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ORIGINAL ARTICLE

Superior response to pegylated interferon and ribavirin in Asians with chronic hepatitis C

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Abstract
Purpose Reported sustained virological response (SVR) rates in Asians with chronic hepatitis C (CHC) exceed those of other ethnic groups, but differences in body weight across races potentially confound this observed superior response. Our aim was to determine whether Asian race independently predicts SVR within a multicultural clinic setting.
Methods Patients with genotype 1, 2 and 3 CHC prescribed peginterferon and weight-based ribavirin were included in this retrospective study. Logistic regression was performed to identify factors associated with SVR.
Results Three-hundred ninety-two patients (BMI 26.9 ± 5.0 kg/m^2, genotype 1 66%, viral load 5.9 ± 0.66 $\log_{10}$ IU/ml, advanced fibrosis 53%) were included in this study. Caucasians comprised 81%, South Asians 9% and Asians (Non-South) 10%. SVR was achieved by 54% overall, but was highest amongst Asians (Non-South) (79%) compared with South Asians (56%, $P = 0.04$) and Caucasians (50%, $P < 0.001$) despite a predominance of genotype 3 infection amongst the South Asians. Asians (Non-South) had the highest SVR rate even amongst those infected with genotype 1 (75%) and those with advanced fibrosis (77%). Independent of viral genotype, Asian (Non-South) race was a strong predictor of SVR (OR 5.10 vs. Caucasians, 95% CI 1.72–17.71, OR 7.84 vs. South Asians, 95% CI 1.62–37.84), as were treatment naïve status (OR 3.85, 95% CI 1.76–8.89), non-diabetic status (OR 3.70, 95% CI 1.30–11.11), non-obesity (OR 2.13, 95% CI 1.06–4.35), peginterferon α2a (2.08 vs. α2b, 95% CI 1.16–3.85), steatosis <10% (OR 2.0, 95% CI 1.05–3.85) and ribavirin exposure (mg/kg/day) (OR 1.13, 95% CI 1.01–1.28).
Conclusion Asian (Non-South) race is a strong independent predictor of SVR.

Keywords Asian · Sustained virological response · Body mass index · Weight · Obesity · Diabetes · Chronic hepatitis C

Abbreviations

BMI	Body mass index
CHC	Chronic hepatitis C
CI	Confidence interval
HCV	Hepatitis C virus
IFN	Interferon
OR	Odds ratio
SVR	Sustained virological response

Introduction

The current standard of care in the treatment of chronic hepatitis C (CHC) is combination therapy with pegylated interferon and ribavirin [1, 2]. A number of viral and host factors impact the likelihood of achieving sustained virological response (SVR). Infection with genotype 1 HCV and high baseline viral load are strongly associated with diminished treatment response rates [1–3]. Host factors associated with reduced rates of SVR include obesity, insulin resistance (and overt diabetes), presence of

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advanced fibrosis or hepatic steatosis and both patterns of hepatic gene expression and polymorphisms of the interferon-λ gene [4–9].

The response to antiviral therapy also appears to be influenced by ethnicity. Reduced rates of SVR have been reported amongst African Americans, Hispanics and South Asians when compared to their Caucasian counterparts [10–12]. In contrast, studies arising from Eastern Asia report high rates of SVR, 79% in patients with genotype 1 and 95% with genotype 2 CHC [13, 14]. The rate of SVR in Asians, not differentiated into South or Asians (Non-South), was significantly higher when compared to Caucasians (65 vs. 45%), but in that study, patients had received only 800 mg/day ribavirin regardless of viral genotype [15]. Whilst the latter reports suggest that Asians have a higher SVR rate than non-Asians, it is possible that the differences were due to systematic differences in how HCV was treated at different sites, such as the policies regarding dose reduction and the use of weight-based ribavirin.

