

Prospective Analysis of Sustained Virologic Response to PEG-Interferon alfa-2b and Ribavirin Treatment in Asian and Hispanic Patients With Chronic Hepatitis C: Results From the WIN-R Trial

B. Freilich,¹ K. Hu,² I. M. Jacobson,³ R. S. Brown, Jr,⁴ N. Afdhal,⁵ P. Kwo,⁶ J. Santoro,⁷ S. Becker,⁸ A. Wakil,⁹ D. Pound,¹⁰ E. Godofsky,¹¹ R. Strauss,¹² D. Bernstein,¹³ S. L. Flamm,¹⁴ N. Bala,¹⁵ V. Araya,¹⁶ L. Griffel,¹⁷ C. Brass¹⁷

#349

¹Research Medical Center, Kansas City, Missouri; ²University of California Irvine, Orange, California; ³Weill Cornell Medical College, New York, New York; ⁴Columbia University Medical Center, New York, New York; ⁵Beth Israel Deaconess Medical Center, Boston, Massachusetts; ⁶Indiana University School of Medicine, Indianapolis, Indiana;

⁷Atlantic Gastroenterology Associates, PA, Egg Harbor Township, New Jersey; ⁸Austin Gastroenterology, Austin, Texas; ⁹East Bay Liver Clinic, San Francisco, California; ¹⁰Indianapolis Gastrointestinal Research Foundation, Indianapolis, Indiana; ¹¹Bach and Godofsky, MD, PA, Bradenton, Florida; ¹²Northwest Georgia Gastroenterology Associates, PC, Marietta, Georgia;

¹³North Shore Long Island Jewish Health System, Manhasset, New York; ¹⁴Northwestern University, Chicago, Illinois; ¹⁵Gastroenterology Consultants, PA, Houston, Texas; ¹⁶Albert Einstein Medical Center, Philadelphia, Pennsylvania; ¹⁷Schering-Plough Research Institute, Kenilworth, New Jersey

Background

- Ethnic origin is an important factor in disease course and response to therapy for patients with chronic hepatitis C.
 - Reduced response to therapy in African American patients, compared with Caucasian patients, has been extensively reported; however, few studies have evaluated disease course and treatment outcomes in Hispanic and Asian patients.
- In Asian and Hispanic patients, specific disease characteristics that may affect treatment outcomes have been reported.
 - Asian patients with chronic hepatitis C are
 - At greater risk than Caucasian patients for hepatocellular carcinoma.¹
 - Likely to be significantly older and have a lower body mass index than patients from other ethnic groups ($P < .001$ for both comparisons).²
 - Hispanic patients with chronic hepatitis C are
 - Less likely to have liver cirrhosis but more likely to have steatosis than Caucasian patients.³
 - Significantly more likely than Caucasian patients to be coinfecting with HIV (20.4% vs 3.9%, $P < .0001$).³
- Studies with standard interferon (IFN) plus ribavirin therapy suggest that ethnic origin may be an important predictor of response.
 - Sustained virologic response (SVR) rates are highest in Asian patients (61%), followed by Caucasian (39%), Hispanic (23%), and African American (14%) patients.²
 - Hispanic patients have higher rates of treatment discontinuation than Caucasian patients (39.8% vs 28.9%, $P = .043$), with a trend toward lower end-of-treatment response (27.3% vs 37%, $P = .08$) and SVR (14.8% vs 22.5%, $P = .1$).³

Aim

- To evaluate SVR rates among Asian and Hispanic patients with chronic hepatitis C who were treated with pegylated interferon (PEG-IFN) alfa-2b (PegIntron[®]) plus ribavirin in the WIN-R trial.

