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# Association of Host Pharmacodynamic Effects and Virologic Response to Peginterferon Alfa-2a/Ribavirin in Patients with Chronic Hepatitis C

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## INTRODUCTION

- Patients receiving peginterferon plus ribavirin therapy for chronic hepatitis C (CHC) frequently experience anemia, neutropenia, thrombocytopenia, and weight loss.[1,2]
- Changes in hematologic parameters and weight loss may be associated with viral response.
  - Greater hemoglobin (Hb) decline may be associated with higher sustained virologic response (SVR) rates[3]
  - Null response may be associated with lower reductions in weight, platelets, and white blood cells than non-null response.[4]
- We conducted a retrospective analysis of pooled data from four trials[5-8] to study the association of virologic response and host pharmacodynamic effects of peginterferon alfa-2a plus ribavirin.

## METHODS

### Patients

- Patients with HCV genotypes 1, 4, 5, or 6 receiving 24 or 48 weeks of combination therapy with peginterferon alfa-2a 180 µg/week plus ribavirin 800, 1000, or 1200 mg/day.
- Data pooled from two registration trials[5,6] and two Phase IV trials involving predominantly Latinos[7] or African Americans.[8]
- Patients who received peginterferon monotherapy, ribavirin and interferon alfa-2b combination therapy (Rebetron), and HIV coinfected patients were excluded from the analysis.

### Outcomes Assessed

- Maximum decreases in hematologic parameters and weight by virologic response status (SVR, relapse, breakthrough, nonresponder).
- SVR rates among patients with and without >3 g/dL decrease in Hb.
- Maximum decreases in hematologic parameters and weight by race/ethnicity.

### Hematologic Decrease and Weight Loss Definitions

- Maximum decrease for each hematologic parameter was defined as the baseline value for the hematologic test – lowest value for the hematologic test on therapy.
- Maximum decrease of body weight was defined as the baseline body weight – lowest value for body weight during treatment and reported as % change from baseline.

### Statistical Analysis

- Maximum decreases in hematologic parameters and % decrease in body weight were initially summarized by viral response status using mean and standard error from the ANOVA models.
- Cirrhosis, an independent predictor of non-SVR, was adjusted if it was significant ($P<.05$).
- Drug exposure was defined as total peginterferon received and total ribavirin received per kg of weight at baseline. Drug exposure was not adjusted for changes in weight while on therapy.
- Backward selection was utilized to remove non-significant ($P>.05$) variables.
- The association between Hb decline and SVR rate was assessed with and without adjusting for drug exposure using logistic regression models with SVR/non-SVR as the dependent variable.
- Missing HCV RNA data was imputed as nonresponse.

## RESULTS

### Baseline Characteristics

- Table 1 presents the demographic and clinical characteristics at baseline for all patients.
- More than 70% of patients were from the 48-week peginterferon alfa-2a plus 1000-1200 mg ribavirin therapy arm.