The response to antiviral therapy does not appear to be uniform amongst all Asians. A small study reports that South Asians infected with the "favourable" genotype 3 HCV have a lower rate of SVR than Caucasians and to other Asian historical controls [12]. The reasons for a superior response in Asians from regions other than South Asia, hereafter referred to as Asians (Non-South), are not evident. Low body weight and body mass index (BMI) are potential factors which confound the high observed rates of SVR in Asians (Non-South). We have previously reported that obesity (BMI $\geq$ 30 kg/m^2) is a negative predictor of SVR, where weight-based dosing of ribavirin was not used [16]. Individuals with low body weight receive a higher dose of ribavirin per kilogram body weight which is shown to be associated with lower relapse and higher SVR rates [17]. Lower body weight is reported to be associated with rapid virological response (RVR), the single best predictor of SVR [18].

Aside from these potential confounders, race-specific host genetic variation may influence the efficacy of interferon-based therapy. Genetic polymorphisms of human leukocyte antigen, TNFα-308 promoter gene, suppressor of cytokine signalling (SOCS)-3 gene and interferon-λ 28B (IL28B) are examples of host-related differences that may influence response to interferon [7–9, 19–22]. Ethnicity may be a surrogate for such genetic polymorphisms; studies are yet to determine how the prevalence of such genetic markers differs between racial groups and specifically how they relate to treatment outcome.

To determine whether there is a true discrepancy in treatment response between Asians (Non-South) and other ethnic groups, we examined the treatment response controlling for confounders including BMI and ribavirin exposure (ribavirin dose per kilogram body weight). To our knowledge, this is the first report comparing the response to the current therapeutic standard of care in Asians (Non-South) to South Asians, to Caucasians treated at a single site.

Patients and methods

This retrospective study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Research Ethics Board of the University Heath Network. All patients infected with genotypes 1, 2 or 3 CHC treated with pegylated interferon-α and ribavirin (outside the context of a clinical trial) from June 2001 to March 2009 at the Toronto Western Hospital were eligible for inclusion. Patients with HCV genotype 1 infection received 48 weeks of either pegylated interferon-α2a 180 mcg weekly plus ribavirin 1,000 or 1,200 mg daily [for body weight (BW) $<$75 or $\geq$75 kg, respectively] or pegylated interferon-α2b 1.5 mcg/kg weekly plus daily ribavirin 800 mg (BW $<$ 65 kg), 1,000 mg (BW = 65–85 kg) or 1,200 mg (BW $>$ 85–105 kg). Patients with genotype 2/3 infection received pegylated interferon-α2a 180 mcg weekly or pegylated interferon-α2b 1.5 mcg/kg weekly plus ribavirin 800–1,200 mg daily according to body weight (aiming for a dose of 13–15 mg/kg). The duration of therapy for genotype 2/3 patients was 24 weeks (standard therapy).

The HCV genotype testing prior to January 2007 was performed using INNO-LiPA HCV genotype assay (Innogenetics, Belgium), between January and November 2007 using Versant HCV Genotype 2.0 Assay (LiPA) (Seimens Healthcare Diagnostics, Tarrytown, NY, USA), for the latter part of the study period using HCVG Genotyping Assay (Third Wave Technologies, Madison, WI, USA). All three assays are able to distinguish HCV genotype 6 from genotype 1.

The clinic database was interrogated for patients' age at initiation of treatment, gender, genotype, pretreatment viral load, diagnosis of diabetes mellitus (type 1 or 2), weight and height, and BMI. For those in whom liver biopsy had been performed as part of standard of care, fibrosis score (Laennec criteria) and steatosis (%) were recorded. The presence of cirrhosis by clinical criteria was also determined (splenomegaly, thrombocytopenia, radiological or clinical evidence of portal hypertension).

Self-reported ethnicity and country of origin were obtained from the database. Patients included were categorised as Caucasian, South Asian or Asian (Non-South). South Asians were patients originating from India, Pakistan, Sri Lanka or Bangladesh. Patients originating from Asian countries other than South Asia were categorised as

Asian (Non-South). Because of their small numbers, patients of ethnicity other than those specified above were excluded from analysis.