Methods

- Prospective, multicenter, community- and academic-based, open-label, investigator-initiated study conducted at 236 sites in the United States.
- Patients**
 - Patients were treatment naive, had chronic hepatitis C, were 18 to 70 years of age, and weighed <125 kg. Additional inclusion criteria included
 - An elevated alanine aminotransferase level within 6 months prior to entry.
 - A liver biopsy specimen consistent with chronic hepatitis C within 36 months prior to entry.
 - Compensated liver disease.
 - An α -fetoprotein level ≤ 100 ng/mL in the year preceding entry.
 - Patients with a positive test result for hepatitis B surface antigen or HIV were excluded.
- Treatment**
 - Patients were randomized (1:1) to receive PEG-IFN alfa-2b 1.5 μ g/kg/wk administered subcutaneously plus oral, daily ribavirin (fixed dose [FD] or weight-based dose [WBD]) for 48 weeks (genotype 1 [G1], 4, 5, or 6) or for 24 or 48 weeks (G2/3). All patients were followed up for 24 weeks.
 - Dose reductions of ribavirin were required for hemoglobin (Hgb) level <10 g/dL, and discontinuation was required for Hgb level <8.5 g/dL.
 - Concomitant use of erythropoietin was permitted in patients undergoing ribavirin dose reduction for Hgb level <10 g/dL.
- Assessments**
 - The primary efficacy end point was SVR, defined as undetectable serum hepatitis C virus (HCV) RNA at week 24 after completion of treatment.
 - The secondary efficacy end point was the difference in SVR rates among patients with G2/3 treated for 24 or 48 weeks.
 - Safety was monitored by clinical and laboratory evaluations.

Results

Patient Flow and Demographics

- 5027 patients were randomized in the WIN-R study, including Asian, Hispanic, and Caucasian patients (Figure 1).
- A separate subanalysis of the WIN-R study was performed to compare WBD versus FD ribavirin among African American patients.⁴
- Baseline demographics for the Caucasian, Asian, and Hispanic patients are shown in Table 1.

