Clinical Experience with Nonstandard Doses of Interferon Alfa-2b and Ribavirin in the Treatment of Chronic Hepatitis C Infection: A Retrospective Analysis

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is the most common blood-borne virus in the United States. Several mono- and combination therapies have been approved by the US Food and Drug Administration for the treatment of HCV, but their routes of administration, dosing approaches, eras of introduction, and actual use in clinical practice and resulting effectiveness have not yet been reported.

Objectives: The aim of this article was to characterize clinical use and virologic response (VR) of the HCV treatments interferon alfa-2b plus ribavirin (IFN + RBV) and peginterferon alfa-2b plus ribavirin (peg-IFN + RBV).

Methods: This retrospective chart review of office-based practices in the United States was conducted at 200 physicians' offices across the United States. We collected data concerning dosing patterns, VR (HCV RNA load, ≤1000 IU/mL or "negative" on polymerase chain reaction qualitative analysis), and adverse events (AEs) from the medical records of a geographically diverse sample of patients receiving treatment for chronic HCV infection in the United States from July 2001 to June 2002. For efficacy assessment, factors that were statistically different at baseline were adjusted using logistic regression. Providers also reviewed the medical records for symptoms or signs consistent with HCV treatment-related AEs.

Results: Data from the records of 675 patients (423 men, 252 women; mean [SD] age of 45.5 [8.2] years; mean [SD] body weight, 80.8 [19.4] kg) were analyzed. At baseline, the IFN + RBV treatment group (330 patients) had significantly higher percentages of black patients (22.1% vs 15.7%; P = 0.032) and patients with hepatic disease based on clinician-reported cirrhosis and liver dysfunction (18.8% vs 9.9%; P < 0.001), and a significantly lower percentage of white patients (60.3% vs 69.6%; P = 0.012) compared with the peg-IFN + RBV treatment group (345 patients). The difference in log-transformed baseline HCV...

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RNA loads between the 2 treatment groups in this study was <1 log unit. A significantly higher percentage of IFN + RBV–treated patients compared with peg-IFN + RBV–treated patients were prescribed HCV therapy on diagnosis (37.3% vs 29.9%; \( P = 0.041 \)), and the mean (SD) duration of treatment was significantly different between the 2 treatment groups (52.5 [37.0] vs 27.5 [15.0] weeks; \( P < 0.001 \)). Peg-IFN + RBV was associated with a higher rate of VR compared with IFN + RBV on univariate analysis (28.5% vs 17.5%; \( P = 0.018 \)). Recommended doses of peg-IFN and higher-than-recommended doses of RBV were associated with an increased likelihood of VR. Higher-than-recommended doses of peg-IFN without a concomitant increase in RBV was not associated with an increased likelihood of VR. The incidences of the 3 most commonly reported AEs in the IFN + RBV group were significantly higher compared with those in the peg-IFN + RBV group: fatigue, 217 (65.8%) versus 185 (53.6%) patients (\( P = 0.001 \)); depression, 147 (44.5%) versus 120 (34.8%) (\( P = 0.009 \)); and anxiety, 87 (26.4%) versus 64 (18.6%) (\( P = 0.014 \)). Nausea, however, was reported in a significantly higher number of patients in the peg-IFN group compared with the IFN + RBV group (74 [21.4%] vs 51 [15.5%]; \( P = 0.045 \)). The frequencies of dose modification and treatment discontinuation due to AEs were similar between the 2 treatments and were similar to or less than those reported in other studies.

**Conclusions:** In this retrospective data analysis of US office-based practices concerning HCV treatment, clinicians were observed to prescribe IFN + RBV at doses that differ from recommendations in the product information (PI), as well as prescribe the RBV component of peg-IFN + RBV at doses that differed from PI recommendations. Although patients treated with peg-IFN + RBV appeared to achieve higher VR compared with those treated with IFN + RBV in our analysis of data from clinical practice, peg-IFN + RBV was associated with lower VR rates compared with those reported in clinical studies. (Curr Ther Res Clin Exp. 2005; 66:433-450) Copyright © 2005 Excerpta Medica, Inc.

**Key words:** hepatitis C, pegylated interferon, interferon alfa-2b and ribavirin, ribavirin, dosing, outcomes.

**INTRODUCTION**

Hepatitis C virus (HCV) is the most common blood-borne virus in the United States, affecting 3.9 million individuals and resulting in 2.7 million chronic infections. Worldwide, chronic HCV infection has an estimated prevalence of ~3%, with 150 million carriers. It is thought that many (50%-95%) HCV-infected individuals in the United States are unaware of their serologic status until they become chronic carriers, yielding higher prevalence rates. Therefore, it is likely that the proportion of people with a duration of HCV infection of 20 years or more would increase significantly by the mid-2010s.