Taking dose reductions or dose interruptions into account, the average daily ribavirin exposure (per kilogram body weight) was calculated for each patient using the equation:

$$(\text{ribavirin dose}_1 \times \text{number of weeks}_1 + \text{ribavirin dose}_2 \times \text{number of weeks}_2 \cdots + \text{ribavirin dose}_n \times \text{weeks}_n)$$

divided by total number of weeks of treatment, divided by body weight (kg).

Null responders (those achieving <2 log drop in viral load after 12 weeks of therapy) were included in the final analysis. Exclusion criteria were: extended duration treatment (>24 weeks in genotype 2/3 patients or >48 weeks in genotype 1); genotype 4, 5 and 6 infection; coexistence of other liver disease (HBV, HIV, autoimmune hepatitis, liver transplantation).

The primary outcome was SVR, defined as a negative HCV RNA PCR 6 months after cessation of antiviral therapy (Roche Amplicor assay, LLD 50 IU/ml, prior to 2007; Taqman assay LLD 15 IU/ml since 2007). Null responders, non-responders (positive HCV RNA at end of treatment) and relapsers (negative HCV RNA at end of treatment with subsequent positive HCV RNA after cessation of therapy) were grouped together and categorised "non-SVR".

Data were analysed using SAS System v.9.1.3 (SAS Institute Inc., NC, USA). Student *t* tests, one way ANOVA, fisher exact test and χ^2 test were performed (where applicable) in order to identify variables to enter the multivariate logistic regression model. BMI was analysed categorically based on World Health Organization definition of obesity (BMI $\geq$ 30) [23] and repeated after recategorising the Asian patients using the suggested race-specific BMI cut-off for obesity (BMI $\geq$ 27.5) [24]. Multiple logistic regression by intention-to-treat (ITT) was performed adjusting for cases with inadequate therapy, and treating those with missing treatment outcomes as non-SVR cases. As the primary aim of the study was to determine the influence of race (as a surrogate for host genetic variation) on treatment outcome, multiple logistic regression analysis was also performed to identify factors independently associated with SVR including *only* patients who received adequate dose and duration of therapy in line with the standard of care and also had a documented treatment outcome [per protocol (PP) analysis]. Inadequate treatment was defined as receiving less than 80% of the prescribed treatment dose for less than 80% of the duration of therapy (due to adverse events or lack of adherence).

Results

During the study period, 475 patients were prescribed pegylated interferon and ribavirin outside of a clinical trial. Eighty-three patients (17.5%) were excluded from the intention-to-treat analysis, and further 57 patients were excluded from the per protocol analysis (details in Fig. 1). Therefore, 392 patients were included in the intention-to-treat analysis and 335 included in the per protocol analysis. The vast majority of the patients (329/392, 84%) were interferon-naïve.

Patients' characteristics

Table 1 lists the characteristics of the 392 patients included in the ITT analysis broken down into ethnic groups. The study cohort comprised Caucasians (81%), Asians (Non-South) (10%) and South Asians (9%). The Asian (Non-South) patients originated from Vietnam (19), China (7), Hong Kong (4), Taiwan (1), Singapore (1), Japan (1), Korea (1), Burma (1), Cambodia (1) and Philippines (3). There were clear differences in the characteristics of the racial groups that could be considered to potentially confound the contribution of race to treatment outcome. Genotype 1 was the most prevalent across the entire cohort (66%), except in South Asians where genotype 3 predominated (79%). Asians (Non-South) had the lowest body weight and the lowest prevalence of obesity (0%), but the highest prevalence of genotype 1 (82%) and highest prevalence of diabetes (18%). When race-specific BMI cut offs were used to redefine obesity in the Asians, the prevalence of obesity for Asians (Non-South) and South Asians were 9 and 58%, respectively. Gender, pretreatment viral load (and prevalence of high viral load >800,000 IU/ml) and type of pegylated interferon prescribed were not significantly different between the ethnic groups.

