Ribavirin Prescribing Practices Among HCPs and the Future of Ribavirin in the Treatment of Chronic Hepatitis C

Off-label use of medication occurs frequently among health-care practitioners (HCPs). The off-label use of ribavirin (RBV) in the treatment of hepatitis C (HCV) is not well described in the literature, but often occurs in clinical practice. The package insert of RBV, which was based on the results of large, multicenter clinical trials, recommends twice daily (BID) dosing. However, the rationale for this dosing regimen remains unclear, as the pharmacokinetics of RBV supports once daily (QD) dosing. This article discusses the history, the proposed mechanism of action (MOA), the pharmacokinetics and the hemolytic anemia associated with RBV. In addition, the RBV prescribing practices among HCPs who treat a high-volume of HCV patients will be revealed. Finally, this article will address the possible role of RBV in the treatment of HCV in the upcoming era of all-oral, interferon-free therapies.

INTRODUCTION

Advances in the treatment of HCV are progressing at an exponential rate. Less than two years ago the introduction to this series, “Hepatitis C-A New Era of Treatment”, introduced the first major advance in the treatment of HCV for over a decade. This article heralded the addition of the protease inhibitors boceprevir (BOC) and telaprevir (TVR) to the backbone of HCV therapy, pegylated interferon (PIFN) and RBV. We are on the cusp of PIFN-free treatment regimens to cure patients with HCV, a truly remarkable advancement. This article will analyze both the dosing regimen of RBV and the potential fate of RBV in the future treatment of HCV.

Why Was New Treatment Discovery for HCVHampered?

Although plagued by suboptimal sustained virologic response (SVR) rates, numerous treatment-limiting adverse events (AEs) and long treatment durations, combination therapy with either interferon alpha (IFN) plus RBV or PIFN plus RBV has been the backbone of HCV therapy since 1998. While HCV was originally cloned in 1989, for nearly 10 years the virus was incapable of being grown in tissue culture and the only animal model was the chimpanzee. As such, research on new treatments was stagnant. In 1999 the development of a selectable HCV replicon cell culture system radically accelerated the drug discovery process. Fortunately, HCV genotype 1(G1), the most common genotype worldwide and the genotype least responsive to treatment with PIFN/RBV, is one of the few HCV isolates capable of replicating in this cell
 Ribavirin, originally synthesized in 1972, is an oral, synthetic, purine nucleoside analog with a broad-spectrum antiviral activity. (Figure 1) When used as a single agent, RBV does not significantly improve liver histopathology or reduce HCV RNA levels, although serum alanine aminotransferase elevations return to normal in some HCV patients. However, when paired with IFN or PIFN, SVR rates dramatically improve. While the mechanism by which RBV boosts SVR rates has not been clearly defined, it is evident that virologic relapse rates after treatment discontinuation are significantly reduced. The importance of RBV in the prevention of virologic relapse has especially been demonstrated in the clinical trials that led to the FDA approval of the first generation protease inhibitors TVR and BOC in combination with PIFN/RBV. It was initially anticipated that RBV may not be a necessary component of treatment when a protease inhibitor was added to PIFN, however, substantially lower SVR rates due to viral breakthrough and viral relapse occurred when RBV was excluded.

There are a number of distinct mechanisms of action proposed for RBV. One indirect MOA involves the competitive inhibition if inosine monophosphate dehydrogenase (IMPDH) by RBV monophosphate which reduces the cellular guanosine triphosphate (GTP) pool. By depleting endogenous GTP, RBV is preferentially taken up by HCV resulting in decreased viral replication. Another indirect MOA of RBV postulates that an immunomodulatory effect occurs by upregulating host T helper 1 (TH1) (antiviral) immune responses that may contribute to enhancing viral clearance. A direct MOA involves the fact that since ribavirin is a nucleoside analogue, its incorporation into the viral genome can lead to lethal mutations. In reacting with the HCV-RNA-dependent RNA polymerase (NS5B), ribavirin can act as a mimic of guanine and adenine blocking viral replication, via a mechanism known as “error catastrophe.” Finally, RBV may have activity in extrahepatic sites of HCV infection, explaining the marked decline in relapse rates with combination therapy without a significant effect on initial antiviral response.

