pISSN 2287-2728
eISSN 2287-285X

CMH Editorial

http://dx.doi.org/10.3350/cmh.2012.18.3.268
Clinical and Molecular Hepatology 2012;18:268-271

Impact of ribavirin dose reduction during treatment in chronic hepatitis C genotype 1 patients

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Keywords: Chronic hepatitis C; Genotype 1; Ribavirin

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Chronically hepatitis C virus (HCV) infects about 180 million people worldwide and it is a major cause of serious liver disease. As sustained virological response (SVR) to anti-HCV therapy avoids progression of liver fibrosis, decreases the risk of hepatocellular carcinoma and improve the survival of patients, antiviral therapy is considered as a crucial option in the management of chronic HCV infection.

After approval of boceprevir and telaprevir, the standard of care treatment for genotype-1 infection is now peginterferon plus ribavirin and a protease inhibitor. However, in the area where these direct-acting antiviral agents are not available, combination therapy with peginterferon plus ribavirin has still become the standard of care in the treatment of patients with chronic hepatitis C virus infection.

Although ribavirin has only a transient effect on HCV clearance in the absence of interferon,[1,2] it greatly enhances SVR rate when given in combination with interferon alfa.[3,4] Ribavirin significantly accelerates the second/third phase of HCV clearance in patients treated with peginterferon, and combination therapy with peginterferon and ribavirin enhances the rates of early virological response (EVR), end of treatment response (ETR), and SVR relative to that with peginterferon alone.[5,6]

The causes for ribavirin dose reduction are anemia, fatigue, rash, depression, anxiety, confusion or insomnia, etc. Anemia is a frequent complication of peginterferon plus ribavirin therapy for which ribavirin dose reduction is the primary management strategy. However, lower SVR rates have been reported in patients who undergo ribavirin dose reduction. Therefore, many clinicians have concerns to improve anemia related symptoms while maintaining ribavirin dose.

Hematologic toxicities of ribavirin with subsequent ribavirin dose reduction may impair response to combination therapy. Reduced ribavirin exposure may be correlated with increased rates of relapse.

Combination therapy yields SVR in approximately 40-45% of patients with HCV genotype 1 and 80% of patients with genotype 2 or 3. Even in genotype 1 patients, SVR occurs more frequently in patients who are able to maintain near full doses of these medications and is reduced substantially in patients who require reduction in the doses of these medications. In contrast, dose reduction does not appear to influence adversely SVR in patients with genotype 2 or 3.[7-9]

The genotype 1 patients who received at least 80% of their total expected cumulative dose of peginterferon and/or ribavirin for at least 80% of the planned duration of therapy (38 weeks) had SVR of 51% compared with only 34% for patients who received

Abbreviations:

ESAs, erythropoiesis-stimulating agents; ETR, end of treatment response; EVR, early virological response; Hb, hemoglobin; SVR, sustained virological response; VR, virological response

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Received : Aug. 13, 2012 / **Accepted :** Aug. 20, 2012

lesser amounts of one or both medications.[7]

The impact of dose reduction appeared to be greatest in patients who required dose reduction within the first 12 weeks of treatment. Patients who received ≥80% of both medication for the full 48 weeks of treatment had SVR of 61% and dose reduction after 12 weeks yielded SVR of 51%. But, patients who received reduced dose before week 12 had SVR of only 34%.[8]

Reddy et al[9] reported that nearly half of patients (43%) experienced ribavirin dose reduction, whereas reductions in peginterferon dose were less common (27%). SVR was not affected adversely by mild to moderate reductions in ribavirin dose, but, SVR rate was reduced in patients who received less than 60% of their ribavirin dose over the 48 weeks.