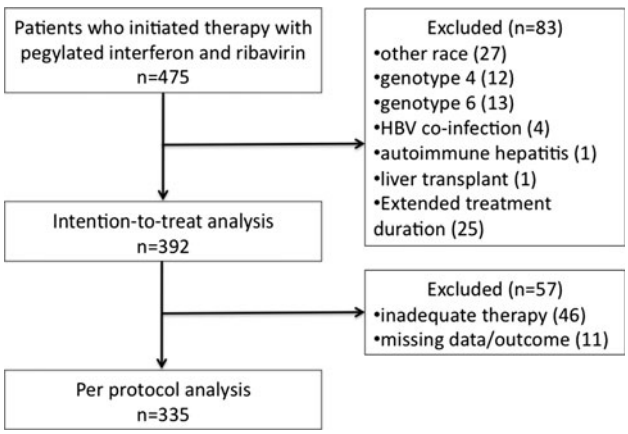

Fig. 1 Patient flow illustrating the characteristics of the intention-to-treat and per-protocol cohorts

Table 1 Patient characteristics (ITT)

Characteristic	Asian (Non-South)	South Asian	Caucasian	*P* value
Number of subjects	39 (10%)	34 (9%)	319 (81%)	
Age (years)	51.5 ± 11.0	46.7 ± 11.2	49.4 ± 9.2	0.105
No. of males	21 (54%)	23 (68%)	215 (67%)	0.236
Genotype				
1	32 (82%)	5 (15%)	223 (70%)	<0.001
2	5 (13%)	2 (6%)	43 13%)	
3	2 (5%)	27 (79%)	53 (17%)	
Pretreatment viral load (log_{10} IU/ml)	6.0 ± 0.6	5.9 ± 0.8	5.8 ± 0.6	0.418
Weight (kg)	59.6 ± 12.0	74.9 ± 12.9	80.4 ± 15.6	<0.001
BMI (kg/m^2)	22.4 ± 3.5	27.5 ± 4.8	27.4 ± 4.9	<0.001
Obese (WHO definition)	0 (0%)	7 (27%)	69 (24%)	<0.001
Obese (Asian definition)	3 (9%)	15 (58%)	69 (24%)	<0.001
Diabetes (type 1 or 2)	7 (18%)	6 (18%)	24 (8%)	0.021
Advanced fibrosis (F3–F4 or clinical features of cirrhosis)	22 (59%)	15 (48%)	171 (58%)	0.577
Steatosis ≥10%	5 (16%)	15 (60%)	73 (27%)	0.001
Treatment naïve status	33 (85%)	33 (97%)	263 (82%)	0.064
PegIFN 2a	18 (46%)	15 (44%)	200 (63%)	0.023
Calculated ribavirin dose received (mg/kg/day)	15.0 ± 3.0	12.7 ± 2.3	12.6 ± 2.4	<0.001
Received "adequate" therapy (>80% dose, 80% duration)	34 (87%)	33 (97%)	275 (86%)	0.203

Data are expressed as *n* (%) or mean ± SD

Pretreatment liver biopsy had been performed in 338 of 392 patients. Fifty three percent of the entire cohort had either biopsy-proven advanced fibrosis (F3–F4) or clinical evidence of cirrhosis; there was no difference in prevalence across the racial groups. Steatosis ≥10% was observed in 28% of the liver biopsies. South Asians had the highest prevalence of steatosis ≥10% (60%) in keeping with the predominance of genotype 3 infection and prevalence of obesity amongst this sub-group.

Dose reduction of peginterferon was required in 8% of patients, and ribavirin dose reduction in 15% of patients, without difference in occurrence of dose reductions across the racial groups. Only two patients required ribavirin dose reduction within the first 4 weeks of therapy (1 Caucasian, 1 South Asian). Taking all dose reductions and interruptions into consideration, Asians (Non-South) received the highest mean calculated ribavirin dose/kg body weight across the racial groups (Table 1).

Sustained virological response

The SVR was achieved by 54% of the cohort; of the remaining 46% who did not achieve SVR, 55 (14%) were null-responders (genotype 1: 52, genotype 2: 1, genotype 3: 2). Figure 2 illustrates the unadjusted rates of SVR broken down into racial groups. Asians (Non-South) had the highest rate of SVR overall (31/39, 79%), higher than in South Asians (19/34, 56%, $P = 0.04$) and Caucasians (161/319, 50%, $P < 0.001$). The higher SVR in Asians (Non-South) was observed despite "traditional" negative predictors of response: SVR was achieved by 24/32 (75%) with genotype 1 CHC and 17/22 (77%) with advanced fibrosis.

