Interferon Responsiveness Does Not Change in Treatment-Experienced Hepatitis C Subjects: Implications for Drug Development and Clinical Decisions

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Background. The purpose of this research was to compare interferon (IFN) responsiveness in treatment-naive and pegylated interferon α-ribavirin (P/R)–experienced subjects and to understand the implications of comparability in IFN responsiveness across treatment courses on drug development and clinical decision making.

Methods. Data from 3750 subjects treated with P/R in 8 trials were reviewed. The change in hepatitis C virus (HCV) RNA at week 4 in response to P/R was compared according to end-of-study (EOS) status (responder, relapser, partial and null responder) for treatment-naive subjects and the previous P/R response status (known as prior relapsers, prior partial responders, and prior null responders at the baseline) for P/R-experienced subjects.

Results. In subjects receiving a first course of P/R treatment (treatment-naive subjects), HCV RNA change after 4 weeks of P/R was correlated with EOS status on a P/R regimen. Importantly, for the first time, we have quantitatively demonstrated that IFN responsiveness in P/R-experienced subjects administered a second course of P/R treatment was similar to the IFN responsiveness in the treatment-naive subjects with corresponding EOS status.

Conclusions. We contend that P/R-experienced subjects are represented within treatment-naive subjects. There are 2 important implications of this finding: (1) from a drug development perspective, a successful direct antiviral plus P/R therapy (IFN-based triple therapy) trial in P/R-experienced subjects may serve as supportive evidence in treatment-naive subjects; and (2) from a clinical decision perspective, previous P/R exposure should not alter new treatment decisions involving IFN-based triple therapy, as the IFN responsiveness to a second course of IFN is comparable.

Traditionally, chronic hepatitis C (CHC) subjects are divided into 2 broad categories (treatment-naive and treatment-experienced) based on their previous exposure to interferon-based therapy, such as pegylated interferon α-ribavirin (P/R) treatment. Treatment-experienced subjects who failed the previous round of P/R treatment are further classified into relapers, partial responders, and null responders: relapers are subjects with hepatitis C virus (HCV) RNA undetectable at the end of P/R treatment, but detectable within 24 weeks of treatment follow-up; partial responders are subjects with greater than or equal to 2 log10 reduction in HCV RNA at week 12, but with a detectable HCV RNA at week 12 of P/R treatment; null responders are those with a less than 2 log10 reduction in HCV RNA at week 12 of P/R treatment [1, 2]. Thus, the order of responsiveness to interferon (IFN)–based therapy (responders > relapers > partial responders > null responders) is embedded within the respective categories.

Empirical data from retreatment with P/R are available for HCV patients who failed prior standard IFN or pegylated-IFN therapy with or without ribavirin.
These subjects are viewed as “difficult to treat” [6], but some subgroups compared to the others have a higher probability of responding with subsequent treatment, specifically those subjects with low viral load, low γ-glutamyltransferase levels [5], and relapers [7]. Retreatment with P/R in subjects infected with genotype 1 HCV has been reported to result in sustained virologic response (SVR; undetectable viral load 24 weeks after the end of treatment) rates of 4%–21% in subjects classified as prior nonresponders (partial and null responders) and 20%–30% in subjects classified as prior relapers [8–11]. Current clinical experiences have not identified any resistance to the IFN-based therapy. This observation, together with the similar response upon retreatment with P/R, suggests that subject IFN response is similar upon initial or second course of P/R treatment and that subjects with characteristics of IFN responsiveness similar to treatment-experienced subjects are represented within the treatment-naïve population. However, there is no systematic investigation assessing IFN responsiveness (based on viral load time course) change after one has received a first or second course of therapy. More importantly, its value to drug development and clinical decision making has not been appreciated.