Approximately 10% to 20% of patients with chronic HCV infection develop progressive hepatic fibrosis, leading to cirrhosis, end-stage hepatic disease, and/or hepatocellular carcinoma within 20 years of HCV diagnosis. A number of risk fac-
tors are associated with HCV progression toward hepatic disease. The primary risk factors include "older age" at the time of infection, male gender, immunosuppression (eg, secondary to HIV), concurrent chronic hepatitis B virus (HBV) infection, and high levels of alcohol consumption (>30 g/d in men, >20 g/d in women). Current standard-of-care therapy for HCV consists of treatment with peginterferon in combination with ribavirin (RBV). In studies, interferon alfa in a pegylated formulation (ie, interferon chemically linked to a polyethylene glycol moiety) has been shown to be more effective compared with nonpegylated interferon. Two pegylated, recombinant, interferon alfa formulations—peginterferon alfa-2a and peginterferon alfa-2b—have been approved by the US Food and Drug Administration (FDA) as monotherapy or in combination with RBV for the treatment of chronic HCV infection in adults with compensated hepatic disease who are naive to interferon treatment. Peginterferon alfa-2b is administered on a weight-adjusted basis in combination with non-weight-adjusted RBV. FDA-approved labeling for peginterferon alfa-2a does not specify weight-adjusted dosing, but suggests weight-adjusted dosing for concomitantly administered RBV. Both interferon alfa and RBV have been associated with dose-limiting toxicities, including neutropenia, thrombocytopenia, and depression (with interferon), and anemia (with RBV).

The standard outcome measures of the effectiveness of HCV treatments include sustained virologic response (SVR), defined as an undetectable serum HCV RNA load (<50 IU/mL or <100 copies/mL) at 24 weeks after discontinuation of therapy. Peginterferon alfa combination therapy has resulted in overall SVRs of 70% to 82% in patients infected with non-1 HCV genotypes (types 2-6) and 41% to 51% in patients infected with HCV genotype 1. Evaluation of virologic response (VR), defined as an undetectable HCV RNA load or a 2-log decrease from baseline in HCV viral load after 12 weeks of therapy, is helpful in identifying individuals who will not respond to further treatment. Failure to achieve VR has a high negative predictive value for achievement of SVR.

With the purpose of characterizing use and outcomes of available HCV treatments in clinical practice, we retrospectively examined dosing patterns, VR, and adverse events (AEs) for 2 interferon alfa-2b-based treatment regimens: interferon alfa-2b in combination with RBV (IFN + RBV) and peginterferon alfa-2b in combination with RBV (peg-IFN + RBV). These treatment regimens were the standard of care at the time of the study.

MATERIALS AND METHODS
This retrospective chart review of office-based practices in the United States was conducted at 200 physicians' offices selected from a national sample of hepatitis specialists provided by the sponsor.

Study Design, Patient Population, and Data Collection
To ensure representation from a geographically diverse population of patients with chronic HCV infection, 200 physicians were recruited from the Inter-
continental Marketing Services (IMS) list of interferon prescribers of a total of 7707 US providers (IMS Prescription Tracking-Xponent, an informational product, received by subscription, containing information concerning location and prescribing information from US physicians, compiled weekly and monthly). Physicians were ranked, in descending order, by the number of interferon prescriptions written between July 2001 and June 2002, and were sent information packets describing the study. The physician's specialty and interferon prescription deciles status were used as key sampling variables. For inclusion, physicians were required to have been treating at least 15 patients with HCV at the time of the study and have a practice that was at least 50% office based. Physicians who were affiliated with a pharmaceutical company (on retainer or paid consultants) or participated in a clinical trial or market research involving HCV within the 3 months before the study were excluded. The intention of selecting providers with a significantly office-based practice was to ensure that patients selected for inclusion represented a mix of acute, chronic, and community-based care and a range of stages of HCV disease severity and progression.

During July and August of 2002, participating physicians reviewed their own patients' medical records to identify adults diagnosed with chronic HCV who had been seen in their respective practices. Each recruited physician was assigned 2 calendar quarters between July 2001 and June 2002 from which to identify the last 6 consecutive HCV-diagnosed patients seen in the office. Data concerning demographic characteristics, HCV treatment and dosing, selected laboratory procedures, and clinical outcomes were transcribed by the physicians from patient medical records onto data-collection forms.

The study design and research protocol were reviewed and approved by the sponsor for compliance with ethics standards, and waivers of consent were obtained from an independent institutional review board. Each patient's record was abstracted by the respective provider, and aggregated data were provided for research purposes by an independent third party. To comply with confidentiality requirements, no patient-identifiable information was collected from providers.

When an interim review of the treatment patterns was performed on the data from the first 551 patients, it was noted that the sample included a preponderance of nontreated patients with HCV, including relatively few patients with concomitant HIV infection. Thus, subsequent physicians were asked to provide data from patients treated specifically for HCV, including those who were concurrently infected with HIV. Data from 447 patients were collected after the interim review.