The overall rates of SVR in genotype 2 and 3 were 82% (41/50) and 70% (57/82), respectively, without significant difference across the racial groups.

Factors associated with SVR

Univariate analysis

The factors associated with SVR by univariate analysis were: Asian (Non-South) race, younger age, treatment naïve status, genotype 2/3 infection, lower body weight, lower BMI and the absence of obesity. Pretreatment viral load, ribavirin dose/kg body weight received, and the type of peginterferon prescribed did not differ significantly between those who achieved SVR and those who did not (Table 2).

Multiple logistic regression by intention-to-treat

The final model included the factors associated with SVR on univariate analysis (including all variables with $P < 0.1$; Table 2) plus the factors identified to be confounders of race (Table 1). The final model therefore included race, viral

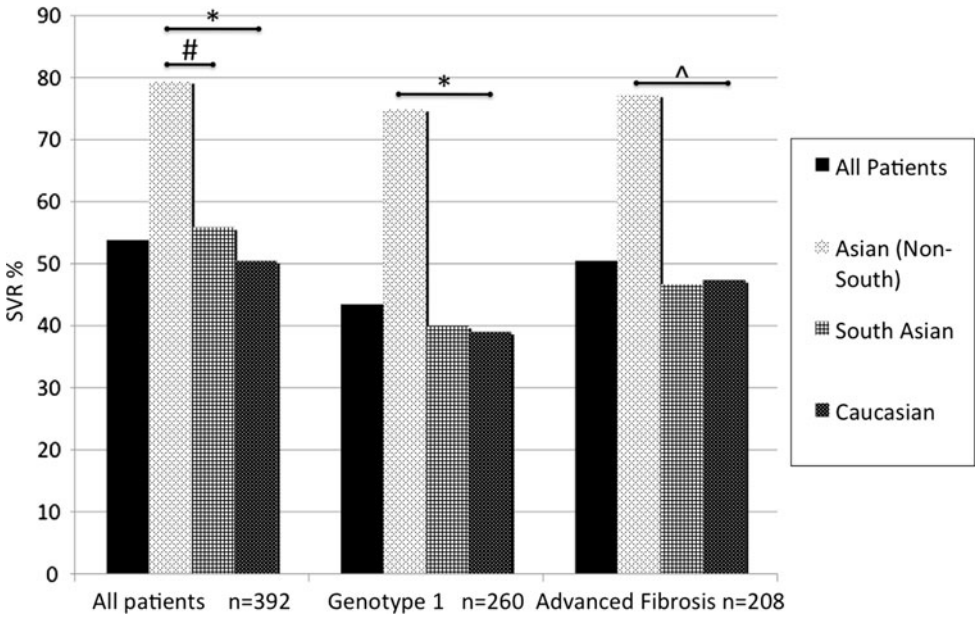

Fig. 2 Unadjusted SVR rates stratified into racial groups. SVR rates observed in Asian (Non-South) significantly higher than Caucasians across all patients, amongst genotype 1 patients and amongst those with advanced fibrosis. $^{*}P < 0.001$, $^{\wedge}P = 0.03$, $^{\#}P = 0.04$

