ABSTRACT

Currently, pegylated interferon α (PEG-IFN α) plus ribavirin (RBV) is the standard of care for the treatment of chronic hepatitis C virus (HCV) monoinfection. Evidence from several randomized clinical studies indicates that this combination provides superior virologic efficacy and comparable tolerability to standard IFN α plus RBV regimens in patients coinfected with human immunodeficiency virus (HIV)/HCV. The AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) study is the largest international, randomized, placebo-controlled study to examine the efficacy and safety of combination therapy with PEG-IFN α-2a plus RBV in patients coinfected with HIV/HCV. In the APRICOT study, the overall rate of sustained virologic response among patients treated with PEG-IFN α-2a plus RBV was 40%, compared to 12% for those patients treated with IFN α-2a plus RBV, considerably higher than reported in other recent trials of this combination in patients coinfected with HIV/HCV. These results indicate that PEG-IFN α-2a plus RBV is superior to standard IFN α-2a plus RBV for treating chronic HCV in patients coinfected with HIV. Pharmacokinetic analysis indicates that RBV had no effect on intracellular levels of lamivudine, stavudine, or zidovudine and does not appear to modify the plasma concentration-time profile of these agents in coinfected patients.

plus RBV had superior virologic efficacy, and discontinuation rates were comparable to those rates for IFN α plus RBV therapy.

The AIDS Pegasis Ribavirin International Coinfection Trial (APRICOT) is the largest international, randomized, placebo-controlled study to compare the efficacy and safety of PEG-IFN α-2a plus RBV with that of IFN α plus RBV in patients coinfected with HIV/HCV.

In the APRICOT study, the overall SVR rate among patients treated with PEG-IFN α-2a plus RBV was 40%, considerably higher than rates reported in other recent randomized studies of this combination in patients coinfected with HIV/HCV, compared to 12% for those patients treated with IFN α-2a plus RBV. In contrast to previous randomized studies, the APRICOT study had a 3-arm design to compare the safety and efficacy of PEG-IFN α-2a plus RBV with that of IFN α-2a plus RBV and PEG-IFN α-2a alone. The findings of APRICOT, the interaction between RBV and antiviral agents, and current strategies for the management of chronic HCV infection in HIV-infected patients are discussed in this article.

APRICOT STUDY

Efficacy

The APRICOT study was conducted at 95 centers in 19 countries between June 2000 and September 2003. A total of 868 patients were randomly assigned in a 1:1:1 ratio to 48 weeks of treatment with 1 of 3 regimens: subcutaneous IFN α-2a 3 MIU 3 times weekly plus oral RBV 400 mg 2 times/day (total daily dose 800 mg); PEG-IFN α-2a 180 µg weekly plus oral placebo 2 times/day; or PEG-IFN α-2a plus RBV 400 mg 2 times/day (total daily dose 800 mg). The 48-week treatment period was followed by a 24-week observation period. Patients were stratified according to HCV genotype (genotype 1 vs other genotypes), CD4+ cell count (<200/mm3 vs ≥200/mm3), HIV treatment (antiretroviral vs no antiretroviral therapy), histologic findings on liver biopsy (cirrhosis vs no cirrhosis), qual-

**Figure. Virologic Responses at the End of Treatment and at the End of Follow-Up, According to HCV Genotype**

A virologic response was defined as an undetectable HCV-RNA level (<50 IU/mL). The number above each bar indicates the percentage, and the numbers below each bar show the number of patients with a response and the total number in the subgroup. Only patients who received at least 1 dose of study treatment are included in this analysis.

\[ P = .008 \text{ for the comparison with IFN α-2a plus RBV.} \]
\[ P < .001 \text{ for the comparisons with IFN α-2a plus RBV and PEG-IFN α-2a plus placebo.} \]

HCV = hepatitis C virus; IFN = interferon; PEG-IFN = pegylated interferon.

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ifying alanine aminotransferase quotient (patient's value at baseline divided by the upper limit of normal for the assay), and geographic region. The primary efficacy endpoint was SVR, defined as a serum HCV-RNA level below the limit of detection of the assay (<50 IU/mL) at the end of 24 weeks of follow-up.

Of the 868 patients randomized, 860 received study medication: 285 in the group receiving IFN α-2a plus RBV, 286 in the group receiving PEG-IFN α-2a plus placebo, and 289 in the group receiving PEG-IFN α-2a plus RBV.15 Patient demographics were similar to those in previous randomized studies in the coinfect population. The patients were predominantly white males with well-controlled HIV infection and HCV genotype 1. The overall rate of SVR at the end of follow-up was significantly higher among patients treated with PEG-IFN α-2a plus RBV than among those patients treated with IFN α-2a plus RBV (40% vs 12%; odds ratio, 5.40; 97.5% confidence interval [CI], 3.20–9.12; \(P < .001\)) or PEG-IFN α-2a plus placebo (40% vs 20%; odds ratio, 2.89; 97.5% CI, 1.83–4.58; \(P < .001\); Figure).15 The rate of SVR was significantly lower among recipients of IFN α-2a plus RBV than among recipients of PEG-IFN α-2a plus placebo (odds ratio, 0.53; 97.5% CI, 0.30–0.91; \(P = .008\)).15 As observed in previous studies in patients coinfected with HIV/HCV, patients infected with HCV genotype 1 had consistently lower rates of SVR than those patients infected with HCV genotypes 2 or 3 (Figure). In patients who had an early virologic response by week 12, 30% in the group receiving IFN α-2a plus RBV, 37% in the group receiving PEG-IFN α-2a plus placebo, and 56% in the group receiving PEG-IFN α-2a plus RBV had SVR at week 72.15

