemic[a]	0	0	
Unknown[a]	84 (58%)	179 (65%)	

Table 1. (*Continued*)

	IL-28B Genotype		
	C/C	non-C/C	P-value
HCV status			
ALT (IU/mL) [b]	109 (14 - 748)	69 (11 - 405)	<.001
AST (IU/mL) [b]	62 (9 - 363)	45 (8 - 173)	n.s.
g-GT (IU/mL)[b]	75 (4 - 1352)	75 (8 - 586)	n.s.
HCV RNA level (x10^6 IU/mL) [b]	2.8 (<.01–133)	1.6 (<.01–61)	<.001
HIV status			
HIV RNA level (x10^3 copies/μl) [b]	-	-	-
CD4 cell count (cells/μl) [b]	n.d.	n.d.	-
HIV mono-infection (n=262)			
Female sex[a]	15 (15%)	30 (19%)	n.s.
Age (years)[b]	50 (28 - 81)	48 (27 - 73)	n.s.
Risk Factors			
I.V. Drugs[a]	0	9 (6%)	n.s.
Blood Transfusion[a]	1 (1%)	0	
Heterosexual[a]	20 (20%)	34 (21%)	
Haemophilia[a]	0	0	
MSM[a,b]	66 (66%)	91 (56%)	
Endemic[a]	10 (10)	28 (17%)	
Unknown[a]	3 (3%)	0	
HCV status			
ALT (IU/mL) [b]	34 (7 - 227)	38 (14 - 279)	n.s.
AST (IU/mL) [b]	30 (11 - 105)	28 (11 - 98)	n.s.
g-GT (IU/mL)[b]	47 (10 - 243)	60 (10 - 669)	n.s.
HCV RNA level (x10^6 IU/mL) [b]	-	-	-
HIV status			
HIV RNA level (x10^3 copies/μl) [b]	23.2 (<.01–66)	26.9 (<.01–79)	n.s.
CD4 cell count (cells/μl) [b]	528 (18 - 1822)	481 (10 - 2161)	n.s.

a C/C genotype showing significantly higher SVR rates relative to patients with the C/T and T/T genotypes combined (HIV-uninfected patients: 30 [65.2%] of 46 vs. 48 [46.6%] of 110; odds ratio, .4; $P = .015$; HIVinfected patients: 28 [50%] of 56 vs. 18 [29%] of 62; odds ratio, .5; $P = .02$) (Table 2A).

Of note, in HIV-infected patients with acute HCV infection, SVR rates only slightly differed between carriers of different IL-28B genotype (Table 2A). Patients with a C/C genotype had somewhat higher treatment response rates (25 [71.4%] of 35) than did individuals with a C/T (20 [58.8%] of 34) and a T/T (3 [60%] of 5) genotype, respectively. However, this difference was not statistically significant. This was also true when only patients with a HCV genotype 1 infection were analyzed (C/C: 19 [73%] of 30; C/T: 10 [54%] of 19; 1 [50%] of 2; $P = .3$) (data not shown).

Next, we performed a univariate analysis to identify the relative contribution of possibly confounding factors (viral load, sex, and HCV genotype) other than IL-28B on outcome of HCV therapy in HCV-HIV–coinfected patients.

In the subgroup of HIV-infected patients with chronic hepatitis C and in patients with chronic HCV mono-infection, both HCV genotype and the IL-28B polymorphism were significantly associated with response to treatment, whereas in HIV-infected individuals with acute hepatitis C, none of the tested factors was a predictor of response (Table 2B).

Discussion

Response to HCV-specific treatment differs between HCV mono-infected patients and individuals with HCV-HIV coinfection but may be affected by the same host genetic factors.

Recently, several independent studies demonstrated that the rs12979860 SNP was significantly associated with response to combination therapy with pegylated IFN-α and ribavirin in HIV-uninfected [3–7] and HIV-infected [7, 8] patients with chronic – HCV infection.

In the present study, we analyzed the potential role of this polymorphism in HIV-infected patients with acute hepatitis C.

Of interest, we found several differences between patients with acute and chronic HCV infection.

Table 2. Association between IL28B rs 12979860 genotype and SVR. 2A. Univariate analysis describing the effect of IL28B rs12979860 on SVR

Genotype	Frequency of SVR (%)	Frequency of NR (%)	Comparison	OR (95% CI)	*P*-value
HIV(+) patients with acute hepatitis C					
T/T	3/5 (60%)	2/5 (40%)	T/T vs. C/C	0.6 [.1–5.8]	*P*=.6
C/T	20/34 (58.8%)	14/34 (41.2%)	C/T vs. C/C	0.6 [.2–1.6]	*P*=.4
C/T + T/T	23/39 (59%)	16/39 (41%)	C/T + T/T vs. C/C	0.2 [.1–1.5]	*P*=.3
C/C	25/35 (71.4%)	10/35 (26.7%)	-	-	-
HIV(+) patients with chronic hepatitis C					
T/T	1/8 (12.5%)	7/8 (87.5%)	T/T vs. C/C	0.1 [.01–1]	*P*=.05
C/T	17/54 (31.5%)	37/54 (69.5%)	C/T vs. C/C	0.5 [.2–1]	*P*=.05
C/T + T/T	18/62 (29%)	44/62 (71%)	C/T + T/T vs. C/C	0.4 [.2–.9]	*P*=.02
C/C	28/56 (50%)	28/56 (50%)	-	-	-
chronic HCV mono-infection					
T/T	6/23 (26.1%)	17/23 (73.9%)	T/T vs. C/C	0.2 [.06–.5]	*P*=.003
C/T	42/87 (48.3%)	45/87 (51.3%)	C/T vs. C/C	0.5 [.2–1]	*P*=.05
C/T + T/T	48/110 (46.6%)	62/110 (53.4%)	C/T + T/T vs. C/C	0.4 [.2–.8]	*P*=.015
C/C	30/46 (65.2%)	16/46 (34.8%)	-	-	-

NOTE. SVR - sustained virological response; OR - odds ratio; NR - non-response; CI - confidence intervall.

