Twelve week post-treatment follow-up predicts sustained virological response to pegylated interferon and ribavirin therapy in HIV/hepatitis C virus co-infected patients

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Objectives: The aim of this study was to evaluate whether the assessment of hepatitis C virus (HCV) RNA serum at 12 weeks after the end of treatment (W12) was as informative as after 24 weeks (W24) for determining sustained virological response (SVR) in HIV/HCV co-infected patients who received a combination of pegylated interferon (PEG-INF) plus ribavirin (PEG-INF/RBV) and had a virological response at the end of treatment.

Methods: Treatment-naive HIV/HCV patients were included in this prospective study if they had completed a full course of therapy with PEG-INF/RBV, had an undetectable serum HCV RNA at the end of treatment and complied with the W12 and W24 schedule for determining HCV RNA. HCV RNA levels were measured using a quantitative PCR assay (detection limit ¼ 15 IU/mL). Positive predictive value (PPV) was defined as the probability of an undetectable serum HCV RNA at W12 and W24 after the end of treatment.

Results: Of 186 patients treated during the study period, 104 (55.9%) were included in the study. At W24, 83 (79.8%) patients had an SVR and 21 (20.2%) had a virological relapse. At W12, HCV RNA was undetectable in 83 (79.8%) patients and all of these had SVR. Undetectable HCV RNA at W12 had a 100% PPV [95% confidence interval (CI) 96.5%–100%] for SVR.

Conclusions: Our results show that undetectable HCV RNA at W12 post-treatment has a high PPV for SVR. Testing for HCV RNA at this moment may therefore be considered an appropriate point in time for identifying SVR and relapse in HIV/HCV co-infected patients receiving treatment with PEG-INF/RBV.

Keywords: hepatitis C virus, human immunodeficiency virus, relapse, sustained viral response

Introduction

Pegylated interferon (PEG-INF) plus ribavirin (PEG-INF/RBV) is the standard treatment for chronic hepatitis C virus (HCV) infection. Achieving a sustained virological response (SVR), associated with durable eradication of infection, is the therapeutic goal for patients with chronic HCV. The SVR for patients with chronic HCV infection is defined as an undetectable serum HCV RNA 24 weeks after discontinuation of treatment (W24). This definition is based on the results of many previous reports showing that the odds of HCV reappearing once SVR has been achieved are very low. For this reason, testing for HCV RNA at W24 is the current gold standard for measuring the success of antiviral therapy in chronic HCV infection.

However, in HCV mono-infected patients, relapses generally occur soon after a successful therapy has been discontinued, and thus several studies have shown that testing HCV mono-infected patients for serum HCV RNA 12 weeks following completion of standard PEG-INF/RBV therapy (W12) could predict SVR.

In Western countries, a significant proportion of patients with chronic HCV infection are also co-infected with HIV.
HIV-associated immune disorders could in theory impair definitive clearance of HCV infection after HCV therapy and alter the timing of an HCV relapse. There is limited information about testing HCV RNA at W12 post-treatment to evaluate SVR in HIV/HCV co-infected patients and studies are needed to clarify this issue.\(^7\) The objective of this study was to evaluate if measuring serum HCV RNA at W12 is as informative as at W24 to predict SVR in HIV/HCV co-infected patients with a virological end of treatment response (ETR).

\section*{Patients and methods}

\subsection*{Patients}

One hundred and eighty-six HIV-infected patients with chronic hepatitis receiving a combination therapy of PEG-INF/RBV were followed prospectively at two reference hospitals in Spain between January 2005 and June 2008. All patients were treatment naive. The criteria used to determine HCV therapy were in accordance with international guidelines.\(^7\) Patients were included in this prospective study if they had completed a full course of therapy with ETR and complied with the 12 week and 24 week post-treatment follow-up schedule for determining serum HCV RNA. Patients who were positive for the hepatitis B surface antigen (HBsAg) were excluded.