**TOLERABILITY**

Overall, 39% of patients withdrew from treatment with IFN α-2a plus RBV, 31% with PEG-IFN α-2a plus placebo, and 25% with PEG-IFN α-2a plus RBV (\(P < .001\) for the comparison between IFN α-2a plus RBV and PEG-IFN α-2a plus RBV; Table 1).15 The most commonly reported side effects were fatigue, fever, and headache, and no difference was observed in the incidence of adverse events among the treatment groups. However, treatment-related adverse events were more frequent in the 2 groups that received PEG-IFN α-2a (10% PEG-IFN α-2a plus placebo and 8% PEG-IFN α-2a plus RBV vs 5% IFN α-2a plus RBV).15

Consistent with the findings of previous randomized studies involving patients coinfected with HIV/HCV, the absolute mean CD4+ cell counts decreased uniformly in all 3 groups during treatment, whereas the mean percentage of CD4+ lymphocytes

### Table 1. Patients Withdrawn From Study Treatment and Adverse Events According to Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Withdrawal from study treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Any reason</td>
<td>111 (39)†</td>
</tr>
<tr>
<td>Adverse events or intercurrent illness</td>
<td>41 (14)</td>
</tr>
<tr>
<td>Insufficient response</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Patient's refusal of treatment</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Laboratory abnormalities‡</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Treatment-related serious adverse events§</td>
<td>15 (5)</td>
</tr>
</tbody>
</table>

* †‡Data on withdrawals and deaths are based on all patients who underwent randomization and received at least 1 dose of study medication. One patient received pegylated interferon (PEG-IFN) α-2a plus ribavirin (RBV), but the patient did not return for a safety assessment. All other analyses included all patients who underwent randomization, received at least 1 dose of study medication, and had at least 1 safety evaluation after baseline. Serious adverse events were defined as fatal or life-threatening events and those events that required or prolonged hospitalization, resulted in persistent or clinically significant disability or congenital anomaly, or required intervention to prevent 1 of the specific serious adverse events listed. 
**Laboratory abnormalities leading to premature withdrawal from study treatment included anemia, lymphopenia, neutropenia, thrombocytopenia, and increased aminotransferase and creatine kinase levels. 
§In the opinion of the investigator, these events were judged to be possibly or probably related to the study treatment.

increased slightly.\textsuperscript{15} In the APRICOT study, there was a beneficial PEG-IFN $\alpha$-associated HIV suppression. Mean HIV-RNA levels decreased by almost a full log for patients who had detectable HIV-RNA at baseline in the groups receiving PEG-IFN $\alpha$-2a plus placebo or PEG-IFN $\alpha$-2a plus RBV, whereas mean HIV-RNA levels remained unchanged in patients receiving IFN $\alpha$ plus RBV (Table 2).\textsuperscript{15}

**EFFECT OF ANTIVIRAL AGENTS ON RIBAVIRIN**

The effect of HCV therapy on the treatment of HIV infection is an important area of study. RBV, a guanosine nucleoside analogue, interferes with the intracellular phosphorylation of zidovudine, lamivudine, and stavudine.\textsuperscript{16,17} In addition, RBV enhances the phosphorylation of didanosine (ddI) metabolism, increasing drug levels and concomitant toxicities.\textsuperscript{18} These toxicities are primarily related to DNA polymerase gamma inhibition, leading to failure of mitochondrial function. RBV should not be used with ddI when treating HCV in HIV-coinfected patients. Another nucleoside or nucleotide analogue should be substituted for ddI in these patients. In a sub-study of APRICOT, RBV had no effect on intracellular levels of lamivudine, stavudine, or zidovudine in participants receiving these drugs. RBV did not appear to modify the plasma concentration-time profile of lamivudine, stavudine, or zidovudine. Therefore, RBV does not appear to affect the metabolism of these agents or their corresponding endogenous nucleoside triphosphates.