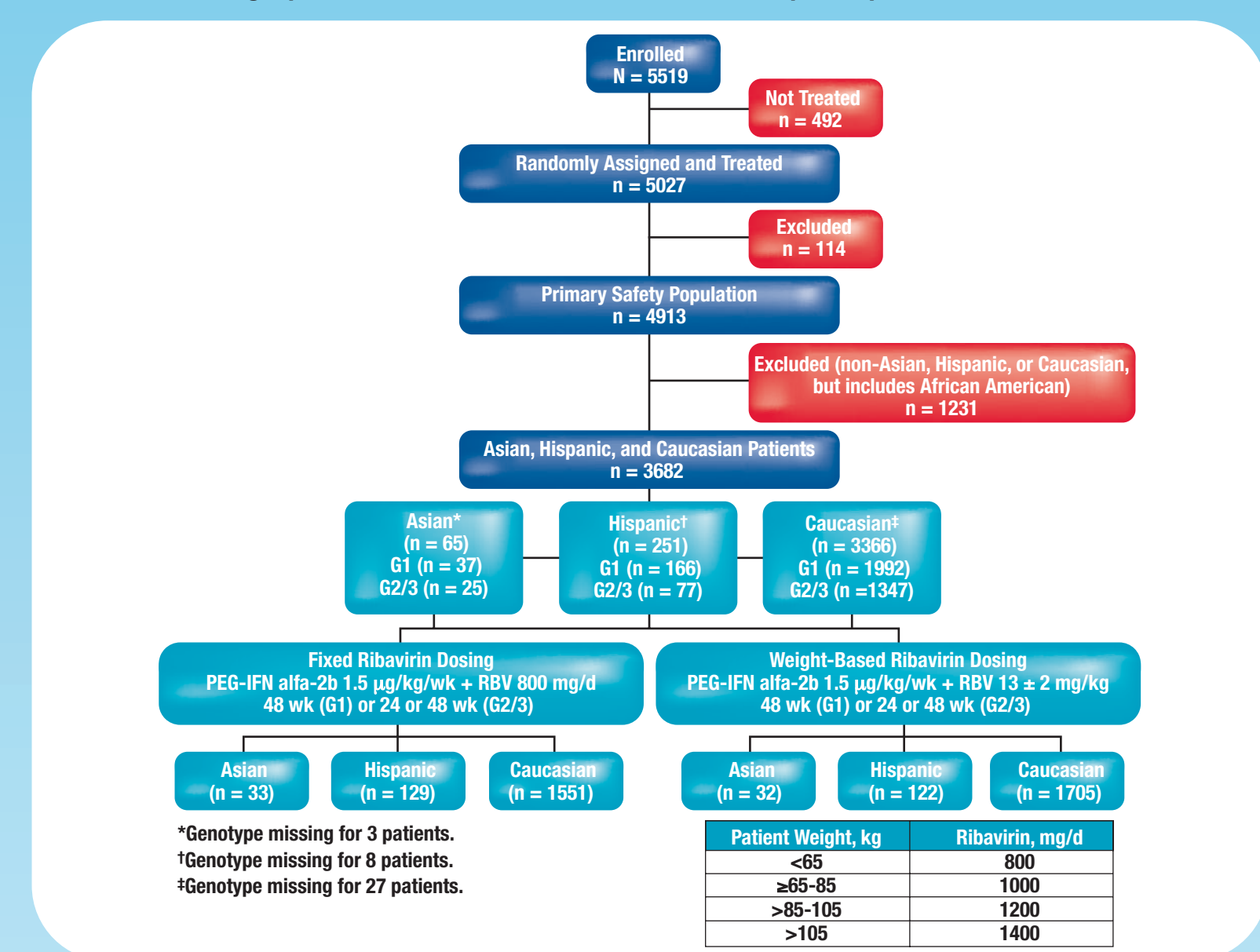


Figure 1. Patient flow

Table 1. Baseline Demographics

	Asian Patients* (n = 65)	Caucasian Patients† (n = 3366)	Hispanic Patients‡ (n = 251)
Mean body weight, kg	77.7	88.3	86.4
Mean body mass index, mg/km ²	27.9	29.6	31.1
Ribavirin dosing, n (%)			
Weight-based	32 (49)	1705 (51)	122 (49)
Fixed	33 (51)	1661 (49)	129 (51)
Baseline viral load, n (%)			
>600,000 IU/mL	26 (45)	1621 (55)	105 (48)
≤600,000 IU/mL	32 (55)	1352 (45)	115 (52)
Genotype, n (%)			
G1	37 (60)	1992 (60)	166 (68)
G2/3	25 (40)	1347 (40)	77 (32)
Baseline METAVIR fibrosis stage, n (%)			
F0, F1, F2	40 (62)	2332 (69)	163 (65)
F3, F4	25 (38)	1034 (31)	88 (35)
Ribavirin dose modification, n (%)			
No	41 (63)	985 (29)	192 (76)
Yes	24 (38)	2380 (71)	59 (24)
PEG-IFN alfa-2b dose modification, n (%)			
No	46 (71)	2472 (73)	201 (80)
Yes	19 (29)	893 (27)	50 (20)
Anemia, n (%)			
No	47 (72)	2590 (77)	202 (81)
Yes	18 (28)	776 (23)	49 (19)
Discontinued due to adverse event, n (%)			
No	54 (83)	2859 (85)	222 (89)
Yes	11 (17)	497 (15)	28 (11)

*In the Asian population analyses, data are missing for the baseline viral load (n = 6), genotype (n = 3), ribavirin dose modification (n = 1), PEG-IFN alfa-2b dose modification (n = 1), and discontinuations due to an adverse event (n = 1).
 †In the Caucasian population analyses, data are missing for the baseline viral load (n = 353), genotype (n = 27), and ribavirin dose modification (n = 10).
 ‡In the Hispanic population analyses, data are missing for baseline viral load (n = 31), genotype (n = 8), ribavirin dose modification (n = 1), PEG-IFN alfa-2b dose modification (n = 1), and discontinuations due to an adverse event (n = 1).
 PEG-IFN = pegylated interferon.

SVR Rates by Ethnic Origin and Genotype

Within-Group Analysis

- In all 3 patient ethnic groups (Asian, Hispanic, and Caucasian patients), SVR rates were lower for patients with G1 than for patients with G2/3 (Figure 2; Table 2).