Data-collection forms were randomly audited and checked against selected patient medical files by an independent data-collection organization (Market Ceritude, LLC, Morristown, New Jersey). An audit for data uniformity, completeness, accuracy, and patterns of completion relative to other data fields was performed on 20% of the physician samples submitted and demonstrated >97% accuracy with source documents. Physicians were paid an honorarium for each completed data-collection form.
HCV Treatment Dosing

The dosing recommendations included in the product information (PI) for IFN + RBV are 3 MIU SC TIW, and RBV 1000 mg/d (weight, ≤75 kg) or 1200 mg/d (weight, >75 kg) PO in 2 divided doses. Recommended dosing for peg-IFN + RBV therapy is peg-IFN 1.5 µg/kg • wk SC plus RBV 800 mg/d PO in 2 divided doses. To assess dosing treatment strategies, the PI-recommended doses of each treatment were compared with the actual doses administered to patients.

Virologic Response

Serum HCV RNA loads at 24 ± 6 weeks from the start of HCV therapy were used for analysis of VR, defined as HCV RNA load ≤1000 IU/mL or a negative result on HCV polymerase chain reaction qualitative analysis (Amplicor, Roche Diagnostics, Indianapolis, Indiana). To be included in the VR analysis, patients must have reached the analysis target of 24 ± 6 weeks of treatment.

Multiple, stepwise logistic regression was used to explore the independent effect of treatment on VR while controlling for differences in relevant risk factors between groups. The order of entry of factors into the stepwise regression models were those variables having a P of ≤0.1. Variables entered into the model included gender, race (white vs nonwhite), age (≤45 vs >45 years), weight (≤78 vs >78 kg), HCV genotype (1 vs non-1), time from HCV diagnosis to initial therapy, actual treatment duration (weeks), hepatic disease severity (mild vs other), baseline HCV RNA load (≤725,000 vs >725,000 IU/mL), baseline alanine aminotransferase (ALT) quotient (≤3 vs >3), and treatment (peg-IFN + RBV vs IFN + RBV). Baseline ALT quotient was defined as the mean of the serum ALT levels before treatment divided by the upper limit of normal (35 U/L).

The effect of modified dosing of peg-IFN + RBV on VR was investigated using logistic regression analyses in 3 different peg-IFN dosing strategies: recommended dose (vs low and high doses combined), low dose (vs recommended and high doses combined), or high dose (vs low and recommended doses combined). In these multivariate efficacy analyses of modified peg-IFN dosing regimens, the dose of RBV was also included as a covariate.

Tolerability Assessment

For assessment of AEs, participating physicians were provided with a list of possible treatment-related AEs, generated from the PIs of products actively used at the time of the study, and asked to identify which AEs they considered treatment related based on their clinical judgment. Providers reviewed the medical records, and if symptoms or signs consistent with HCV treatment–related AEs were originally recorded, these were indicated on the data-collection form. Providers could enter additional HCV-related “free-text” AEs if they were captured in the medical record but not prelisted on the data-collection instrument.

Hemoglobin (Hb) concentrations, platelet counts, and neutrophil counts obtained during the course of treatment were recorded. For the purpose of
analysis, accepted normal laboratory values were used to define the inci-
dence and severity of the hematologic events of study-defined anemia, throm-
boctopenia, and neutropenia, independent of investigator-reported AEs, as
follows: anemia: Hb <13 g/dL for males, <12 g/dL for females; thrombocytope-
nia: platelet count <130,000 cells/μL; neutropenia: absolute neutrophil count
<1000 cells/μL. Severe hematologic AEs were defined according to the criteria
in the peg-IFN PI,24 as follows: severe anemia: Hb <8 g/dL; severe thrombocyto-
penia: platelet count <50,000 cells/μL; severe neutropenia: absolute neutro-
phil count <500 cells/μL.

The frequency of dosing modification and discontinuation of HCV therapy
due to AEs were determined for each treatment group based on recorded
events. It is important to note that this retrospective chart review did not
supersede or preclude reporting AEs to manufacturers or to the FDA. All
patients who entered the study and started IFN + RBV or peg-IFN + RBV HCV
treatment were included in the tolerability analysis.

Statistical Analysis
Summary statistics for continuous variables included number of subjects,
mean, median, SD, and minimum and maximum values. Categorical variables
were summarized using patient counts and percentages, gender (female vs
male), race (white vs nonwhite), HCV genotype (1 vs non-1), hepatic disease
severity (mild vs other), and treatment (peg-IFN + RBV vs IFN + RBV). A
Cochran-Mantel-Haenszel univariate test adjusted for baseline genotype was
used to determine overall between-group differences in VR. AEs were summa-
rized and compared using the $\chi^2$ or Fisher exact test. Analysis of variance was
used to compare differences between continuous variables. Stepwise logistic
regression was used to generate a final model. All statistical analyses were per-

RESULTS
The sample of consecutively enrolled practitioners included 130 gastroenterol-
ogists, 50 infectious disease specialists, and 20 hepatologists (mean duration of
practice, 14 years). These physicians provided records from a total of 998 HCV-
diagnosed patients for review. Of these individuals, 778 (78.0%) were treated for
HCV and 220 (22.0%) were not treated. Of the treated patients, 330 (42.4%) were ini-
tially prescribed IFN + RBV (203 men, 127 women; mean [SD] age, 46.0 [8.7] years),
345 (44.3%) peg-IFN + RBV (220 men, 125 women; mean [SD] age, 45.0 [7.7] years),
and 103 (13.2%) received other therapies.