This research compared IFN responsiveness (defined as the change from baseline in HCV RNA by week 4 after P/R treatment) in P/R-experienced and treatment-naive subjects. This is the first investigation that quantitatively demonstrates a similar viral dynamic response to P/R treatment among treatment-naïve subjects per their subsequent treatment outcome and treatment-experienced subjects per their previous treatment outcome. Data from initial and subsequent P/R treatment were not available for individual subjects; instead, the manuscript compares HCV RNA response from treatment-naïve subjects, stratified according to end-of-treatment outcomes, with treatment-experienced subjects stratified based on previous treatment outcomes. The purpose of this research is to attempt to understand the implications of similar IFN responsiveness in subjects across initial or second P/R treatment courses for drug development and clinical decisions.

METHODS

Data

The individual level data (Table 1) for 2996 treatment-naïve and 754 P/R-experienced subjects injected with genotype 1 HCV who completed P/R treatment (peginterferons α-2a or -2b in combination with ribavirin) and had week 4 HCV viral load data available from 8 trials [12–19] across 4 programs were combined under the US Food and Drug Administration’s (FDA’s) Antiviral Information Management System (AIMS) database [20] (ie, all subjects who discontinued treatment due to adverse events, protocol violation, and so forth, or who were missing week-4 HCV viral load data were not included).

<table>
<thead>
<tr>
<th>Table 1. Data Included in the Analyses</th>
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<td>Program</td>
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<td>Previously untreated population</td>
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<td>Previously P/R-treated population</td>
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Abbreviations: ACHIEVE, Efficacy of Albumin Interferon Alfa-2b With Ribavirin Compared With Peg-IFN Alfa-2a With Ribavirin in IFN Naive Patients; ADVANCE, Phase 3 Study of Telaprevir in Combination With Pegasys and Copegus in Treatment-Naive Subjects With Genotype 1 HCV; IDEAL, Peginterferon Dose Evaluations for Previously Untreated Subjects With Chronic Hepatitis C Infected With Genotype 1; P/R, pegylated interferon α-ribavirin; PROVE, Study of VX-950 in Combination With Peginterferon Alfa-2a (Pegasys), With and Without Ribavirin (Copegus) in Subjects With Hepatitis C; REALIZE, Safety and Efficacy Study of Telaprevir in Chronic, Genotype 1, Hepatitis C Patients That Failed Previous Standard Treatment; RESPOND, Boceprevir in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin; SPRINT, Safety and Efficacy of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1.

*Subjects completed the study.
in the analysis data set). These data were submitted to the FDA through New Drug Application (NDA) and Investigational New Drug (IND) submissions where P/R treatments were either the control arm for investigational antiviral drugs (3 programs) or studied in the Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (P03471). Specifically, the data included treatment-naive and P/R-experienced subjects administered either 48 weeks of pegylated IFN-α (peginterferon α-2a or -2b) in combination with ribavirin (Copegus or Rebetol) or P/R-experienced subjects administered 4 weeks of P/R lead-in followed by boceprevir or telaprevir triple therapy.

Data Analysis

The change from baseline in HCV RNA at week 4 in response to P/R treatment (IFN responsiveness) was plotted by grouping subjects according to the end-of-study (EOS) response status (responder, relapser, partial and null responders) for treatment-naive subjects. For P/R-experienced subjects, IFN responsiveness was plotted according to the previous P/R response (known as prior relapser, prior partial and prior null responders at the baseline). Further, the association between IFN responsiveness and the EOS SVR outcome (binary endpoint) was assessed by a logistic regression method corrected for baseline viral load, body mass index, age, sex, race (black or not), cirrhosis status, HCV genotype 1 subtype (1a or 1b), and peginterferon α-2a or -2b. A simple linear correlation between a baseline factor and the EOS SVR and no interaction were assumed in the logistic regression model.

RESULTS

In this research, we confirmed the HCV RNA change from baseline assessed at week 4 when treated with P/R was a strong predictor of the SVR outcome (Figure 1). The odds ratio of achieving SVR for a 1-log10 decline in HCV RNA at week 4 when treated with P/R was 2.8 (95% confidence interval [CI], 2.6–3.0). For subjects with HCV RNA change from baseline >4.2 log10 at week 4, the observed SVR rate was more than 85% (403 out of 470). The probability of SVR in these subjects was also much higher than the 40% to 45% SVR rate observed in the overall population. Other important predictors of SVR were baseline viral load, age and cirrhosis status. The results of the logistic regression are summarized in Table 2. Peginterferon α-2a versus -2b treatment was not a significant predictor of SVR.