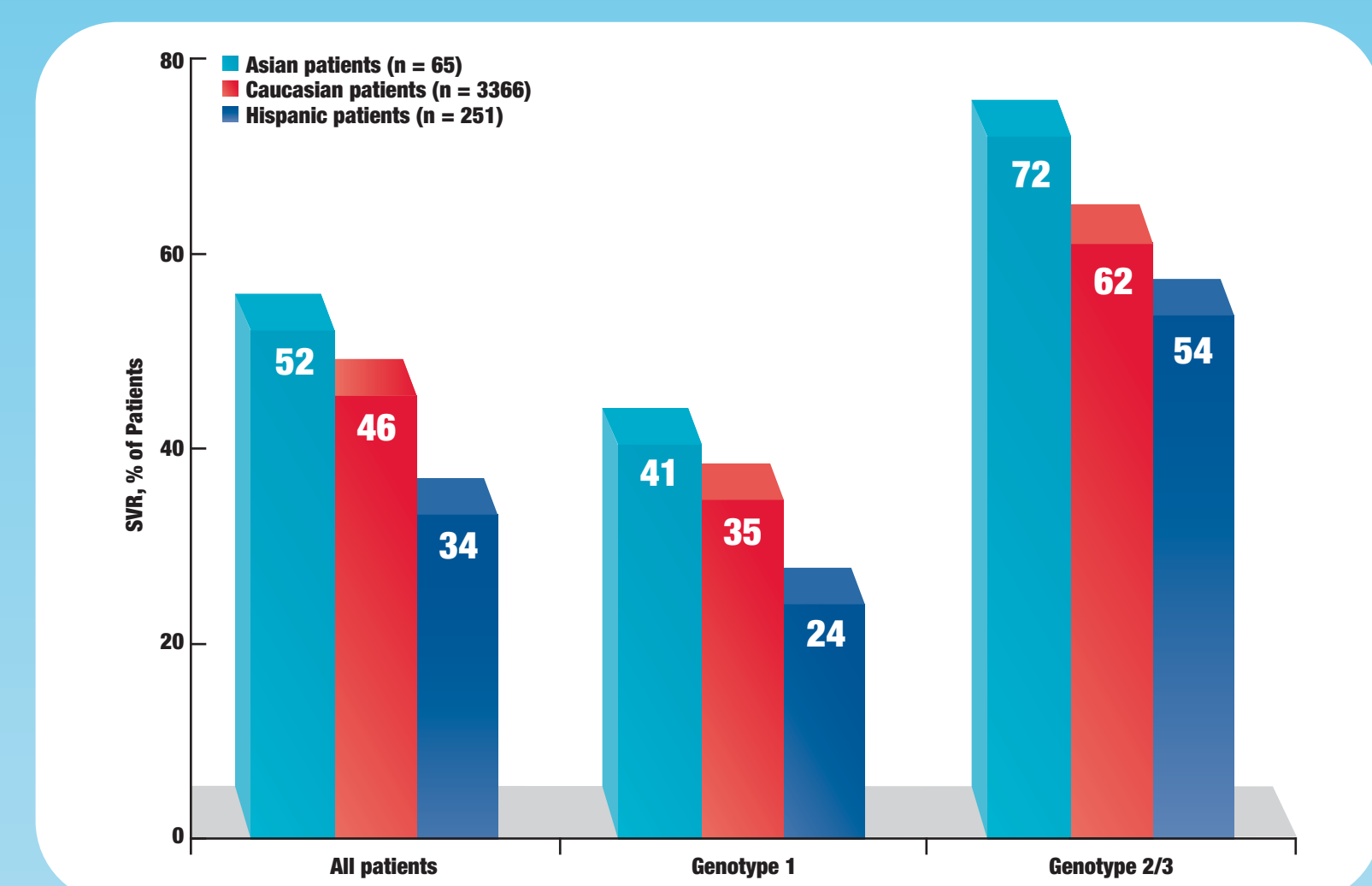


Figure 2. SVR rates stratified by viral genotype

Table 2. SVR Rates Stratified by Genotype

	Between-Group Analysis			
	Asian Patients vs Hispanic Patients, %	P	Asian Patients vs Caucasian Patients, %	P
Overall	52 vs 34	.0057	52 vs 46	.2925
Overall WBD	66 vs 32	.0008	41 vs 35	.4762
Overall FD	39 vs 35	.6299	72 vs 62	.2943
G1	47 vs 23	.0502	47 vs 37	.3898
WBD	45 vs 25	.3677	35 vs 33	.8426
G2/3	86 vs 53	.0456	86 vs 63	.1003
WBD	55 vs 54	.9500	55 vs 60	.7011

SVR = sustained virologic response; G1 = genotype 1; G2/3 = genotype 2/3.
 SVR = sustained virologic response; G1 = genotype 1; G2/3 = genotype 2/3.