Of 778 patients who were treated, 666 had all dosing data available, whereas
112 had at least 1 dosing-data element missing and therefore were excluded
from the analysis. Also, 154 patients discontinued therapy for any reason.
Nontreated individuals and those who received other therapies are not dis-
cussed further.
Demographic and Clinical Characteristics

The combined study population (675 patients) was predominantly male (62.7%) and white (65.0%), with a mean (SD) age of 45.5 (8.2) years and a mean (SD) body weight of 80.8 (19.4) kg. The majority (87.9%) were not concomitantly infected with other hepatitis viruses. Most (417 [61.8%]) of the patients were diagnosed with HCV genotype 1, whereas 106 (15.7%) had an unknown genotype status. At baseline, the IFN + RBV treatment group had significantly higher percentages of black patients (22.1% vs 15.7%; P = 0.032) and patients with hepatic disease based on clinician-reported cirrhosis and hepatic dysfunction (18.8% vs 9.9%; P < 0.001), and a significantly lower percentage of white patients (60.3% vs 69.6%; P = 0.012) compared with the peg-IFN + RBV treatment group (Table I). The difference in log-transformed baseline HCV RNA loads between the 2 treatment groups in this study was <1 log unit (P = 0.023). There were no significant differences between the 2 treatment groups with respect to HIV or HBV comorbidities. A significantly higher percentage of IFN + RBV-treated patients were prescribed HCV therapy on diagnosis compared with peg-IFN + RBV-treated patients (37.3% vs 29.9%; P = 0.041), and the mean (SD) duration of treatment was significantly different between the 2 treatment groups (52.5 [37.0] vs 27.5 [15.0] weeks; P < 0.001).

HCV Treatment Dosing

Data concerning HCV treatment dosing were available for 325 (98.5%) of the IFN + RBV-treated patients and 341 (98.8%) of the peg-IFN + RBV-treated patients.

Clinicians prescribed the IFN component of IFN + RBV treatment in accordance with PI29-recommended doses (3 MIU TIW) in 322 of 325 (99.1%) patients in the IFN + RBV treatment cohort, whereas 3 (0.9%) patients received less-than-recommended doses. The RBV dosing component of this therapy was less consistent with PI29-recommended doses: of 135 patients who weighed ≤75 kg, 25 (18.5%) received doses above (>1200 mg/d), and 21 (15.6%) received doses below (<800 mg/d) the PI29-recommended doses of RBV. Of 190 patients who weighed >75 kg, 48 (25.3%) received doses of RBV below (<800 mg/d) that recommended in the PI29; the remaining patients (142/190 [74.7%]) were treated with recommended doses.