\subsection*{Treatment regimens}

All individuals were treated with either PEG-INF \(\alpha\)2a or PEG-INF \(\alpha\)2b at doses of 180 \(\mu\)g or 1.5 \(\mu\)g/kg/week, respectively, in combination with a weight-adjusted dose of oral ribavirin (1000 mg/day for \(<\)75 kg and 1200 mg/day for \(\geq\)75 kg). Following international guidelines,\(^7\) patients with HCV genotypes 1 or 4 received either 48 or 72 weeks of treatment, and patients with HCV genotype 3 received 24 or 48 weeks of treatment, in accordance with the decision of the physician responsible for the patient. At weeks 12 and 24, PEG-INF/RBV was discontinued in non-responding individuals.

\subsection*{Definitions of virological responses}

ETR and SVR were defined as an undetectable serum HCV RNA at the end of therapy and at 24 weeks following the end of treatment, respectively. A non-response was defined as a detectable serum HCV RNA at the end of treatment. Virological breakthrough was defined as detectable plasma HCV RNA after week 24 of therapy in patients with a previously undetectable HCV viral load. Virological relapse (VR) was defined as an undetectable serum HCV RNA at the end of treatment and a detectable serum HCV RNA at the 24 week post-treatment follow-up.

\subsection*{Virological evaluation}

Plasma HCV RNA load measurements were performed using a quantitative PCR assay (Cobas TaqMan, Roche Diagnostic Systems Inc., Pleasanton, CA, USA), with a detection limit of 15 IU/mL.

\subsection*{Statistical analysis}

The descriptive statistics of the patients are reported. Continuous variables are summarized as means \(\pm\) SD and categorical variables as frequencies and percentages. The positive predictive value (PPV) was defined as the probability that an undetectable serum HCV RNA would occur at W12 and W24 following the end of treatment.

\section*{Results}

A total of 186 HIV patients infected with chronic HCV were treated with PEG-INF/RBV during the study period. The baseline characteristics of all patients are shown in Table 1. Of the initial population treated, 82 patients (44.1\%) experienced early virological failure or viral breakthrough during treatment, were discontinued prematurely because of adverse effects or were lost to follow-up before they achieved ETR. Overall, only 104 (55.9\%) of the initial population completed a full course of therapy and achieved ETR. All of these complied with the W12 and W24 post-treatment follow-up schedules. At W24, 83 (79.8\%) patients had an SVR and 21 (20.2\%) had a VR.

At W12, serum HCV RNA was undetectable in 83 (79.8\%) patients and all achieved SVR (Table 2). No relapse was observed after W12. Undetectable HCV RNA at W12 had a 100\% (95\% CI 96.5\%–100\%) PPV for SVR.

\section*{Discussion}

This study, carried out on a cohort of HIV/HCV co-infected patients treated with PEG-INF/RBV, suggests that testing HCV

\begin{table}[h]
\centering
\caption{Baseline characteristics of patients}
\begin{tabular}{|l|c|c|c|}
\hline
Characteristics & ETR & SVR & VR \\
\hline
\textbf{N} & 104 & 83 & 21 \\
\textbf{Male, n (%)} & 84 (80.8) & 67 (80.7) & 17 (81.0) \\
\textbf{Age in years, mean (SD)} & 40.9 (5.5) & 40.9 (5.6) & 41.6 (5.1) \\
\textbf{BVL >600000, n (%)} & 56 (53.8) & 41 (49.4) & 15 (71.4) \\
\textbf{Genotypes 1 and 4, n (%)} & 49 (47.1) & 35 (42.2) & 14 (66.7) \\
\textbf{CD4 <250 cells/mm\(^3\), n (%)} & 12 (11.5) & 9 (10.8) & 3 (14.3) \\
\textbf{Category C (CDC), n (%)} & 34 (32.7) & 30 (36.1) & 4 (19.0) \\
\textbf{HAART, n (%)} & 85 (81.7) & 68 (81.9) & 17 (81.0) \\
\textbf{Liver fibrosis F3/F4, n (%)} & 41 (39.4) & 26 (31.3) & 15 (71.4) \\
\textbf{Cirrhosis, n (%)} & 23 (22.1) & 18 (21.7) & 5 (23.8) \\
\textbf{Interferon \(\alpha\)2a, n (%)} & 75 (72.1) & 59 (71.1) & 16 (76.1) \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Serum HCV RNA outcome during the 24 week post-treatment follow-up}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Serum HCV RNA (follow-up)} & \textbf{Patients with HCV RNA (-)} & \textbf{Patients with SVR} & \textbf{PPV (95\% CI)} \\
\hline
\textbf{End of treatment} & 104 & 83 & 79.8\% (71.3\%–86.7\%) \\
\textbf{W12} & 83 & 83 & 100\% (96.5\%–100\%) \\
\textbf{W24} & 83 & 83 & 100\% (96.5\%–100\%) \\
\hline
\end{tabular}
\end{table}