Between-Group Analysis

- Overall SVR rates (Figure 2; Table 2).
 - Overall SVR rates were lowest among Hispanic patients (34% vs 46% for Caucasian patients, $P = .0002$, and 34% vs 52% for Asian patients, $P = .0057$). There was no significant difference in the overall SVR rates between Caucasian and Asian patients.
- SVR rates by genotype (Figure 2; Table 2).
 - SVR rates were lowest among Hispanic patients, across all genotypes.
 - Among patients with G1, SVR rates were lowest among Hispanic patients (24% vs 35% for Caucasian patients, $P = .005$, and 24% vs 41% for Asian patients, $P = .0449$).
 - Among patients with G2/3, SVR rates among Hispanic patients were lower, but not significantly different (54% vs 62% for Caucasian patients, $P = .1443$, and 54% vs 72% for Asian patients, $P = .1038$).
 - There were no significant differences in the SVR rates between Caucasian and Asian patients across all genotypes.

SVR Rates by Ethnic Origin and Ribavirin Dosing

Within-Group Analysis

- Overall SVR rates (Figure 3; Table 3).
- Among Hispanic patients, SVR rates were similar between patients receiving WBD or FD ribavirin (32% vs 35%, $P = .60$).
- Among Asian patients, overall SVR rates were greater among those receiving WBD ribavirin than among those receiving FD ribavirin (66% vs 39%, $P = .04$).
 - On further analyses of SVR rates among Asian patients by genotype, the WBD ribavirin appears to have benefit over FD ribavirin among patients with G2/3 (86% vs 55%, $P = .0987$) but not among patients with G1 (47% vs 35%, $P = .4579$).
- Among Caucasian patients, the SVR rates were similar among patients receiving WBD or FD ribavirin (47% vs 44% $P = .070$), irrespective of genotype.