In 234 of 345 (67.8%) patients in the peg-IFN + RBV group, the doses of both therapeutic components actually administered differed significantly from those recommended in the PI29. Initial weight-adjusted doses of peg-IFN differed from PI24-recommended doses in 177 (51.9%) patients (120 [35.2%] patients, higher; 57 [16.7%] patients, lower), with administered doses ranging from 25% to 88% above and 17% to 67% below the PI24-recommended dose of 1.5 μg/kg · wk (Figure 1). In the same treatment group, 238 (69.8%) patients received doses of RBV that were 25% to 75% higher than that recommended in the PI27 (800 mg/d) (Figure 2). One (0.3%) patient received a dose of 600 mg/d RBV.
Table I. Demographic and clinical characteristics of the study patients (N = 675).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IFN + RBV (n = 330)</th>
<th>Peg-IFN + RBV (n = 345)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>46.0 (8.7)</td>
<td>45.0 (7.7)</td>
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<tr>
<td>Sex, no. (%)</td>
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<td></td>
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<tr>
<td>Male</td>
<td>203 (61.5)</td>
<td>220 (63.8)</td>
<td>0.55</td>
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<tr>
<td>Female</td>
<td>127 (38.5)</td>
<td>125 (36.2)</td>
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<td>Weight, mean (SD), kg</td>
<td>82.3 (20.0)</td>
<td>79.4 (18.7)</td>
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<td>Race, no. (%)*</td>
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<tr>
<td>White</td>
<td>199 (60.3)</td>
<td>240 (69.6)</td>
<td>0.012</td>
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<tr>
<td>Black</td>
<td>73 (22.1)</td>
<td>54 (15.7)</td>
<td>0.032</td>
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<td>Other/unknown</td>
<td>58 (17.6)</td>
<td>51 (14.8)</td>
<td>0.324</td>
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<td>Concomitant disease, no. (%)*</td>
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<tr>
<td>Cirrhosis</td>
<td>62 (18.8)</td>
<td>34 (9.9)</td>
<td>&lt;0.001</td>
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<td>HIV</td>
<td>46 (13.9)</td>
<td>38 (11.0)</td>
<td>0.25</td>
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<td>HBV</td>
<td>30 (9.1)</td>
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<td>HCV genotype, no. (%)</td>
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<td>1</td>
<td>204 (61.8)</td>
<td>213 (61.7)</td>
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<td>Non-1</td>
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<td>90 (26.1)</td>
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<td>64 (19.4)</td>
<td>42 (12.2)</td>
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<td>Prior liver transplantation, no. (%)</td>
<td>13 (3.9)</td>
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<td>Liver biopsy performed, no. (%)</td>
<td>270 (81.8)</td>
<td>280 (81.2)</td>
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<td>Hepatic disease severity, no. (%)</td>
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<td>Mild</td>
<td>106 (32.1)</td>
<td>160 (46.4)</td>
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<tr>
<td>Moderate</td>
<td>121 (36.7)</td>
<td>98 (28.4)</td>
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<td>Severe</td>
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<td>17 (4.9)</td>
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<tr>
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<td>70 (21.2)</td>
<td>70 (20.3)</td>
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<td>HCV RNA load, mean (SD), log copies</td>
<td>5.53 (0.99)</td>
<td>5.71 (0.72)</td>
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<td>(n = 209)</td>
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<td>(n = 226)</td>
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<td>ALT concentration, mean (SD), IU/L</td>
<td>98.4 (62.0)</td>
<td>89.6 (73.2)</td>
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<td>(n = 274)</td>
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<td>(n = 288)</td>
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<td>ALT quotient, mean (SD)</td>
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<td>2.56 (2.09)</td>
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<td>(n = 274)</td>
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<td>(n = 288)</td>
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<tr>
<td>Prescribed HCV therapy at diagnosis, no. (%)</td>
<td>123 (37.3)</td>
<td>103 (29.9)</td>
<td>0.041</td>
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<td>Treatment duration, mean (SD), wk</td>
<td>52.5 (37.0)</td>
<td>27.5 (15.0)</td>
<td>&lt;0.001</td>
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<td>(n = 330)</td>
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<td>(n = 335)</td>
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(continued)
Table I. (Continued)

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<thead>
<tr>
<th>Characteristic</th>
<th>IFN + RBV (n = 330)</th>
<th>Peg-IFN + RBV (n = 345)</th>
<th>P</th>
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<td>Primary medical insurance, no. (%)*</td>
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<td>HMO/PPO</td>
<td>195 (59.1)</td>
<td>219 (63.5)</td>
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<td>Medicaid</td>
<td>53 (16.1)</td>
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<td>FFS</td>
<td>37 (11.2)</td>
<td>51 (14.8)</td>
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<tr>
<td>Other</td>
<td>37 (11.2)</td>
<td>24 (7.0)</td>
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<tr>
<td>Unknown</td>
<td>8 (2.4)</td>
<td>9 (2.6)</td>
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</tbody>
</table>

IFN = interferon alfa-2b; RBV = ribavirin; peg-IFN = pegylated interferon alfa-2b; HBV = hepatitis B virus; HCV = hepatitis C virus; ALT = alanine aminotransferase; HMO = health maintenance organization; PPO = preferred provider organization; FFS = fee for service.

*Percentages may not add to 100% due to rounding.

Efficacy

Virologic Response at 24 ± 6 Weeks of Treatment

Five hundred twelve patients reached the analysis target of 24 ± 6 weeks of treatment. The remaining 266 patients who had not yet reached 24 weeks post-treatment were excluded from the analysis. VR was noted in a higher proportion of peg-IFN + RBV-treated patients compared with IFN + RBV–treated patients in the univariate (28.5% vs 17.5%; P = 0.018) and the multivariate (OR, 1.68; P = 0.028) analyses (Table II). Logistic regression model covariates associated with VR included non-1 genotype (OR, 4.09; P < 0.001), lower baseline HCV RNA load (OR, 3.13; P < 0.001), white race (OR, 2.18; P = 0.006), and female gender (OR, 1.70; P = 0.024).

Effects of Modified Dosing of Peg-IFN + RBV on Virologic Response

Recommended Dose of Peg-IFN

Administration of peg-IFN at the PI24-recommended dose was associated with an increased likelihood of VR (OR, 2.58; P = 0.012) (Table III), as was higher-than-recommended RBV dose (OR, 2.37; P = 0.043). Other factors associated with an increased likelihood of VR included baseline HCV RNA load ≤725,000 IU/mL (OR, 5.62; P < 0.001), non-1 genotype (OR, 5.44; P < 0.001), and female gender (OR, 2.42; P = 0.023).

