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Race or Genetic Makeup for HCV Treatment Decisions?

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To the Editor

Examining data from the VA healthcare system, Su et al(1) report high overall response rates with direct-acting antiviral regimens for hepatitis C, but also that 8 weeks of ledipasvir/sofosbuvir was less effective in black patients than whites. They suggest 8-week treatment is contraindicated in black patients.

Rather than race, it is preferable to use an individual's genetic makeup as the basis for clinical decisions. *IFNL4* genotypes are strongly associated with spontaneous HCV clearance and response to interferon- α treatment for hepatitis C; higher frequencies of unfavorable *IFNL4* alleles in blacks explained racial differences in those outcomes(2). *IFNL4* genotype may also explain lower response to ledipasvir/sofosbuvir in black patients.

Previously, we showed that *IFNL4* rs12979860 ('IL28B') genotype was associated with relapse after 8-week therapy with ledipasvir/sofosbuvir in ION-3 (3). Here we expand that analysis to include published data from two other treatment groups with at least 10 patients who suffered relapse after receiving ledipasvir/sofosbuvir in phase III trials: ION-4 (HCV/HIV co-infected; 12-week treatment)(4) and seven pooled clinical trials of patients with compensated cirrhosis (12-week treatment)(5). Full rs12979860 genotype data were published for ION-3 and ION-4 (Table 1) with relapse rates of 0–2% for rs12979860-CC

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genotype compared to 9–10% for rs12979860-TT. Combining those studies reveals a highly significant association across genotype categories ($p_{\text{trend}} = 0.0002$); patients with rs12979860-TT genotype were ~4.5 times more likely to relapse than those with rs12979860-CC. For the cirrhotic patients, data on all three genotype categories were not published, however, rs12979860-CC patients had a 1.2% relapse rate (Table 1).

Our analysis is limited because individual patient data were unavailable. Also, although rs12979860 marks the functional *IFNL4* G/TT variant, the latter is a better predictor of treatment response, especially in black patients(2). Therefore, we may have underestimated the association between *IFNL4* genotype and relapse.

Individual level data from populations of diverse racial composition are needed to fully explore relationships between *IFNL4* genotype, race and treatment response. With its large number of HCV-infected patients, the VA healthcare system could address this important question.

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Proportions of patients who suffered virological relapse in response to treatment with ledipasvir/sofosbuvir, by *IFNL4* rs12979860 genotype.

Table 1

Study (Relapses / Total)	ION-3 (20 / 423)		ION-4 (10 / 322)		ION-3 and ION-4 Combined**			Cirrhosis (15 / 307)	
	Relapse	p-value	Relapse	p-value	RR	95% CI	p-value	Relapse	p-value
<i>IFNL4</i> rs12979860									
CC	1.8%		0.0%					1.2%	
CT	4.9%		1.6%		2.74	0.74–10.17		5.8% ⁺	
TT	9.1%	0.03 [*]	10.3%	0.001 [*]	4.58	1.26–16.56	0.0002 [*]		

RR, relative risk of virological relapse; 95% CI, 95% confidence interval

^{*} p-value for trend;

^{**} Cochran-Mantel-Haenszel statistics were used to calculate combined relapse rates