**Table 1. Patient Demographic and Baseline Characteristics**

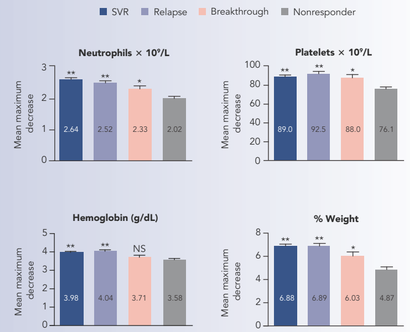
| Characteristic | Total (N=1778) |
|---|---|
| Males, n (%) | 1183 (66.5) |
| Age, years | |
| Mean (SD) | 44.5 (9.7) |
| Range | 18.0, 76.0 |
| BMI, kg/m$^2$ | |
| Mean (SD)* | 27.5 (5.2) |
| <25 kg/m$^2$, n (%) | 614 (34.9) |
| 25–<30 kg/m$^2$, n (%) | 708 (40.3) |
| ≥30 kg/m$^2$, n (%) | 435 (24.8) |
| Race, n (%) | |
| Non-Latino Caucasian | 1272 (71.5) |
| Latino Caucasian | 287 (16.1) |
| African American | 131 (7.4) |
| Other | 88 (4.9) |
| ALT quotient ≤3 × ULN, n (%) | 1328 (74.7) |
| HCV genotype, n (%) | |
| 1 | 1711 (96.2) |
| 4, 5, or 6 | 67 (3.8) |
| HCV RNA $\log_{10}$ IU/mL, mean (SD)† | 6.1 (0.7) |
| >800,000 IU/mL, n (%) | 1161 (65.3) |
| METAVIR activity score, mean (SD)‡ | 1.6 (0.6) |
| Cirrhosis or transition to cirrhosis, n (%) | 314 (17.7) |
| Treatment arm, n (%) | |
| 48-week peginterferon alfa-2a + 1000–1200 ribavirin | 1269 (71.4) |
| 24-week peginterferon alfa-2a + 1000–1200 ribavirin | 136 (7.6) |
| 48-week peginterferon alfa-2a + 800 ribavirin | 262 (14.7) |
| 24-week peginterferon alfa-2a + 800 ribavirin | 111 (6.2) |
| Duration of treatment, weeks, mean (SD) | 38.9 (13.2) |
| 24-week treatment arm (n=247) | 23.4 (3.5) |
| 48-week treatment arm (n=1531) | 41.4 (12.5) |

SD=standard deviation; BMI=body mass index; ALT=alanine aminotransferase; ULN=upper limit of normal; HCV=hepatitis C virus.
*n=1757; †n=1777; ‡n=1495.

### Change in Hematologic Parameters and Weight by Virologic Response Category

- In this analysis:
  - 42% of patients achieved SVR (n=750)
  - 23% of patients relapsed (n=415)
  - 10% of patients had breakthrough (n=184)
  - 24% of patients were nonresponders (n=429).
- Approximately one third of the breakthrough and non-responder patients completed at least 44 weeks of treatment.
- Cirrhosis was associated with significantly smaller declines in neutrophils and platelets, and as a result was included in the final models.

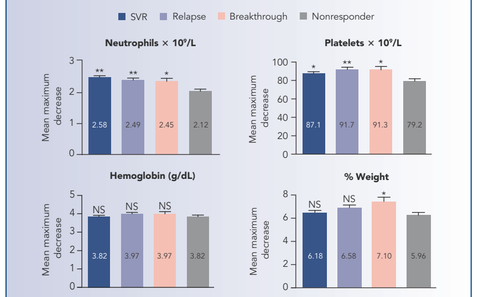
**Figure 1a. Mean Maximum Decreases from Baseline by Virologic Response Status**




NS=not significant.
*$P<.01$ vs. nonresponders; **$P<.0001$ vs. nonresponders.
Figure shows cirrhosis-adjusted least squares means for neutrophils and platelets. For hemoglobin and weight, cirrhosis is not significant and adjustment was not required.
Error bars represent standard error.
SVR: undetectable HCV RNA at 24-weeks post-end of treatment (EOT).
Relapse: undetectaat EOT but detectable or missing test at 24 weeks post-EOT.
Breakthrough: undetectable HCV RNA during treatment but detectable or missing test at EOT.
Nonresponder: no undetectable HCV RNA test during treatment or at EOT.

- The analysis suggests that virologic response was associated with maximum decrease from baseline in neutrophils, platelets, Hb, and weight (Figure 1a).
- After adjusting for drug exposure (Figure 1b), decreases in neutrophils and platelets were still significantly different between patients achieving HCV RNA undetectability and nonresponders.

**Figure 1b. Adjusted Mean Maximum Decreases from Baseline by Virologic Response Status**




NS=not significant.
*$P<.01$ vs. nonresponders; **$P<.0001$ vs. nonresponders.
Figure shows least squares means adjusted for cirrhosis and drug exposure (total peginterferon and total ribavirin received per kg of weight at baseline) if significant.
Error bars represent standard error.