Lower-than-Recommended Dose of Peg-IFN

There was no association found between the administration of a lower-than-recommended dose of peg-IFN and the likelihood of VR, whereas higher-than-recommended RBV dose (OR, 2.23; 95% CI of OR, 1.01–5.18), baseline HCV RNA load ≤725,000 IU/mL (OR, 4.74; P < 0.001), and non-1 genotype (OR, 4.81; P < 0.001) seemed to be associated with the likelihood of VR.
Figure 1. Weight-dose relationship of the pegylated interferon alfa-2b (peg-IFN) component received by patients in the peg-IFN + ribavirin treatment group (n = 345). PI = product information.24

Higher-than-Recommended Dose of Peg-IFN
Administration of a higher-than-recommended24 dose of peg-IFN was not associated with an increased likelihood of VR. Factors that were associated with an increased likelihood of VR using this dosing strategy included higher-than-recommended RBV dose (OR, 2.24; 95% CI of OR, 1.02–5.24), baseline HCV RNA load ≤725,000 IU/mL (OR, 5.76; P < 0.001), non-1 genotype (OR, 6.03; P < 0.001), and female gender (OR, 2.22; P = 0.035).

Tolerability
Clinician-Reported Adverse Events
Three hundred forty-five and 330 patients receiving peg-IFN + RBV and IFN + RBV, respectively, were included in the tolerability analysis. Clinician-reported AEs that occurred in both treatment groups with a frequency of >10% included the following conditions: fatigue (402 [59.6%]), influenza-like symptoms (330 [48.9%]), depression (267 [39.6%]), anemia (216 [32.0%]), headache (174 [25.8%]), myalgia (161 [23.9%]), anxiety (151 [22.4%]), weight loss (143 [21.2%]),
Figure 2. Weight-dose relationship of ribavirin (RBV) received by patients in the pegylated interferon alfa-2b + RBV treatment group (n = 345). (Product information [PI] recommends dose is 800 mg/d, regardless of body weight.)

Table II. Factors associated with virologic response (hepatitis C virus [HCV] RNA load, ≤1000 IU/mL at 24 ± 6 weeks of treatment), determined by logistic regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-1 genotype</td>
<td>4.09</td>
<td>2.49-6.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline serum HCV RNA load, ≤725,000 IU/mL</td>
<td>3.13</td>
<td>1.95-5.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race</td>
<td>2.18</td>
<td>1.27-3.87</td>
<td>0.006</td>
</tr>
<tr>
<td>Peg-IFN + RBV</td>
<td>1.68</td>
<td>1.06-2.68</td>
<td>0.028</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.70</td>
<td>1.07-2.70</td>
<td>0.024</td>
</tr>
</tbody>
</table>

OR = odds ratio; peg-IFN = pegylated interferon alfa-2b; RBV = ribavirin.
Table III. Factors associated with virologic response (hepatitis C virus [HCV] RNA load, ≤1000 IU/mL at 24 ± 6 weeks of treatment) determined by logistic regression models based on pegylated interferon alfa-2b (peg-IFN) dosing.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Dose</th>
<th>Low Dose*</th>
<th>High Dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Baseline serum HCV RNA load ≤725,000 IU/mL</td>
<td>5.62</td>
<td>2.67–12.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-1 genotype</td>
<td>5.44</td>
<td>2.51–12.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peg-IFN dose</td>
<td>2.58</td>
<td>1.24–5.48</td>
<td>0.012</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.42</td>
<td>1.14–5.27</td>
<td>0.023</td>
</tr>
<tr>
<td>Higher-than-recommended27 (≥800 mg/d)</td>
<td>2.37</td>
<td>1.05–5.66</td>
<td>0.043</td>
</tr>
<tr>
<td>RBV dose</td>
<td>1.26</td>
<td>0.53–3.10</td>
<td>0.610</td>
</tr>
</tbody>
</table>

OR = odds ratio; RBV = ribavirin.
*Less than the product information (PI)24-recommended dose of 1.5 μg/kg · wk.
†More than the PI24-recommended dose of 1.5 μg/kg · wk.
insomnia (139 [20.6%]), musculoskeletal pain (125 [18.5%]), nausea (125 [18.5%]), neutropenia (107 [15.9%]), fever (99 [14.7%]), injection-site reaction (96 [14.2%]), and alopecia (84 [12.4%]). The incidences of the 3 most commonly reported AEs in the IFN + RBV group were significantly higher compared with those in the peg-IFN + RBV group: fatigue, 217 (65.8%) versus 185 (53.6%) patients ($P = 0.001$); depression, 147 (44.5%) versus 120 (34.8%) ($P = 0.009$); and anxiety, 87 (26.4%) versus 64 (18.6%) ($P = 0.014$). Nausea, however, was reported in a significantly higher number of patients in the peg-IFN group compared with the IFN + RBV group (74 [21.4%] vs 51 [15.5%]; $P = 0.045$).