In treatment-naive subjects, IFN responsiveness was correlated with EOS status after P/R treatment (Figure 2). As expected, P/R responders demonstrated the greatest HCV RNA change from baseline at week 4 followed by relapers and partial responders, whereas null responders had the lowest change. Importantly, for the first time, we found that IFN responsiveness to a second course of P/R treatment for P/R-experienced subjects was similar to the treatment-naive group with corresponding EOS status (ie, the median HCV RNA change from baseline in prior relapers [baseline status] was −2.3 log10 compared to −2.2 log10 in relapers [EOS status]; −1.2 log10 in prior partial responders [baseline] compared to −1.5 log10 in partial responders [EOS status]; −0.9 log10 in prior null responders [baseline] compared to −0.6 log10 in null responders [EOS status]; Table 3). In other words, the distribution of HCV RNA change from baseline at week 4 was similar for each subgroup irrespective of previous treatment experience (treatment naive or P/R experienced).

DISCUSSION

The results described in this report confirmed that for subjects infected with genotype 1 HCV the HCV RNA change from

| Table 2. Logistic Regression Analysis for Covariates Associated With Sustained Virologic Response Outcome After Pegylated Interferon α-Ribavirin Therapy |
|---------------------------------|-----------------|----------------|
| Covariate                       | Odds Ratio (95% CI) | P Value |
| Baseline viral load (1 log increase) | 0.372 (316, 438) | <.0001 |
| Age (1 year increase)           | 0.975 (964, 986)  | <.0001 |
| Cirrhosis (yes vs no)           | 0.350 (224, 547)  | <.0001 |

Abbreviation: CI, confidence interval.
baseline at week 4 when treated with P/R is a strong predictor of the SVR outcome. This finding is consistent with the common opinion that HCV RNA reduction at week 4 is a strong predictor for P/R treatment outcome [21–25]. Furthermore, this predictive ability of HCV RNA reduction at week 4 to describe treatment outcome supports our selection of HCV RNA reduction at week 4 as a metric for comparing IFN responsiveness between P/R-experienced and treatment-naive subjects.

For the first time, our analyses quantitatively demonstrated that IFN responsiveness for a second course of P/R treatment in subjects infected with genotype 1 HCV does not change after the first course of P/R treatment. This is unlike HIV where treatment failure frequently leads to resistance and worst treatment outcomes to subsequent courses of treatment with drugs in the same class. One of the limitations of this manuscript is that paired treatment data for individual subjects (ie, HCV RNA change from baseline at week 4 from both the first course and a subsequent course of treatment) were not available for those patients who were P/R-experienced, nor were the interval between treatments considered in the analysis. Rather, comparisons were made between HCV RNA response from treatment-naive subjects, stratified according to end-of-treatment outcomes and P/R-experienced subjects stratified based on previous treatment outcome. It was observed that HCV RNA response at week 4 was similar between these stratified groups. This observation was not unexpected, as the outcome of HCV IFN-based therapy is mainly affected by baseline factors (eg, fibrosis, age, race, HCV genotypes, and baseline viral load).

In addition, the host factor of interleukin (IL)–28B genotype, encoding interferon-λ-3 (IFN-λ-3), is a strong predictor

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Table 3. Comparison of Interferon Responsiveness (log10 change from baseline in Hepatitis C Virus RNA) at Week 4 Between Treatment-Naive and pegylated interferon α-ribavirin–Experienced Subjects by Their End of Study or Baseline Status, Respectively

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<thead>
<tr>
<th>(N) Mean (Median: P10, P90)*</th>
<th>Treatment Naive</th>
<th>P/R Experienced</th>
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<tr>
<td>Relapser</td>
<td>(N = 583) −2.5</td>
<td>(N = 440) −2.5</td>
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<td>(−2.2: −4.4, −1.0)</td>
<td>(−2.3: −4.7, −0.9)</td>
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<tr>
<td>Partial</td>
<td>(N = 489) −1.7</td>
<td>(N = 211) −1.5</td>
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<td>(−1.5: −3.2, −0.7)</td>
<td>(−1.2: −3.0, −0.5)</td>
</tr>
<tr>
<td>Null</td>
<td>(N = 538) −0.7</td>
<td>(N = 103) −1.0</td>
</tr>
<tr>
<td></td>
<td>(−0.6: −1.2, −0.2)</td>
<td>(−0.9: −1.6, −0.3)</td>
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Abbreviation: P/R, pegylated interferon α-ribavirin.