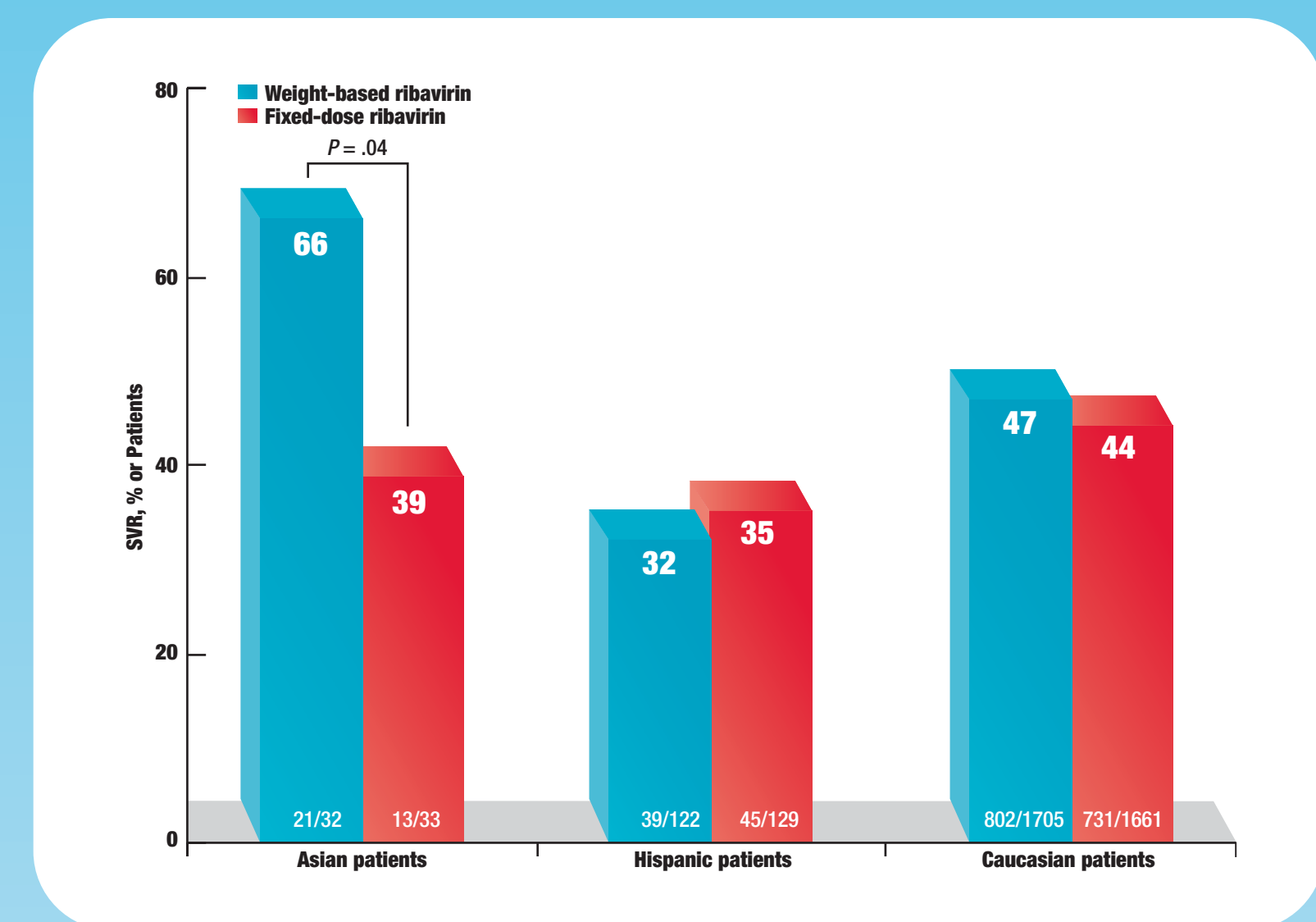


Figure 3. SVR rates stratified by ribavirin dose

Table 3. SVR Rates Stratified by Genotype and Ribavirin Dose

	Asian Patients vs Hispanic Patients, %		Asian Patients vs Caucasian Patients, %		Hispanic Patients vs Caucasian Patients, %	
		P		P		P
Overall	52 vs 34	.0057	52 vs 46	.2925	34 vs 46	.0002
Overall WBD	66 vs 32	.0008	41 vs 35	.4762	32 vs 47	.0013
Overall FD	39 vs 35	.6299	72 vs 62	.2943	35 vs 44	.0410
G1	47 vs 23	.0502	47 vs 37	.3898	23 vs 37	.0145
WBD	45 vs 25	.3677	35 vs 33	.8426	25 vs 33	.1397
G2/3	86 vs 53	.0456	86 vs 63	.1003	53 vs 63	.2428
WBD	55 vs 54	.9500	55 vs 60	.7011	54 vs 60	.3805

SVR = sustained virologic response; WBD = weight-based dose; FD = fixed dose; G1 = genotype 1; G2/3 = genotype 2/3.

Between-Group Analysis

- Overall SVR rates.
 - Among patients receiving WBD ribavirin, the SVR rates were lower in Hispanic patients (32% vs 47% for Caucasian patients, $P = .0013$ and 32% vs 66% for Asian patients, $P = .00008$). There was no significant difference in SVR rates between Caucasian patients and Asian patients receiving WBD ribavirin.
 - Among patients receiving FD ribavirin, the SVR rates among Asian patients were not significantly different than those among Caucasian or Hispanic patients. However, SVR rates were lower among Hispanic patients (35% vs 44% for Caucasian patients, $P = .0410$ and 35% vs 39% for Asian patients, $P = .6299$).
- SVR rates by genotype.
 - Among patients with G1 receiving WBD or FD ribavirin, there was no significant difference between patients of different ethnic origin.
 - Similar results were observed among patients of different ethnic origin with G2/3 receiving WBD or FD ribavirin.
 - SVR rates were lower among Hispanic patients.

SVR Rates by Baseline Characteristics

- SVR rates according to baseline characteristics are presented in Table 4.
- SVR rates were lower in patients with high baseline viral load (>600,000 IU/mL).
- Among Asian patients, WBD ribavirin ($P = .037$) and G2/3 ($P = .017$) were significantly associated with improved SVR rates.
- Among Hispanic patients, G2/3 ($P < .0001$) and baseline METAVIR fibrosis stage F0-F2 ($P = .038$) were significantly associated with higher SVR rates.
- Among Caucasian patients, high baseline viral load ($P < .0001$) and G1 were significantly associated with lower SVR rates.