Shiffman et al[10] reported that the impact of dose reduction during the first several weeks of treatment on SVR has also been assessed in patients with prior nonresponders to interferon-based therapy during retreatment with peginterferon and ribavirin. Stepwise reduction in the dose of either peginterferon and/or ribavirin during first 20 weeks of treatment from ≥80% to ≤60% of the planned total dose was associated with a stepwise decline in SVR from 20-21% to 11-13%. In contrast, reducing the dose of these medication after week 20 in patients whose HCV RNA had already become undetectable did not appear to adversely influence SVR.[10]

Virological response (VR) at week 20 and SVR rates were dependent on the doses of both peginterferon and ribavirin. In patients who received >80% of the maximal cumulative peginterferon dose, both week 20 VR and SVR remained relatively stable as long as mean ribavirin dose were greater than approximately 2 mg/kg per day and 5.5 mg/kg per day, respectively. Increasing ribavirin dose above these values did not appear to increase either week 20 VR and SVR. In contrast, for patients who received <80% of the total cumulative peginterferon dose, increasing the dose of ribavirin appeared to enhance both week 20 VR and SVR.[11]

The patients who interrupted ribavirin dosing for more than 1 week or who missed >14 days of ribavirin during the first 12 weeks of treatment had SVR of only 9%. Discontinuing ribavirin permanently reduced SVR to only 3%. Bronowicki et al[12] also reported that permanently discontinuing ribavirin increased breakthrough from 2% to 12% and relapse from 29% to 42%.[12]

In previous studies of treatment-naïve patients, anemia requiring dose reduction was observed in approximately 20-25% of patients.[3,13-15] In the other study of retreatment in prior nonresponders, approximately half of the ribavirin dose reductions and nearly 75% of peginterferon dose reductions were due to hematologic toxicities of these drugs. The high frequency of cytopenia in patients treated for chronic hepatitis C led to studies of erythropoietin-alfa and other hematopoietic growth factor to limit the impact of anemia, neutropenia, and thrombocytopenia and the need to reduce doses of peginterferon and ribavirin.

Because lower SVR rates have been reported in patients who underwent ribavirin dose reduction, many clinicians and patients prefer to avoid ribavirin dose reduction and instead use erythropoiesis-stimulating agents (ESAs) to improve anemia related symptoms while maintaining ribavirin dose.[9-11]

A randomized, double-blind, placebo-controlled trials in patients treated with peginterferon and ribavirin demonstrate that erythropoietin-alfa was highly effective in correcting ribavirin-associated hemolytic anemia, limiting the need for ribavirin dose reduction, and improving quality of life.[16,17]

Unexpectedly, the SVR rate was significantly higher in anemic patients independent of ESAs use compare with non-anemic patients. Importantly, 1-step ribavirin dose reduction by 400 or 600 mg/day used with peginterferon alfa-2a was not associated with lower SVR rate, higher relapse rate, or improved safety outcomes compared with more gradual 2-step ribavirin dose reduction strategy used with peginterferon alfa-2b.

Sulkowski et al[18] reported that SVR was significantly higher among patients who developed anemia compared with who did not (48.8% vs 36.7%, $P<0.001$). SVR rates also varied according to the maximum hemoglobin (Hb) decline during treatment, measured as the absolute Hb decline from baseline and as relative decrease in Hb level from baseline.

SVR rate was significantly higher for patients with an absolute Hb decline >3 g/dL compared with those with maximum declines ≤3 g/dL. Similarly, small relative decline in Hb ≤21% was associated with a significantly lower SVR rate.

The magnitude of Hb loss is a pharmacodynamic marker of ribavirin exposure, correlating more closely with antiviral effect than the ingested ribavirin dose. As this relationship could be the result of an impaired physiologic response to ribavirin in non-anemic patients, other research data showed that high plasma ribavirin concentration are associated with higher Hb decline and virological response in peginterferon plus ribavirin treated patients.[19-22]

Advantage of erythropoietin in terms of SVR has not determined yet. According to recent meta-analysis data by Alavian et al,[23] patients who developed anemia and received erythropoietin as adjuvant therapy had a significantly higher rate of SVR compared with those with anemia who underwent ribavirin dose reduction as standard care with RR of 1.83 (95% CI 1.41-2.37).

 http://dx.doi.org/10.3350/cmh.2012.18.3.268

However, ESAs might not be completely safe. Hypertension, headache, reaction at injection site, increased number of platelets in the blood, severe thrombocytopenia and antibody-mediated pure red cell aplasia during anti-HCV therapy are rare complications of ESAs adjuvant therapy.[24-27] Therefore, more prospective studies about effectiveness and safety are needed.

Conflicts of Interest

The authors have no conflicts to disclose.

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