*Change from baseline in hepatitis C virus RNA at week 4 (log10).
of the response to IFN-based treatment. Genetic polymorphisms upstream of IL-28B were found to be associated with an approximately 2-fold change in response to treatment [26]. Subjects who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype. The lower response rate in the African American population may be explained in part by a higher prevalence of the “T” allele in the polymorphic IL-28B gene in African American subjects [27]. Unfortunately, evaluation of IL-28B could not be performed in this analysis, as IL-28B data were not available. However, most importantly, the development of viral resistance to P/R after exposure to P/R treatment has not been definitively identified. The results presented here support the general clinical observation of the lack of resistance to P/R treatment by demonstrating similar responses to P/R for treatment-naive and P/R-experienced subjects.

The results presented here are consistent with the observed low SVR rates (5%–20%) reported after retreatment with P/R for IFN-experienced subjects. In the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial for HCV patients who failed prior standard IFN therapy with or without ribavirin [28], ≥4-log_{10} decline in serum HCV RNA occurred in 178 out of 764 subjects after the retreatment with P/R for 20 weeks. Although these subjects were previous failures on IFN-based therapy, response (decline in HCV RNA) to a second course of P/R treatment was achieved. As one would expect for previous relapers or nonresponders, the majority of these subjects (82%) later broke through or relapsed. Theoretically, one would expect a 0% SVR in previously P/R-failed subjects if the treatment response was identical; however, it is unrealistic as there are several patient-related factors (eg, motivation, adherence, tolerability, etc.) that cannot be replicated between repeated treatments [29]. More importantly, if there was development of resistance to P/R treatment, it would not be possible to achieve SVR in subjects who previously did not respond to the same treatment. Along these lines, Gerner et al. [7] reported that retreatment with IFN-α plus ribavirin may be useful in subjects who relapsed in a previous antiviral treatment but seems not to be useful in nonresponders. Thus, the characteristics of relapers are potentially overlapping with characteristics of subjects who responded to the first course of P/R treatment and could have achieved SVR.

With this observation, we contend that P/R-experienced subjects are represented within treatment-naive subjects. In other words, if we consider a treatment-naive population, P/R-experienced subjects should represent a fraction that will be identified as nonresponders or relapers if administered P/R treatment. As approximately 53% of subjects do not respond successfully to the P/R treatment, the patients with characteristics similar to the P/R-experienced population represent the majority of a treatment-naive population. There are 2 important implications of this finding:

1. From a drug development perspective, a successful trial for a direct antiviral agent (DAA) plus P/R therapy (IFN-based triple therapy) in P/R-experienced subjects may serve as supportive evidence in treatment-naive subjects. Here, we only focus on evidence needed for regulatory decision making. For future IFN-based DAA trials, inclusion of P/R-naive and experienced subjects in the same study stratified by prior response seems worth considering.

2. From a clinical decision perspective, previous P/R exposure should not alter new treatment decisions involving IFN-based triple therapy, as the IFN responsiveness to second courses of IFN are comparable.

This “bridging” of data combined with empirical clinical data provided critical evidence for the FDA’s decisions on telaprevir [30] and boceprevir [31].

Notes

Acknowledgments. Data for these analyses were submitted to the US Food and Drug Administration by Merck, Vertex, and Human Genome Sciences as part of their new drug applications.

Disclaimer. The opinions and information in this manuscript are those of the authors, and do not represent the views and/or policies of the US Food and Drug Administration.

Potential conflicts of interest. All authors: No reported conflicts.

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