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Address reprint requests to: Fernando Azpiroz, MD, Hospital General Vall d'Hebron, Digestive System Research Unit, Barcelona, Spain 08035. e-mail: fernando.azpiroz@telefonica.net; fax: (34) 93 489 44 56.

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## Use of Ribavirin in Patients With Chronic HCV Genotype 1: When Enough Is Really Enough

**See “Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a and ribavirin” by Bronowicki J-P, Ouzan D, Asselah T, Desmorat H, Zarski J-P, Foucher J, Bourliere M, Renou C, Tran A, Meilin P, Hezode C, Chevalier M, Bouvier-Alias M, Chevaliez S, Montestruc F, Lonjon-Domanec I, Pawlotsky JM, on page 1040.**

The most effective treatment for chronic hepatitis C virus (HCV) infection is the combination of peginterferon and ribavirin.<sup>1,2</sup> Approximately 40%–45% of patients with HCV genotype 1 and up to 80% of patients with HCV genotypes 2 or 3 achieve a sustained virologic response (SVR) following treatment with these agents. The ability to achieve a SVR in patients with chronic HCV infection depends on 3 factors: (1) the patient must first achieve a virologic response; (2) the patient must remain HCV RNA undetectable during the remainder of treatment; and (3) the patient must not relapse after treatment is discontinued. Both peginterferon and ribavirin appear to play very different roles in these processes.

Interferon has both antiviral and immunomodulatory properties. The former directly inhibits HCV replication and is responsible for the initial rapid phase I decline in HCV RNA observed within the first few days of initiating treatment.<sup>3,4</sup> Interferon also stimulates the immune response against hepatocytes infected with HCV by mobilizing T lymphocytes and

natural killer cells, and modulating cytokine release.<sup>5,6</sup> These effects are primarily responsible for the much slower phase II decline in HCV RNA that occurs over weeks to months. As a result, the primary role of interferon is viral clearance and higher doses of interferon or peginterferon have been shown to increase virologic response.<sup>7–9</sup> In contrast, these properties of interferon do little to prevent relapse. Approximately 45% of patients relapsed following treatment with interferon monotherapy and this is largely unchanged when higher doses of interferon or peginterferon are utilized. Thus, increasing the dose of interferon or peginterferon in and of itself has not translated into a higher SVR.

Ribavirin appears to enhance SVR by both enhancing virologic response and reducing relapse. In those studies where standard interferon or peginterferon monotherapy have been compared with combination therapy with ribavirin, virologic response increased from 24% to 50% and 59% to 69% respectively.<sup>1,10</sup> However, the major impact of ribavirin is to reduce relapse, which declined from about 45% to 51% in patients treated with only interferon or peginterferon to 18%–24% in patients who received combination therapy.<sup>1,10</sup> As a result, the addition of ribavirin has led to a marked increase in SVR from 13% to 38% in patients treated with standard interferon<sup>10</sup> and from 29% to 56% in patients treated with peginterferon.<sup>1</sup> The mechanisms by which ribavirin acts to enhance response and reduce relapse remain obscure. Ribavirin appears to have no significant direct antiviral action against HCV. The administration of this agent as monotherapy does not affect serum HCV RNA levels.<sup>11</sup> Ribavirin is a purine analog, a weak inhibitor of

the enzyme inosine monophosphate dehydrogenase, and it inhibits RNA-dependent RNA polymerase. Based on these actions, it has been hypothesized that ribavirin may modulate the T-cell response, inhibit HCV RNA replication, or act by being incorporated into the HCV virion where it acts as a mutagen.<sup>12,13</sup>

The greatest limitation in treating patients with chronic HCV are the adverse events of peginterferon and ribavirin.<sup>1,2,14</sup> More than 20% of patients who receive combination therapy must either alter the dose, temporarily interrupt, or prematurely discontinue either 1 or both of these agents. Previous studies have demonstrated that reducing the dose of peginterferon or ribavirin within the first 12 weeks of treatment in patients with HCV genotype 1 is associated with a decline in SVR.<sup>15-17</sup> In contrast, reducing the dose of these medications after week 12 or in patients who were already HCV RNA undetectable did not appear to impact SVR. Alternatively, continuing ribavirin monotherapy after 48 weeks of combination therapy did not reduce relapse.<sup>18</sup> Such observations suggest that the effect of ribavirin is exerted early during treatment and that this agent may no longer be needed after HCV RNA has become undetectable in serum. If this is correct, then either reducing the dose or discontinuing ribavirin at week 24 in patients who have already become HCV RNA undetectable may reduce the adverse events associated with treatment without impacting SVR. This hypothesis was recently evaluated by Bronowicki et al<sup>19</sup> and the results of this randomized controlled trial appear in this current issue of GASTROENTEROLOGY.

