Coinfection with hepatitis C virus (HCV) is common among persons infected with the human immunodeficiency virus (HIV). Treatment regimens based on standard interferon α (IFN α) and ribavirin (RBV) are recommended for chronic HCV, but they pose special concerns in patients coinfected with HIV, particularly those patients who are receiving antiretroviral therapy. Recently, several randomized studies comparing the safety and efficacy of pegylated interferon α (PEG-IFN α) plus RBV to IFN α plus RBV for the treatment of HCV in HIV-coinfected patients have been completed. In the AIDS Clinical Trials Group A5071 and RIBAVIC (sponsored by the French National Research Group) trials, superior sustained virologic responses were obtained with PEG-IFN α plus RBV compared to IFN α plus RBV for the treatment of HCV in HIV-coinfected patients. Findings from these studies suggest that PEG-IFN α plus RBV regimens provide superior rates of sustained virologic response (SVR) even in the absence of virologic clearance. An overview of these studies is presented.

ADVANCED STUDIES IN MEDICINE

2005;5(4C):S366-S370

ABSTRACT

Coinfection with hepatitis C virus (HCV) is common among persons infected with the human immunodeficiency virus (HIV). Treatment regimens based on standard interferon α (IFN α) and ribavirin (RBV) are recommended for chronic HCV, but they pose special concerns in patients coinfected with HIV, particularly those patients who are receiving antiretroviral therapy. Recently, several randomized studies comparing the safety and efficacy of pegylated interferon α (PEG-IFN α) plus RBV to IFN α plus RBV for the treatment of HCV in HIV-coinfected patients have been completed. In the AIDS Clinical Trials Group A5071 and RIBAVIC (sponsored by the French National Research Group) trials, superior sustained virologic responses were obtained with PEG-IFN α plus RBV compared to IFN α plus RBV for the treatment of HCV in HIV-coinfected patients. Findings from these studies suggest that PEG-IFN α plus RBV regimens provide superior rates of sustained virologic response (SVR) even in the absence of virologic clearance. An overview of these studies is presented.

HEPATITIS C VIRUS THERAPY IN PATIENTS WITH HIV

One of the goals of HCV treatment is viral eradication. In early studies, Soriano et al found that viral eradication can be achieved with IFN-α treatment in patients coinfected with HIV/HCV. However, higher titers of HCV RNA in HIV-coinfected patients, along with qualitative and quantitative alterations in immune function, may make this goal difficult to achieve. Therefore, improvement in or delayed progression of fibrosis may be a more realistic goal for most coinfected patients. Additional benefits of HCV treatment in patients with HIV may include improved tolerability and effectiveness of HAART.

Despite the potential benefits of HCV treatment, there are several issues to be considered when using anti-HCV therapy in patients coinfected with HIV/HCV. Common side effects of IFN-α include influenza-like symptoms, depression, thrombocytopenia, and neutropenia. RBV therapy is also associated with dose-dependent hemolytic anemia, birth defects, and drug interactions with antiretroviral agents. Hematologic side effects, most notably anemia, may be particularly severe in coinfected patients because of a high prevalence of anemia and limited erythroid reserves that may be associated with comorbid disease or concurrent antiretroviral-induced myelosuppression.

Although anemia can be managed by reducing the RBV dose, this may have an undesired effect of reducing SVR rates. The use of erythropoietin, which can counteract RBV-related anemia, may therefore be an important adjunct to therapy in coinfected persons. In addition, drug interactions between RBV and certain antiretroviral agents could result in decreased efficacy and increased toxicity of these agents. RBV antagonizes the in vitro anti-HIV activity of the thymidine analogues zidovudine and stavudine by inhibiting intracellular phosphorylation needed for their antiviral activity. Fortunately, this interaction does not appear to be observed in vivo. However, RBV also enhances formation of the active metabolite of didanosine (ddI), resulting in increased activity and, particularly, increased risk of mitochondrial toxicity in patients receiving this nucleoside analogue. Finally, RBV may also increase the risk of other nucleoside reverse transcriptase inhibitor-related mitochondrialopathy, including peripheral neuropathy, pancreatitis, hepatic steatosis, and lactic acidosis.

Table. Results from Randomized Trials Evaluating PEG-IFN α plus RBV with Standard IFN α plus RBV for Treating Patients Coinfected with HIV/HCV