Table 2 Univariate analysis: factors associated with SVR–ITT analysis

Characteristic	SVR	No SVR	*P* value
Number of subjects	211 (54%)	181 (46%)	
Age (years)	48.2 ± 10.1	50.9 ± 8.8	0.004
No. of males	134 (64%)	125 (69%)	0.293
Race			
Asian (Non-South)	31 (79%)	8 (21%)	0.003
South Asian	19 (56%)	15 (44%)	
Caucasian	161 (51%)	158 (49%)	
Genotype			
1	113 (54%)	147 (81%)	<0.001
2	41 (19%)	9 (5%)	
3	57 (27%)	25 (14%)	
Pretreatment viral load ($\log_{10}$ IU/ml)	5.8 ± 0.8	5.9 ± 0.5	0.081
Weight (kg)	75.2 ± 15.7	81.1 ± 16.7	<0.001
BMI (kg/m^2)	26.1 ± 5.0	27.9 ± 4.9	<0.001
Obese (WHO definition)	33 (17%)	43 (28%)	0.029
Obese (Asian definition)	38 (20%)	49 (32%)	0.019
Diabetes (Type 1 or 2)	15 (7%)	22 (12%)	0.109
Advanced Fibrosis (F3–F4 or clinical features of cirrhosis)	105 (54%)	103 (61%)	0.255
Steatosis ≥10%	43 (24%)	50 (33%)	0.107
Treatment naïve status	194 (92%)	135 (75%)	<0.001
PegIFN 2a	134 (64%)	99 (55%)	0.095
Calculated ribavirin dose received (mg/kg/day)	13.0 ± 2.7	12.8 ± 2.5	0.359
Received "adequate" therapy (>80% dose, 80% duration)	189 (90%)	153 (85%)	0.130

Data are expressed as *n* (%) or mean ± SD

genotype (2/3 vs. 1), age, baseline viral load, steatosis (<10 vs. ≥10%), pretreatment status (naïve vs. previous IFN exposure), ribavirin exposure (mg/kg/day), BMI category (non-obese vs. obese) and diabetic status (non-diabetic vs. diabetic) and type of peginterferon (α2a vs. α2b) (Table 3). Fibrosis stage (F0–F2 vs. F3–F4 or clinical evidence of cirrhosis) and "adequacy of therapy" were also retained as covariates because of their previously reported influence on SVR. The final model was also adjusted for gender as it was observed in post-hoc univariate analysis that a significantly higher proportion of males received peginterferon α2a than peginterferon α2b (70.4 vs. 59.7%, $P = 0.038$).

Table 3 Multiple logistic regression of factors influencing SVR

Predictor	Intention-to-treat			Per protocol		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Race						
Asian (Non-South) versus Caucasian	5.10	1.72–17.71	0.005*	4.56	1.52–15.89	0.010*
South Asian versus Caucasian	0.65	0.21–2.08	0.459	0.64	0.20–2.07	0.446
Contrast						
Asian (Non-South) versus South Asian	7.84	1.62–37.84	0.009*	7.13	1.46–34.84	0.014*
Genotype 2/3 versus 1	8.32	4.06–18.22	<0.001*	8.38	3.89–19.52	<0.001*
Age (years)	0.98	0.95–1.01	0.263	0.98	0.95–1.02	0.366
Baseline viral load (log_{10} IU/ml):	0.75	0.49–1.15	0.193	0.80	0.51–1.25	0.328
Fibrosis: Advanced versus Early	1.58	0.87–2.94	0.140	1.42	0.87–2.94	0.277
Steatosis <10% versus ≥10%	2.00	1.05–3.85	0.036*	1.75	0.91–3.57	0.098
Pretreatment status: naïve versus Previous IFN exposure	3.85	1.76–8.89	0.001*	2.95	1.29–7.11	0.012*
Ribavirin dose received (mg/kg/day)	1.13	1.01–1.28	0.041*	1.11	0.98–1.27	0.099
BMI <30 versus ≥30 kg/m^2	2.13	1.06–4.35	0.034*	2.38	1.15–5.00	0.022*
Non-diabetic versus Diabetic	3.70	1.30–11.11	0.018*	3.70	1.23–12.50	0.025*
Pegylated interferon type (2a vs. 2b)	2.08	1.16–3.85	0.014*	2.04	1.11–3.85	0.022*
Gender (male vs. female)	0.84	0.44–1.59	0.593	0.77	0.39–1.50	0.440
Received "adequate" versus "inadequate" therapy	1.06	0.42–2.67	0.899	–	–	–

* Variables reaching statistical significance ($P < 0.05$)

Asian (Non-South) race was clearly identified as a strong independent predictor of SVR (OR 5.10, 95% CI 1.72–17.71 vs. Caucasians; contrast OR 7.84, 95% I 1.62–37.84 vs. South Asians). The additional independent predictors of SVR were genotype 2/3 infection, treatment naïve status, non-diabetic status, BMI < 30, peginterferon α2a, steatosis <10% and ribavirin dose received (mg/kg/day). When the analysis was repeated after recategorising the Asian patients using the race-specific definition of obesity, obesity remained a negative predictor of SVR (OR 0.36, 95% CI 0.18–0.72, $P = 0.004$).