\section*{Ethical aspects}

This study was designed and performed according to the Helsinki declaration and was approved by the Ethics Committees of both participating hospitals.
RNA at W12 using a sensitive test with a lower detection limit of 15 IU/mL may be considered an appropriate time point for assessing virological response and identifying SVR and relapse in HIV/HCV co-infected patients.

As is the case with HCV mono-infected patients, achieving an undetectable serum HCV RNA at W24 is the current therapeutic objective when treating HIV-infected patients with chronic HCV. However, studies in HCV mono-infected patients show that testing HCV RNA at W12 may be considered an appropriate time point for assessing virological response. These studies have found that a more sensitive assay can detect residual serum HCV RNA in patients classified as having ETR with a less sensitive assay, reclassifying them as early relapses. For this reason, a low-sensitivity HCV RNA assay (detection limit 15 IU/mL) may be an obstacle to early identification of patients with SVR. Martinot-Peignoux et al. evaluated 573 HCV mono-infected patients who received a combination of PEG-INF/RBV and had ETR to determine whether assessing serum HCV RNA at W12 using an assay with a detection limit of 5–10 IU/mL was as informative as at W24 for evaluating the SVR. At W12, serum HCV RNA was undetectable in 409 patients, and 408 patients had an SVR (PPV 99.7%, 95% CI 99.1%–100%). Aghemo et al. obtained similar results (PPV 100%) using two HCV RNA assays with detection limits of 15 IU/mL and 50 IU/mL for 32 and 258 patients, respectively. In our study, using a HCV RNA commercially available assay with a detection limit of 15 IU/mL, no cases of relapse were observed between W12 and W24, and undetectable HCV RNA at W12 had a 100% PPV for SVR.

Information about the timing of HCV relapse in HIV/HCV co-infected patients is scarce. In one study, carried out on 143 HIV/HCV co-infected patients treated with PEG-INF/RBV who achieved ETR, all but 2 (45/47, 95.7%) relapses occurred before W12. Phylogenetic analysis suggested that HCV re-infection occurred in one patient, and the possibility that the second patient might have been exposed again to the same source that was the cause of her original infection could not be discounted. Despite the special characteristics of HIV/HCV co-infected patients, our results suggest that HIV co-infection does not seem to increase the risk of HCV relapse beyond W12 after completion of HCV therapy.

Early knowledge of the post-treatment response status in patient therapy is likely to have a positive effect on the management of HCV patients. Reducing the post-treatment follow-up period to 12 weeks from the current standard of 24 could lead to a reduction in the costs associated with monitoring responses, improve patient care and enable relapsed patients to pursue alternative therapies earlier.

On the other hand, several studies have shown that the value of measuring serum HCV RNA at W12 to assess SVR is independent of whether the patient is treated with standard or pegylated interferon (α2a or α2b), the interferon dose or whether ribavirin is added to PEG-INF. However, whether the predictive value of measuring serum HCV RNA at W12 to assess SVR also holds true for re-treating patients who have failed a previous course of interferon-based therapy remains to be established.

In summary, our results show that undetectable HCV RNA at W12 of the post-treatment follow-up has a 100% PPV (95% CI 96.5%–100%) for SVR, suggesting that testing for HCV RNA at this point using a sensitive test with a detection limit of 15 IU/mL may be considered an appropriate time point for assessing virological response and identifying SVR and relapse in HIV/HCV co-infected patients treated with PEG-INF/RBV for chronic HCV. Studies are needed to confirm these results.

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References