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Treatment Duration</th>
<th>PEG-IFN α Regimen</th>
<th>RBV Regimen</th>
<th>End-of-Treatment Response (PEG-IFN α plus RBV vs IFN α plus RBV)</th>
<th>Sustained Virologic Response (PEG-IFN α plus RBV vs IFN α plus RBV)</th>
<th>Treatment Discontinuation (adverse events; PEG-IFN α plus RBV vs IFN α plus RBV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laguno et al</td>
<td>95</td>
<td>48 wk for genotypes 1 and 4; 24 wk for genotypes 2 and 3</td>
<td>800–1200 mg/day</td>
<td>800–1200 mg/day</td>
<td>N/A</td>
<td>44% vs 21% (intent to treat;  $P = .017$)</td>
<td>12% vs 17% ( $P = .565$)</td>
</tr>
<tr>
<td>Chung et al</td>
<td>134</td>
<td>48 wk for all genotypes</td>
<td>600 mg/day escalated to 1000 mg/day</td>
<td>600 mg/day escalated to 1000 mg/day</td>
<td>41% vs 12% ( $P &lt; .001$)</td>
<td>27% vs 12% ( $P = .03$)</td>
<td>12% in both groups</td>
</tr>
<tr>
<td>Carrat et al</td>
<td>412</td>
<td>48 wk for all genotypes</td>
<td>800 mg/day</td>
<td>800 mg/day</td>
<td>35% vs 21% ( $P = .001$)</td>
<td>27% vs 20% ( $P = .047$)</td>
<td>17% vs 16% ( $P = .70$)</td>
</tr>
<tr>
<td>Torriani et al</td>
<td>868</td>
<td>48 wk for all genotypes</td>
<td>800 mg/day</td>
<td>800 mg/day</td>
<td>47% vs 14% (N/A)</td>
<td>40% vs 12% ( $P &lt; .001$)</td>
<td>12% vs 14% ( $P &lt; .001$)</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN α = interferon α; N/A = data not available; PEG-IFN α = pegylated interferon α; RBV = ribavirin.
clinical experience with peg-ifn α plus RBV in HIV/HCV coinfection

Efficacy

Recently, several large randomized clinical trials comparing PEG-IFN α plus RBV with IFN α plus RBV in patients coinfected with HIV/HCV have been completed (Table).10-13 The ACTG A5071 study compared the safety and efficacy of PEG-IFN α-2a at 180 µg/week with IFN α-2a at 6 MIU 3 times weekly for 12 weeks followed by 3 MIU 3 times weekly for 36 weeks, each combined with RBV on a dose-escalation schedule (600 mg/day for 4 weeks, 800 mg/day for 4 weeks, and then 1000 mg/day for the remainder of the study). Liver biopsy was performed in patients who had no virologic response (serum HCV RNA, ≥60 IU/mL) after 24 weeks of therapy, and only histologic responders (experiencing a ≥2 point improvement in hepatic activity index) were permitted to continue therapy to 48 weeks. Virologic responders at 24 weeks were allowed to complete the course of therapy, and biopsy was performed in these subjects at 48 weeks. The rate of end-of-treatment virologic response was higher in the group receiving PEG-IFN α-2a plus RBV compared to the group receiving IFN α-2a plus RBV (41% vs 12%; P <.001; Table).11 Treatment with PEG-IFN α-2a plus RBV was also associated with a significantly higher SVR rate than the IFN α-2a plus RBV treatment (27% vs 12%; P = .03; Table).11 As in studies of HCV monoinfection, patients with HCV genotypes other than genotype 1 had significantly higher rates of response to PEG-IFN α-2a compared to patients with genotype 1 (Figure 1).11 For patients with genotype 1 infection, the rate of SVR was only 14% in the group receiving PEG-IFN α-2a plus RBV and 6% in the group receiving IFN α-2a plus RBV, whereas for those patients infected with other HCV genotypes (mainly genotypes 2 and 3), the respective rates of SVR were 73% and 33% (P <.001 compared to genotype 1 infections).11 Among week-24 virologic nonresponders who underwent liver biopsy, histologic response was observed in 35% of patients, despite the absence of a significant decrease in HCV viremia. Among virologic responders at 24 weeks, 52% of patients experienced histologic improvement at week 48.11 Lack of an early virologic response (clearance or 2 log10 reduction of HCV RNA from baseline) at week 12 was uniformly predictive of failure to achieve an SVR (negative predictive value, 100%; Figure 2).11

Two randomized studies, RIBAVIC and the study by Laguno et al, evaluated the use of PEG-IFN α-2b plus RBV in patients coinfected with HIV/HCV.10,12 In 412 coinfected patients, the RIBAVIC trial (sponsored by the French National Research Group) compared PEG-IFN α-2b at 1.5 µg/kg/week with IFN α-2b at 3 MIU 3 times weekly; each was combined with a flat dose of RBV 800 mg/day (Table).12 As in the ACTG A5071 trial, end-of-treatment responses and SVR rates were significantly higher for PEG-IFN α-2b plus RBV compared to IFN α-2b plus RBV. The SVR rate was 27% for PEG-IFN α-2b plus RBV compared to 20% for IFN α-2b plus RBV (P = .047).12 The negative predictive value of virologic response at week 12 for SVR was 87%.