**Hematologic Adverse Events**

Statistically similar rates of anemia (33.0% vs 31.0%), thrombocytopenia (6.4% vs 8.7%), and neutropenia (15.2% vs 16.5%) were observed in the IFN + RBV and peg-IFN + RBV groups, respectively. The incidence of hematologic AEs defined as severe included thrombocytopenia (4.5% with IFN + RBV, 2.3% with peg-IFN + RBV), neutropenia (≤1% with IFN + RBV, 0 with peg-IFN + RBV), and anemia (≤1% in both groups).

**Dose Modification and Treatment Discontinuation**

The frequencies of dose modification due to AEs were statistically similar between the 2 treatment groups (10.3% with IFN + RBV vs 11.3% with peg-IFN + RBV), as was the frequency of discontinuation of therapy due to AEs (10.6% vs 8.7%).

Discontinuation of therapy due to depression was not statistically different between the IFN + RBV–treated patients and the peg-IFN + RBV–treated patients (9 [2.7%] vs 6 [1.7%]).

Seventy-one of 330 (21.5%) patients treated with IFN + RBV and 11 of 345 (3.2%) treated with peg-IFN + RBV switched from their initial HCV treatment to another HCV treatment during the study period. IFN + RBV–treated patients switched treatments due to poor response (42 [12.7%] patients), the availability of a new peginterferon alfa treatment (15 [4.5%]), AEs (11 [3.3%]), noncompliance (1 [0.3%]), or lack of insurance coverage or patient desire (1 [0.3%] each). Of the peg-IFN + RBV–treated patients who switched treatment, 7 (2.0%) switched due to an AE (6 due to anemia and 1 due to depression), or lack of insurance coverage or efficacy (2 [0.6%] each).

**DISCUSSION**

This retrospective review of charts from patients with chronic HCV infection was designed to provide insight into patterns of use of IFN + RBV and peg-IFN + RBV therapies in clinical practice, and to explore the effects of dosing regimens outside PI recommendations on drug effectiveness and tolerability. This study showed that IFN + RBV tended to be administered consistently with doses recommended in the PI, but the same was not true for peg-IFN + RBV.
therapy: clinicians treated fewer than half of patients with recommended doses of peg-IFN, and well over two thirds of patients with doses of RBV in excess of the recommended dose. The IFN + RBV treatment group had larger percentages of black patients and patients with severe hepatic disease at baseline compared with the peg-IFN + RBV treatment group; both of these are characteristics of patient populations who are more difficult to treat compared with other patient populations with HCV. In addition, a significantly higher percentage of IFN + RBV–treated patients were prescribed HCV therapy at the time of diagnosis compared with peg-IFN + RBV–treated patients. This finding may reflect more prompt clinical intervention in more seriously ill patients, or it may be an epoch effect. Because IFN + RBV therapy became available in February 1991, its use might have coincided with a period during the 1990s when physicians viewed the diagnosis of HCV infection with more alarm. IFN + RBV–treated patients were treated for a longer mean duration compared with peg-IFN + RBV–treated patients, likely due to the timing of FDA approval of the use of IFN + RBV and peg-IFN (December 2002 and January 2001, respectively) and the time period of data collection (July 2001 to June 2002).

Treatment with the P24-recommended dose of peg-IFN was associated with an increased likelihood of attaining VR, whereas the administration of higher or lower doses of peg-IFN did not significantly affect VR. Patients treated with higher-than-recommended doses of RBV in the peg-IFN + RBV group had a greater likelihood of achieving VR relative to those treated with the P27-recommended dose. Patients who received peg-IFN + RBV treatment were also more likely to achieve VR compared with those treated with IFN + RBV, a finding that should be viewed in light of the risk factors (AEs) noted earlier. Other factors found to increase the likelihood of VR in logistic regression analysis were infection with virus of non-1 genotype, baseline HCV RNA load ≤725,000 IU/mL, white race, and female gender.

Interferon and RBV both have been associated with dose-limiting treatment-related AEs, the incidences of which generally do not differ significantly after 24 or 48 weeks of therapy. In addition, these AEs usually resolve with dose reductions or cessation of therapy. Use of interferon, pegylated or nonpegylated, has been associated with AEs including neuropsychiatric (depression, anxiety, insomnia, irritability, emotional lability, suicidal ideation), hematologic, and gastrointestinal events; fatigue; and influenza-like symptoms (myalgia, musculoskeletal pain, fever, malaise, headache). Other, less common, interferon-related AEs include injection-site reaction, pruritus, alopecia, weight loss, and dyspepsia. RBV has been associated with cytopenia, especially hemolytic anemia.