Table 4. SVR Rates According to Baseline Demographic Variables

	Asian Patients* (n = 65)	Caucasian Patients† (n = 3366)	Hispanic Patients‡ (n = 251)
Ribavirin dosing			
Weight-based	21/32 [§] (66)	797/1690 (47)	39/122 (32)
Fixed	13/33 (39)	728/1653 (44)	45/129 (35)
Baseline viral load			
>600,000 IU/mL	10/26 (40)	662/1621 [§] (41)	29/105 (28)
≤600,000 IU/mL	21/32 (66)	714/1352 (53)	43/115 (37)
Genotype			
G1	15/37 [§] (41)	695/1992 [§] (35)	40/166 [§] (24)
G2/3	18/25 (72)	830/1347 (62)	41/77 (54)
Baseline METAVIR fibrosis stage			
F0, F1, F2	24/40 (60)	1089/2332 (47)	62/163 [§] (39)
F3, F4	10/25 (40)	450/1034 (44)	22/88 (25)
Ribavirin dose modification			
No	21/40 (53)	1076/2380 (45)	65/191 (34)
Yes	13/24 (54)	462/985 (47)	18/59 (31)
PEG-IFN alfa-2b dose modification			
No	27/45 (60)	1130/2472 (46)	69/200 (35)
Yes	7/19 (37)	408/893 (46)	14/50 (28)
Anemia			
No	26/47 (55)	1123/2590 (43)	66/203 (33)
Yes	8/18 (44)	416/776 (54)	18/48 (38)
Discontinued due to adverse event			
No	29/54 (54)	1433/2859 [§] (50)	81/222 [§] (37)
Yes	5/10 (50)	104/495 (21)	2/28 (7)

*In the Asian population analyses, data are missing for the baseline viral load (n = 6), genotype (n = 3), ribavirin dose modification (n = 1), PEG-IFN alfa-2b dose modification (n = 1), and discontinuations due to an adverse event (n = 1).
 †In the Caucasian population analyses, data are missing for baseline viral load (n = 393), genotype (n = 27), and ribavirin dose modification (n = 10).
 ‡In the Hispanic population analyses, data are missing for baseline viral load (n = 31), genotype (n = 8), ribavirin dose modification (n = 1), PEG-IFN alfa-2b dose modification (n = 1), and discontinuations due to an adverse event (n = 1).
 § $P < .05$, $IP < .0001$, $IP < .01$ versus the alternative baseline group within the same ethnic population.
 SVR = sustained virologic response; PEG-IFN = pegylated interferon.

Summary

- Among Hispanic patients, overall SVR rates were lower than those among Caucasian or Asian patients.
 - G2/3 and low baseline viral load were identified as significant predictors of treatment outcome.
- Asian patients achieved higher overall SVR rates than Caucasian patients or Hispanic patients.
 - WBD ribavirin and G2/3 were identified as predictors of SVR.
- Among Caucasian patients, having low baseline viral load and G2/3 were identified as predictors of SVR.

Conclusions

- Hispanic patients with chronic hepatitis C represent a particularly treatment-resistant population. Additional studies are required to identify factors that will improve SVR rates in this ethnic group.
- Overall WBD ribavirin is more effective than FD ribavirin.
- Asian patients achieve overall SVR rates that are at least equivalent to those observed among Caucasian patients.
 - WBD ribavirin is more effective among Asian patients, especially among G2/3.
 - Additional studies among a greater number of Asian patients are required to confirm results observed in this study.

References

- Nguyen MH et al. *Clin Gastroenterol Hepatol*. 2004;2:820-824.
- Hepburn MJ et al. *Am J Med*. 2004;117:163-168.
- Cheung RC et al. *Am J Gastroenterol*. 2005;100:2186-2193.
- Jacobson IM et al. *Hepatology*. 2004;38:61A.

Supported by Schering-Plough

B. Freilich, K. Hu, I. M. Jacobson, R. S. Brown, Jr, N. Afdhal, P. Kwo, J. Santoro, S. Becker, A. Wakil, D. Pound, E. Godofsky, R. Strauss, D. Bernstein, S. L. Flamm, N. Bala, V. Araya have received research support from Schering-Plough; B. Freilich, I. M. Jacobson, R. S. Brown, Jr, N. Afdhal, P. Kwo are all members of the Speakers Bureau for Schering-Plough; L. Griffel, C. Brass are employees of Schering-Plough Research Institute

Presented at the 57th Annual Meeting of the American Association for the Study of Liver Diseases; October 27 – 31, 2006; John B. Hynes Convention Center, Boston, Massachusetts