In a smaller study, Laguno et al evaluated the efficacy and safety of IFN α-2b plus RBV with that of PEG-IFN α-2b plus RBV in 95 previously untreated patients with HCV coinfected with HIV.10 Patients

---

**Figure 1. End-of-Treatment Response and SVR in Patients Coinfected with HIV/HCV Randomized to Receive PEG-IFN α-2a plus RBV or IFN α-2a plus RBV**

---

*P = .03 compared with IFN α-2a plus RBV.

1P <.01 compared with genotype 1.

HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN α-2a = interferon α-2a; PEG-IFN α-2a = pegylated interferon α-2a; RBV = ribavirin; SVR = sustained virologic response.

Data from Chung et al.11
were randomly assigned to treatment with IFN α-2b (3 MIU 3 times weekly) or PEG-IFN α-2b (100–150 µg once weekly, adjusted to body weight) plus RBV (800–1200 mg/day, adjusted to body weight). In this study, an SVR at 48 weeks was observed in 44% of patients in the group receiving PEG-IFN α-2b plus RBV compared to only 21% of those patients in the group receiving IFN α-2b plus RBV (P = .017; Table). Patients infected with HCV genotype 1 had higher response rates with PEG-IFN α-2b plus RBV compared to IFN α-2b plus RBV (38% vs 7%; P = .007). Sustained virologic response rates in patients with HCV genotypes 2 and 3 were 53% and 47% with PEG-IFN α-2b plus RBV and IFN α-2b plus RBV, respectively (P = .730).

**Tolerability**

Prior reports of HIV/HCV treatment with IFN-α-based regimens demonstrated high rates of patient dropout, often (although not exclusively) attributed to adverse event-related drug intolerance. In the ACTG A5071 trial, the combination of PEG-IFN α-2a plus RBV was well tolerated in patients coinfected with HIV/HCV. The discontinuation rate (12%) was similar in both treatment groups and was comparable to discontinuation rates reported in monoinfected patients with HCV in registration trials of PEG-IFN α-2a plus RBV. These findings agree with those reported by Laguno et al for PEG-IFN α-2b plus RBV. In contrast, a much higher rate of discontinuation and severe adverse events was reported in the RIBAVIC trial, in which 39% of patients discontinued treatment, 17% of patients because of severe adverse events. The primary serious adverse events were development of mitochondrial injury leading to liver failure, lactic acidosis, or pancreatitis. Mitochondrial toxicity occurred most frequently in patients being treated with ddI before and during RBV treatment (odds ratio for ddI, 45%; 95% confidence interval = 7.2-infinity).

In ACTG A5071, a significant decrease in CD4+ cell count was noted by 24 weeks of therapy. However, a slight increase in percentage of CD4+ cells was observed from baseline to week 24 (+3.5% for PEG-IFN α-2a plus RBV vs +2.5% for IFN α-2a plus RBV; P = .14). No significant decrease in CD4+ cell count was noted in subsequent weeks of treatment. At the end of follow-up, a return to baseline levels was noted. HIV-1–RNA levels did not change appreciably during the study, and no clinical progression of HIV to AIDS was observed during the study period. A similar effect on CD4+ cell counts was observed with PEG-IFN α-2b plus RBV.

**Conclusions**

Data from several large randomized studies clearly demonstrate that the combination of PEG-IFN α and RBV provides superior efficacy in achieving an SVR compared to the combination of standard IFN α and RBV. As with HCV monoinfection, significantly high-

---

**Figure 2. Predictive Value of an Early Virologic Response**

HCV = hepatitis C virus; SVR = sustained virologic response.

er response rates were achieved in patients with genotypes 2 and 3. Although PEG-IFN α plus RBV was well tolerated in the ACTG A5071 trial, higher rates of discontinuation because of serious adverse events were reported in the RIBAVIC trial. These results suggest that dose escalation of RBV may play a role in enhancing drug tolerability. However, this may need to be weighed against reductions in SVR rate.

To date, no anti-HCV agents have received approval for treatment of chronic HCV in patients coinfected with HIV. Therefore, the management of chronic HCV in patients coinfected with HIV has been based on clinical experience with HCV monoinfection. Evidence from the completed randomized studies support the use of PEG-IFN α plus RBV as the standard of care for treating chronic HCV in patients infected with HIV. However, several factors, including HCV genotype, extent of liver disease, and exposure to HAART, should be taken into account when considering a patient for PEG-IFN α plus RBV therapy. Evidence of histologic improvement, despite the absence of a significant decrease in HCV viremia observed in the ACTG A5071 trial, suggests that IFN-α–based therapy may provide benefits independent of its antiviral effects and supports the need for investigation of maintenance strategies, especially in patients coinfected with HIV/HCV who have moderate-to-advanced fibrosis. Use of early predictors of virologic futility in patients infected with HCV receiving PEG-IFN α plus RBV may also allow the earlier termination of a medication that will not provide benefit while frequently being associated with adverse events. Based on the striking findings of the RIBAVIC study, patients should be switched from ddI-containing regimens before initiating combination therapy for HCV to avoid potentially harmful interactions between RBV and ddI.

REFERENCES