As peginterferon type (α2a vs. α2b) was observed to be a statistically significant predictor of SVR in the final model, a post-hoc analysis was performed which demonstrated that this finding translated to absolute (albeit unadjusted) SVR rates in our non-randomised cohort of 78 versus 81% in Asians (Non-South) ($P = 1.0$), 80 versus 58% in South Asians ($P = 0.02$), and 54 versus 45% in Caucasians ($P = 0.11$) for peginterferon α2a vs α2b, respectively.

Per protocol analysis

To ensure that the observed influence of race on treatment outcome was not confounded by the inclusion of patients that received inadequate therapy or follow-up, per protocol analysis was performed excluding these 57 cases (5 Asians (Non-South), 4 South Asians and 48 Caucasians). SVR was achieved by 79% of Asians (Non-South), 63% of South Asians and 52% of Caucasians. Asian (Non-South) race remained a strong independent predictor for SVR (OR 4.56, 95% CI 1.52–15.89 compared with Caucasians; contrast OR 7.13, 95% CI 1.46–34.84 vs. South Asians) in addition to genotype 2/3 infection, treatment naïve status, non-diabetic status, the absence of obesity and peginterferon α2a (Table 3). Intuitively, ribavirin dose (mg/kg/day) was not found to significantly influence SVR in the PP analysis as, by definition, all cases in the PP analysis had received "adequate" therapy. Steatosis was also no longer found to be significantly associated with SVR in the PP analysis, demonstrating its marginal influence on treatment outcomes, and emphasising the more important role of the host metabolic risk factors, namely obesity and diabetes, in influencing SVR.

Discussion

Within our multicultural outpatient clinic, we have demonstrated that Asian (Non-South) race is a strong independent predictor of sustained virological response to antiviral therapy. An overall SVR of 79% was observed in this group despite a higher mean age, 82% prevalence of genotype 1 infection, 59% prevalence of advanced liver fibrosis and a higher prevalence of diabetes in this cohort.

There are a number of strengths to our study that have allowed thorough testing of our hypothesis. Our uni-centric multicultural clinic population allowed the unique opportunity to compare treatment responses in multiple racial groups receiving the same standard of care. We identified

differences in characteristics between the racial groups which potentially confound the contribution of race/ethnicity to the observed response to antiviral therapy; as anticipated Asians (Non-South) had lower body weight and thus received the highest dose of ribavirin per kg/body weight. Adjustment was made for both the confounders of body weight and the occurrence of ribavirin dose reductions by calculating ribavirin dose *exposure* per kilogram body weight. Having considered all these confounders, we have clearly demonstrated that Asian (Non-South) race is a strong and independent predictor of treatment response.

The distinction made between South Asians and Asians (Non-South) was decided upon in the light of small study which showed that South Asians with genotype 3 CHC had an inferior response to antiviral therapy when compared to Caucasians [12]. However, many subjects in the study by Freshwater et al. [25] had advanced fibrosis which is known to be associated with poor response to therapy. Having adjusted for confounders including fibrosis, we found no such difference in SVR rate between South Asians and Caucasians. Furthermore, distinguishing South Asians from Asians (Non-South) allowed us to demonstrate the superior response to antiviral therapy in Asians (Non-South) when compared with both South Asians and Caucasians.