A total of 516 patients with HCV genotype 1 were treated with pegylated interferon  $\alpha$ -2a, 180  $\mu$ g/week and ribavirin 800 mg/d. At week 24, 69% (358 patients) were HCV-RNA negative and randomized to either continue peginterferon and ribavirin or to discontinue ribavirin and remain on peginterferon monotherapy through treatment week 48. At the end-of-follow-up, SVR was significantly greater ( $P = .004$ ) in patients who remained on combination therapy compared with patients who stopped ribavirin at week 24 (68% vs 53%). The decline in SVR associated with the premature discontinuation of ribavirin was the result of breakthrough or relapse. As soon as ribavirin was discontinued, patients began to develop breakthrough. At week 30, 6 weeks after ribavirin was stopped, 5.2% of patients had developed recurrence of HCV RNA and this increased to 11.7% by week 48. In contrast, only 2.5% of patients who were randomized to remain on both peginterferon and ribavirin developed breakthrough. Interestingly, all of these patients also discontinued treatment prematurely secondary to adverse effects associated with these medications. It therefore appears that either an interruption or premature discontinuation in ribavirin dosing is the primary reason for breakthrough in patients who became HCV RNA undetectable during treatment. Relapse also increased significantly ( $P = .02$ ) in patients who prematurely discontinued ribavirin. After 24 weeks of follow-up, 27% of patients who remained on combination therapy had relapsed compared with 35% of patients who discontinued ribavirin at week 24. However, the relapse rate observed in patients who discontinued ribavirin prematurely was still far below that observed in patients treated with peginterferon monotherapy in previous studies (35% vs 50%). This provides further evidence that the primary impact of ribavi-

rin occurs early during the course of treatment or prior to the patient becoming HCV RNA undetectable.

It should be of no surprise to anyone that overall SVR of the study population declined when ribavirin was prematurely discontinued. However, it should not be overlooked that over half of the patients who were HCV RNA undetectable at week 24 and then stopped ribavirin still achieved an SVR. Those patients who were most likely to achieve an SVR despite prematurely discontinuing ribavirin were those who had first achieved a rapid virologic response and were HCV RNA undetectable within 1 month of initiating treatment. Indeed, prior studies have demonstrated that patients with rapid virologic response have an SVR approaching 90% and this occurs regardless of the treatment they receive, whether peginterferon and ribavirin, peginterferon monotherapy or standard interferon and ribavirin.<sup>20</sup> In the study by Bronowicki et al,<sup>19</sup> those patients who achieved a rapid virologic response also had an SVR approaching 90% regardless of whether they remained on, or prematurely discontinued, ribavirin. In contrast, the absence of or premature discontinuation of ribavirin increased relapse in patients who became HCV RNA undetectable after week 4 in both a previous study and in the current study by Bronowicki et al.<sup>19</sup>

Significant progress has been made over the past decade in our understanding of chronic HCV and the manner in which peginterferon and ribavirin should best be used. It is now becoming quite clear that treatment should no longer be standardized and uniformly administered to all patients regardless of response. Rather, treatment should be closely monitored by performing HCV RNA at frequent intervals and adjusted based on the observed virologic response. For example, patients with HCV genotype 1 who achieve a rapid virologic response have an SVR approaching 90% even if they prematurely discontinue the use of ribavirin.<sup>19,20</sup> As a result, if a patient with rapid virologic response developed an adverse event dose reduction, discontinuing ribavirin at and possibly even before week 24 would be an acceptable approach. A recent study has even suggested that such patients may only require 24 weeks of therapy.<sup>21</sup> In contrast, HCV genotype 1 patients who do not achieve a rapid virologic response must remain on combination therapy for at least 48 weeks, and the current study by Bronowicki et al<sup>19</sup> has demonstrated that prematurely discontinuing ribavirin in such patients is associated with both breakthrough and an increased rate of relapse. However, 2 recent studies have demonstrated that relapse can be reduced in patients with HCV genotype 1 who become HCV RNA undetectable between weeks 4 and 24 by prolonging treatment with these agents from 48 to 72 weeks.<sup>22,23</sup>

Our improved understanding of how peginterferon and ribavirin should be used to treat chronic HCV comes at a time when we are about to embark on the next era of HCV treatment with protease and polymerase inhibitors. There is no doubt that these new drugs will be used in concert with peginterferon and many believe that ribavirin will also be necessary to reduce relapse. However, as we have already seen, ribavirin appears to exert its effect early during the course of treatment and may be stopped prematurely in those patients who achieve a rapid virologic response. Thus, if the use of antiviral agents along with peginterferon and ribavirin significantly enhances rapid virologic response, it is conceivable that the majority of these patients could possibly stop riba-

virin after just a few months and remain on either peginterferon alone or peginterferon and the antiviral agent for a longer period of time. Controlled clinical trials designed similar to the study of Bronowicki et al<sup>19</sup> will be required to evaluate if the same paradigm exists when using an antiviral agent and peginterferon and help to determine when enough ribavirin is really enough.

**MITCHELL L. SHIFFMAN**

*Hepatology Section*

*Virginia Commonwealth University Medical Center*

*Richmond, Virginia*

**VINOD K. RUSTGI**

*Metropolitan Liver Diseases*

*Fairfax, Virginia*

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Address requests for reprints to: Mitchell L. Shiffman, MD, Hepatology Section, Virginia Commonwealth University Medical Center, Box 980341, Richmond, Virginia 23298. e-mail: mshiffma@vcu.edu; fax: (804) 828-4945.

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