First, in HIV-infected individuals with acute hepatitis C, carriage of a IL28B C/C genotype was associated with higher HIV RNA levels ($P = .09$) but lower CD4 cell counts, compared with patients with a non-C/C genotype ($P = .01$), whereas in chronic co-infection, C/C carriers had lower HIV loads than did non-C/C carriers and no association was found between Il28B genotype and CD4 cell counts. Of note, these differences were also found after stratification of patients according to highly

Table 2B. Multivariate regression model describing the effect of independent predictors on SVR

	Multivariable model	OR (95% CI)	*P*
HIV/Acute HCV (n=74)	HCV genotype 1	1[a]	
	HCV genotype non-1	1.5 (.5–4.6)	*.45*
	HCV load > 6 x10^5 IU/mL	1[a]	
	HCV load < 6 x10^5 IU/mL	1.1 (.4–3.3)	*.8*
	Female	n.a.	
	Male		
	IL- 28 C/T + T/T	1[a]	
	IL-28 C/C	1.7 (.7–4.6)	*.27*
HIV/Chronic HCV (n=118)	HCV genotype 1	1[a]	
	HCV genotype non-1	2.4 (1.1–5.4)	*.026*
	HCV load > 6 x10^5 IU/mL	1[a]	
	HCV load < 6 x10^5 IU/mL	3.8 (.95–15.4)	*.59*
	Female	1[a]	
	Male	0.4 (.1–2.5)	*.4*
	IL- 28 C/T + T/T	1[a]	
	IL-28 C/C	4 (1–13.8)	*.028*
HCV genotype 1	1[a)]		
	HCV genotype non-1	4.2 (2.1–8.5)	*<.001*
	HCV load > 6 x10^5 IU/mL	1[a]	
	HCV load < 6 x10^5 IU/mL	1.5 (.8–2.9)	*.19*
	Female	1[a]	
	Male	0.92 (.5–1.7)	*.8*
	IL- 28 C/T + T/T	1[a]	
	IL-28 C/C	1.9 (1.1–3.3)	*.022*

active antiretroviral therapy and infecting HCV genotype (data no shown). Of interest, none of these associations were observed in HIV mono-infected patients.

Second, HCV RNA levels were significantly different between carriers of a C/C and non-C/C genotypes in HIV-infected patients with acute infection but not in those with chronic hepatitis C.

Finally, the association between IL-28B rs12979860 genotypes and SVR rates was less pronounced in acutely infected patients. Although in both HIV-infected patients with acute and chronic hepatitis C carriers of a C/C genotype had higher response rates, compared with non-C/C carriers, this difference failed to reach statistical significance in patients with acute hepatitis C (71.4% vs. 59%; the *P* value was not statistically significant). This was also true when only patients with acute HCV GT 1 infection were analyzed (73% vs. 54%; the *P* value was not statistically significant). This may in part be attributable to inclusion of an insufficient number of patients in our study. However, sample size calculation revealed that ~300 patients with acute HCV GT1 infection would be needed to achieve statistical significance, which suggests a rather low predictive value of the IL28B in HIV-infected patients with acute hepatitis C.

Moreover, response rates in acutely HCV-infected carriers of a T allele were significantly higher than in T allele carriers with chronic hepatitis C (23 [59%] of 49 vs 29 [32%] of 62; $P = .013$) and even exceeded SVR rates in the chronically infected patients with a C/C genotype (28 [50%] of 56). Thus, high response rates in acute hepatitis C may just mask the effect of the IL28B polymorphism in this subpopulation of coinfected patients.

Currently, it is only incompletely understood how the rs12979860 polymorphism affects hepatitis C virus infection. SNP IL28B rs12979860 maps ~3 kb upstream of the IL28B gene and has been shown to be in linkage disequilibrium with a genetic variant in the IL28B gene (213A→G, K70R, rs8103141) and may thus affect function of type III IFN IL28B [3].

IFN-λ1, another member of the type III IFNs, has been shown to inhibit HCV in a dose- and time-dependent fashion and recent in vitro data suggest that IFN-λ3 may have functions comparable to those of IFN-λ1 [12, 13].

Thus, it is somewhat counter-intuitive that C allele carriage was associated with significantly higher HCV RNA levels, compared with the T allele. However, similar data have been presented by Ge et al [3], who discussed that this may relate to the recently demonstrated association between high expression of and nonresponse to pegylated IFN [14]. Thus, Ge and colleagues suggested that the *IL28B* polymorphism may affect intrahepatic ISG expression, thereby affecting both viral load and treatment response. In line with this hypothesis, Honda et al [15] demonstrated an association between Il28B genotype and expression of IFN-stimulated genes. Of note, IFN-stimulated gene expression positively correlated with g-GT serum levels. In this context, it is of interest that we found an association between high g-GT levels and Il28B non-C/C genotypes in coinfected but not in HCV mono-infected patients. Whether this finding reflects high IFN-stimulated gene expression remains to be evaluated. However, low g-GT levels were associated with SVR in HIV-HCV–coinfected patients (odds ratio, 4; $P = .007$) but not in those with HCV mono-infection.

Taken together, our data suggest that effects of the IL28B SNPs may differ in HIV-infected patients with chronic and acute hepatitis C.

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