Given the manner and the timing in which data concerning AEs were collected in this study, our findings likely reflect a lower incidence of AE reporting than would be expected in prospective, controlled clinical trials. Because the methodology was a retrospective data analysis, providers were subjectively interpreting the relationship between the AE and the timing of the patient visit.
Whether these relationships were cause–effect or temporal was not controlled for, which limits the generalizability of the findings. The severity of AEs was not analyzed in this study. In this study, AEs that were more likely to occur in the IFN + RBV group included fatigue, depression, and anxiety. Both groups had lower AE rates compared with those reported in controlled clinical trials with more rigorous reporting requirements. Although a direct comparison of AEs across studies cannot be made due to differences in study populations, design, and data-collection and reporting methodologies, it is noteworthy that the incidence of anemia, thrombocytopenia, and neutropenia were not statistically different between the 2 treatments, contrary to the nearly 3-fold greater frequency reported in the IFN + RBV PI versus the peg-IFN + RBV PIs. The presence of these AEs, normally associated with RBV dosing, may reflect the higher doses of RBV prescribed in the peg-IFN + RBV treatment group. The incidence of “severe” thrombocytopenia was higher (4.5% vs 1.0%) and that of severe neutropenia was lower (<1% vs 11%) in patients receiving IFN + RBV in this study compared with laboratory findings from 24- and 48-week clinical trials reported in the IFN + RBV PI. In the peg-IFN + RBV treatment group, 2.3% of patients experienced severe thrombocytopenia compared with <1% in the peg-IFN + RBV PIs (48-week trial). There were no cases of severe neutropenia in the peg-IFN + RBV treatment group in this study, compared with a reported incidence of 4% in the PI. Severe anemia was rare with both treatments in this study, consistent with PI reports.

The frequencies of dose modification (10.3% in IFN + RBV–treated patients and 11.3% in peg-IFN + RBV–treated patients) and treatment discontinuation due to AEs (10.6% and 8.7%, respectively) were similar to or less than those reported in other studies. Manns et al reported dose-modification rates of 34% (IFN + RBV) and 42% (peg-IFN + RBV) and treatment-discontinuation rates of 13% (IFN + RBV) and 14% (peg-IFN + RBV) due to any AE with 48 weeks of therapy. The PIs for IFN + RBV and peg-IFN + RBV report rates of 26% and 42%, respectively, for dose modification, and rates of 19% and 19% to 14%, respectively, for discontinuation of therapy due to AEs.

Peginterferon alfa-2a was not included in the present study because the treatment was not commercially available until the end of the year for which we collected data (July 2001 to June 2002). The focus of this study was to examine biases in prescribing and dosing of products that were the standard of care during the year for which data were collected. These same biases and confusion may persist, even with newer and more effective treatments. Many of the treatment regimens and patterns used during the year for which data were collected are still used. Patient characteristics and the comorbid conditions continue to be relevant, and differences in dosing (weight based vs time based) are still issues.

Potential biases in this study are those associated with retrospective data collection and their interpretation by physicians in a chart-review process. Participating physicians were clinicians experienced in the treatment and management of HCV (a mean of 14 years of practice) and were, by the definition of
study inclusion criteria, a subgroup that actively treated large numbers of patients with HCV but were not actively involved in clinical trials. Office-based practitioners were selected in an attempt to avoid hospital-based biases in drug dosing, timing, and treatment. Physician expertise and clinical experience with HCV treatment may be also an unrecognized confounding variable that contributed to the treatment success of patients treated with nonrecommended dosing regimens, and may not be a generalizable model applied to other providers. In addition, bias may have been introduced when the sampling criteria were modified during the study, to actively increase the number of patients treated and patients concurrently infected with HIV.

Although clinical benefits (VRs sustained 6 months after the cessation of therapy) have been seen with higher, weight-based doses (1000 or 1200 mg/d) of RBV in combination with peginterferon alfa-2a in patients with genotype 1 infection, it has not been determined whether the clinical benefit of higher doses of RBV in combination with peg-IFN observed in this study would be similarly sustained. Dose modification, switching treatments, and discontinuation of treatment were not frequent in the studied patient population, suggesting that treatment-limiting AEs were not excessive, despite the clinical-use pattern of nonrecommended dosing regimens.

CONCLUSIONS

The results of this retrospective data analysis of patients receiving treatment for chronic HCV infection in the United States from July 2001 to June 2002 suggest that peg-IFN + RBV was more likely to produce VR at 24 ± 6 weeks of treatment compared with IFN + RBV in the patients studied. RBV administered at higher-than-recommended doses in combination with peg-IFN appeared to offer some clinical benefits (improved VR, 28.5%) to patients with chronic HCV infection. Administration of a higher-than-recommended dose of peg-IFN without a concomitant increase in RBV dose was not associated with an increased likelihood of VR.

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REFERENCES


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