**RBV – Induced Hemolytic Anemia**

The most dose-limiting adverse event associated with RBV is hemolytic anemia. After entering the circulation, a significant portion of RBV is transported into the erythrocyte and metabolized into various phosphorylated derivatives. Because of the lack of phosphatase activity in erythrocytes, these phosphorylated metabolites of RBV are trapped intracellularly and accumulate over time, leading to depletion of intracellular adenosine triphosphate (ATP), impaired ATP–dependent oxidative respiration, increased oxidative stress and impaired membrane integrity. This cascade of events culminates in hemolysis.

Within the first four weeks of starting RBV, most patients experience a rapid decline in hemoglobin of between 2–3 g/dL. Approximately half of patients on combination PIFN/RBV have a hemoglobin decline of 4 g/dL. RBV-induced hemolytic anemia is the main cause of dose reductions and treatment discontinuation in patients taking PIFN/RBV. The addition of a protease inhibitor, either boceprevir (BOC) or telaprevir (TVR), to PIFN/RBV in the treatment of patients with...
G1 HCV increases the risk of anemia. In clinical trials of BOC triple therapy vs. matched controls treated with PIFN/RBV, 49% of patients experienced anemia, defined as a hemoglobin level <10 g/dL, and 26% of patients required RBV dose reduction due to anemia vs. 29% and 13%, respectively, in the control group. In clinical trials of TVR triple therapy vs. matched controls treated with PIFN/RBV, 36% of patients experienced a hemoglobin level <10 g/dL, and 32% of patients required RBV dose reduction due to anemia vs. 17% and 12%, respectively, in the control group.

Real-life experience has been associated with an even higher occurrence and severity of anemia compared with that seen in TVR-based triple therapy clinical trials. Reasons for this are likely multifactorial and include the fact that patients typically excluded from clinical trials (i.e. sicker patients with advanced liver disease) are now being treated. Another unforeseen cause for the high degree of anemia occurring post-TVRIIR approval may be related to the FDA guideline recommending TVR administration with a high fat meal, which was not a requirement during clinical trials. Coadministration of RBV with a high-fat meal increases absorption, bioavailability, and Cmax, leading to an increased incidence and greater severity of anemia. These factors should be taken into consideration currently as well as when evaluating future treatment regimens that include RBV.

Identification of The Inosine Triphosphatase Gene

The inosine triphosphatase (ITPA) gene encodes a protein that hydrolyses inosine triphosphate (ITP). ITPA deficiency is a benign red cell enzymopathy that leads to both the buildup of ITP in red blood cells and to enhanced toxicity of purine analogue drugs. In 2010, Fellay and colleagues identified single nucleotide polymorphisms (SNPs) of ITPA that reduce or prevent RBV-induced hemolytic anemia. Thus, HCV patients with RBV-resistant ITPA genotypes have less RBV-induced hemolytic anemia, less RBV dose reductions and less RBV discontinuations with PIFN/RBV combination therapy, as well as with BOC or TVR triple therapy. Thus, testing patients for ITPA variants may assist in identifying which patients may better tolerate RBV and may help to individualize future treatment regimens.

RBV Pharmacokinetics and Dosing Schedule

In healthy adults, the elimination half-life ($t_{1/2}$) of RBV is approximately 120 to 170 hours after a single oral dose. The single dose pharmacokinetics and bioavailability of RBV has been shown to be independent of hepatic dysfunction. After twice daily (BID) dosing of RBV the $t_{1/2}$ is approximately 270 hours. The long washout $t_{1/2}$ of RBV reflects its accumulation in red blood cells, in addition to other tissue compartments. While the pharmacokinetics of RBV supports once daily (QD) dosing, RBV HCV clinical trials have been conducted utilizing BID administration. As such, FDA approval of RBV resulted in a BID-dosing schedule.