### Patients with Maximum Decrease in Hb >3 g/dL

- Figure 2 shows the predicted percentage of SVR among patients with Hb >3 g/dL decline vs. ≤3 g/dL decline before (Figure 2a) and after (Figure 2b) adjusting for total drug exposure.
- After adjusting for drug exposure, the difference in SVR was no longer significant (odds ratio=1.29, $P=.02$ before adjusting for drug exposure; odds ratio=0.88, $P=.30$ after adjusting for drug exposure).

**Figure 2. Association of Decrease in Hb with SVR**

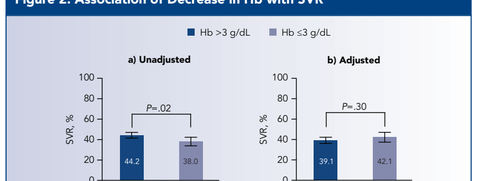
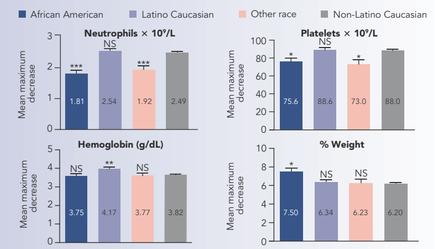



Figure shows predicted percentages of SVR from logistic regression models before and after adjusting for total exposure for peginterferon alfa-2a and total ribavirin exposure per kg. Cirrhosis was adjusted in both models.
*P*-values are from the corresponding tests for odds ratios.
Error bars represent 95% confidence intervals.

### Change in Hematologic Parameters and Weight by Race/Ethnicity

- African Americans had smaller declines in neutrophils and platelets than Latino and non-Latino Caucasians but greater weight loss (Figure 3).

**Figure 3. Adjusted Mean Maximum Decreases from Baseline by Race/Ethnicity**




NS=not significant.
*$P<.01$ vs. non-Latino Caucasians; **$P<.001$ vs. non-Latino Caucasians; ***$P<.0001$ vs. non-Latino Caucasians.
Figure shows least squares means adjusted for cirrhosis and drug exposure (total peginterferon and total ribavirin received per kg of weight at baseline) if significant.
Error bars represent standard error.

- Latinos had greater Hb decline than the non-Latino Caucasians and African Americans.
- The overall effects of race/ethnicity on the hematologic and weight declines were statistically significant both before and after adjusting for drug exposure ($P<.05$).

## CONCLUSIONS

- In general, maximum decreases from baseline in hematologic variables and weight were associated with virologic response.
- After adjusting for drug exposure, only decreases in neutrophils and platelets were independently associated with virologic response, suggesting that anemia and weight loss may be more sensitive to changes in drug exposure.
- African Americans experienced different pharmacodynamic effects compared with non-Latino and Latino Caucasians. Future analyses should explore possible explanations for this relative disparity including analysis of the *IL28B* genotype.[9]

## REFERENCES

1. Fried MW. *Hepatology.* 2002;36:S237-S244.
2. Seyam MS, Freshwater DA, O'Donnell K, Mutimer DJ. *J Viral Hepat.* 2005;12:531-535.
3. Sulkowski, M, et al. *J Hepatol.* 2009;50:551.
4. Lindsay KL, Morishima C, Wright EC, et al. *Clin Gastroenterol Hepatol.* 2008;6:234-241.
5. Fried MW, Shiffman ML, Reddy KR, et al. *N Engl J Med.* 2002;347:975-982.
6. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. *Ann Intern Med.* 2004;140:346-355.
7. Rodriguez-Torres M, Jeffers LJ, Sheikh MY, et al. *N Engl J Med.* 2009;360:257-267.
8. Jeffers LJ, Cassidy W, Howell CD, et al. *Hepatology.* 2004;39:1702-1708.
9. Suppiah V, Moldovan M, Ahlenstiel G, et al. *Nat Genet.* 2009;41:1100-1104.

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