**CONCLUSIONS**

Evidence from recent randomized studies indicates that PEG-IFN $\alpha$ plus RBV is the treatment of choice for patients coinfected with HIV/HCV; it has superior virologic efficacy, and its tolerability is comparable to that of standard IFN $\alpha$ plus RBV. An SVR of 40% was achieved with PEG-IFN $\alpha$-2a plus RBV in the APRICOT study. Overall efficacy in patients coinfected with HIV/HCV appears to be decreased when compared to efficacy in HCV-monoinfected patients, particularly among those patients with HCV genotype 1 infection. This decrease may be caused by the higher HCV viral load in patients coinfected with HIV/HCV. Of particular interest in APRICOT, HCV therapy did not negatively affect the control of HIV infection.

Several factors may account for the considerably higher response rates achieved in patients treated with PEG-IFN $\alpha$-2a plus RBV in the APRICOT study than in other recent randomized clinical trials of PEG-IFN $\alpha$ plus RBV in patients coinfected with HIV/HCV.\textsuperscript{12-14} These factors include study design, different type of PEG-IFN $\alpha$ in 2 studies, different dose of RBV, and differences in patient populations. Although the AIDS Clinical Trial Group (ACTG) A5071 and APRICOT studies used equivalent doses of RBV, ACTG A5071 used a dose-escalation regimen (starting RBV at 600 mg once daily and increasing to 1000 mg within 12 weeks), whereas the APRICOT study used a fixed 800-mg dose. Although the cumulative dose in the ACTG trial averaged more than 800 mg/day, it was “back loaded,” leading to speculation that higher rates of SVR may be seen if higher doses could be provided earlier in treatment. Therefore, the timing rather than

**Table 2. Changes in HIV Status According to Treatment Group*\textsuperscript{15}**

| Variable | Pegylated Pegylated Pegylated Interferon $\alpha$-2a plus Interferon $\alpha$-2a plus Interferon $\alpha$-2a plus Ribavirin (n = 288) Placebo (n = 286) Ribavirin (n = 288) |
|-----------------|-----------------|-----------------|-----------------|
| **Number of patients (%)** | **Number of patients (%)** | **Number of patients (%)** |
| **Changes in HIV disease status** | **Changes in HIV disease status** | **Changes in HIV disease status** |
| **Change in CD4+ count** | **Change in CD4+ count** | **Change in CD4+ count** |
| Cells/mm$^3$ | $-131 \pm 176 (161)$ | $-135 \pm 173 (176)$ | $-157 \pm 176 (203)$ |
| Percentage | $+1.3 \pm 5.9 (123)$ | $+1.4 \pm 6.3 (135)$ | $+3.0 \pm 8.2 (160)$ |
| **Change in HIV-1 RNA, log$_{10}$ copies/mL** | **Change in HIV-1 RNA, log$_{10}$ copies/mL** | **Change in HIV-1 RNA, log$_{10}$ copies/mL** |
| All patients | $+0.088 \pm 0.726 (163)$ | $-0.219 \pm 0.925 (173)$ | $-0.205 \pm 0.831 (204)$ |
| Patients with detectable HIV-1 RNA at baseline$^\dagger$ | $+0.016 \pm 1.010 (56)$ | $-0.789 \pm 1.013 (67)$ | $-0.696 \pm 0.924 (82)$ |

\textsuperscript{*}Values shown are mean ($\pm$SD) changes from baseline at 48 weeks, with the number of patients shown in parentheses. Only patients who received 48 weeks of treatment are included. CD4$^+$ percentage indicates percentage of CD4$^+$ lymphocytes.

\textsuperscript{$\dagger$}Detectable levels were $\geq50$ copies/mL.

Adapted with permission from Torriani et al. N Engl J Med. 2004;351:438-450.\textsuperscript{15}
the dose of RBV may have a critical effect on virologic response. In addition to dose and timing of RBV, the use of different types of PEG-IFN α (PEG-IFN α-2a in ACTG and APRICOT and PEG-IFN α-2b in RIBAVIC) may have had an effect on patient response. Ongoing studies are comparing PEG-IFN α-2a with PEG-IFN α-2b in patients coinfected with HIV/HCV.

Liver pathology may also have had an effect on virologic response. In the ACTG A5071 and RIBAVIC trials, liver pathology was more advanced—a negative prognostic marker for treatment outcome—than it was in the APRICOT study. Serious adverse events, including liver failure, lactic acidosis, or pancreatitis, were highest in the RIBAVIC trial, particularly in patients who were taking ddI before and during use of RBV. Therefore, patients should be switched from ddI-containing regimens before starting PEG-IFN α plus RBV. Data from a subset of the APRICOT trial showed that RBV had no effect on intracellular levels or metabolism of lamivudine, stavudine, or zidovudine. Therefore, these antiviral agents can be used as part of highly active antiretroviral therapy in patients receiving HCV therapy with PEG-IFN α plus RBV without risk of additional toxicity.

The results of APRICOT clearly demonstrate that the combination of PEG-IFN α-2a plus RBV can be an effective and safe treatment for chronic HCV infection in HIV-infected patients. Furthermore, this combination does not appear to have a negative impact on the course of HIV infection.

REFERENCES