Our findings strongly support the hypothesis that a race-specific genetic component has an effect on the response to pegylated interferon and ribavirin that overrides previously described factors shown to influence response to antiviral therapy. Recent work demonstrates that host genetic variation in IL28B predicts treatment-induced viral clearance in genotype 1-infected populations [7–9]. The prevalence and influence of this genetic variation differ in Japanese [9] when compared to Caucasians and African Americans [7, 8]. Although these recent findings were reported in separate studies differing in design and population base (and therefore subject to confounding), they appear to account for the variation in SVR rates observed across ethnic groups. Host genetics may also account for the difference in prevalence of metabolic disease (namely obesity and diabetes) across the races, thereby indirectly influencing the response to antiviral therapy.

We cannot exclude the influence of a *viral* (rather than *host*) factor since infections were likely to be acquired in different parts of the world where the distributions of viral geno-subtypes are different. HCV-1b is the dominant genotype in Asia–Pacific [26], whereas in Ontario (Canada), approximately 50% of genotype 1 is 1a and 50% is 1b (personal communication, Public Health Lab, Ontario, Canada). Nevertheless, it is interesting to note that in Japan, 59.4% SVR in genotype 1b [27] is not greatly superior to SVR reports for genotype 1 around the world.

We did account for one important *viral* factor by using viral genotype assays that are able to distinguish genotype 6 (almost exclusively originating from South-Eastern Asia) from genotype 1. As the reported SVR rate in genotype 6 patients is 86% (significantly higher than that of genotype 1, 52%) [28], it was essential that this distinction be made. The INNO-Lipa and original Versant HCV genotype line probe assay have been reported to mischaracterise genotype 6 (subtypes 6c-6n) for genotype 1 [29]. All 13 genotype 6 cases identified and excluded from the present study were diagnosed using the INNO-LiPA, indicating that the assay was able to distinguish genotype 6 from 1 in our population. A recent study found no difference in SVR rate between Asian Americans and Caucasians with genotype 1 CHC when cases genotyped by the INNO-LiPA method were excluded [30]; however, they did not account for important host factors such as ribavirin dose reductions (which occurred significantly more often amongst their Asian patients) and the presence of type 2 diabetes (60% more prevalent in Asian Americans than non-Hispanic American Caucasians [31]); these factors may have biased their findings. In addition to distinguishing Asian (Non-South) from South Asian race, we demonstrated the independent influences of total ribavirin exposure (mg/kg/day), obesity and diabetes on SVR which were not addressed by the latter study [30].

Although a large, prospective trial has demonstrated similar SVR rates for peginterferon α2a compared with α2b [32], adjustment for ribavirin exposure in the present study (which was not performed in the aforementioned study) uncovered a statistically significant association between peginterferon α2a and SVR over peginterferon α2b in keeping with other recent reports [33–35]. However, we interpret this observation with caution since the primary aim of this non-randomised study was not to address the issue of peginterferon type on SVR, but rather the influence of ethnicity; the inclusion of "peginterferon type" in the final analysis merely served to adjust for any variation in peginterferon type administered between ethnic groups. Furthermore, the lower limit of the 95% confidence interval for the odds ratio for SVR of peginterferon 2a vs 2b approaches 1. Therefore, although the observation was statistically significant, we cannot conclude from our study that a clinically significant difference in influence of peginterferon type on SVR exists.

The present study was not accounted for to determine whether the difference in SVR observed was owing to a difference in early viral kinetics or the rate of null response, non-response or relapse. In a study from Taiwan early viral kinetics at week 4 (but not SVR) are reported to be influenced by BMI [36], but we have not observed this to be the case in Caucasians [37]. Evaluation of these secondary outcomes within a large sample size of patients of differing ethnic groups may give further insight into effects of race on treatment outcomes that we have identified. Additionally,

advanced fibrosis and baseline viral load were not demonstrated to be independently associated with SVR in our cohort; we do not dispute their likely influence on SVR as reported by numerous much larger trials of antiviral therapy for CHC, but our findings suggest that race is a very strong predictor of SVR, superceding even these "classical" predictors of treatment response.

In summary, after considering all potential confounders, we report that individuals of Asian (Non-South) race have a superior response to pegylated interferon and ribavirin when compared to Caucasians and South Asians. This finding may influence the way Asian (Non-South) patients contemplating antiviral therapy are counselled and also supports the recent findings of a host genetic basis for response to antiviral therapy.

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