The Importance of Pill Burden on Medication Adherence

In a meta-analysis of fifty-two studies conducted across diverse disease states, adherence to medication was shown to be superior when patients were dosed once-daily compared with patients dosed twice daily or more frequently. Similarly, in a study conducted in organ transplant recipients, it was concluded that the most reliable predictor of adherence was the simplicity of the medication regimen. The number and frequency of pills ingested, i.e. pill burden, has been shown to have a significant effect on adherence, quality of life (QOL), morbidity and mortality in patients with a variety of conditions.
of chronic conditions such as hypertension, human immunodeficiency virus, cardiovascular disease, type 2 diabetes, osteoporosis and ulcerative colitis. Patients with chronic HCV are also found to have improved SVR rates and superior outcomes when adherence to prescribed treatment regimens are improved. Two trials have evaluated the impact of streamlining RBV pill burden on adherence rates in HCV patients. Results from a single-center, observational study of 92 HCV patients demonstrated that those taking PIFN plus fewer, higher-dose RBV tablets, a 400 or 600 mg RBV tablet available in a unit dose blister pack, experienced less AEs (predominantly gastrointestinal), improved QOL, better medication adherence and a trend toward superior SVR rates compared with patients taking PIFN plus the standard multiple 200 mg RBV tablets. Both medication regimens amounted to the same total dose of RBV, but the compact, higher dose blister pack resulted in a lower pill burden than the traditional 200 mg RBV tablets.

These results were confirmed in a multicenter trial comparing the same regimen of fewer high-dose RBV tablets vs. standard 200 mg dose RBV. Results similarly showed that patients taking the standard higher pill burden 200 mg dose RBV were more likely to prematurely discontinue treatment and less likely to adhere to prescribed therapy at weeks 12 and 24 compared with those taking fewer, higher dose RBV tablets. Figure 2. Simplifying RBV dosing regimens by reducing pill count, for example, will likely become an even more important factor leading to enhanced adherence and improved outcomes when all oral once-daily direct acting antiviral (DAA) regimens become the mainstay of future HCV treatment regimens.

**RBV QD vs. BID Dosing**

Once-daily 1200 mg RBV dosing has been shown to be pharmacokinetically comparable to 600 mg BID dosing at steady-state, demonstrating bioequivalence of dosing regimens. Figure 3.

The efficacy and adherence to treatment with PIFN plus once-daily RBV was retrospectively evaluated in 49 injection drug users (IDUs) with HCV G1-4. This study demonstrated that RBV administered up to 1200 mg QD resulted in SVR rates superior to that of studies using standard BID dosing of RBV. Figure 4. Importantly, both of these trials demonstrated a comparable safety profile without an increased incidence of anemia with RBV QD vs. RBV BID dosing regimens.

Osinusi and colleagues evaluated 60 treatment naïve

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**Figure 3.** No Significant Difference in Pharmacokinetic Parameters between RBV 1200 mg QD compared with RBV 600 mg BID at steady state. From Balk JM et al. Once daily dose regimen of ribavirin is pharmacokinetically comparable to twice daily dose regimen. The 62nd American Association for the Study of Liver Diseases Annual Meeting (AASLD), November 4-8, 2011, San Francisco, CA, Poster 1356.

**Figure 4.** SVR in 49 HCV patients on PIFN plus RBV QD. From Waizmann M et al. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a and once-daily ribavirin. J Substance Abuse Treat 2010; 38:338-45.
patients with G1, deemed difficult to treat, in a Phase II study with the NS5b nucleotide polymerase inhibitor, sofosbuvir (GS-7977) 400 mg QD in combination with either low-dose RBV (600 mg QD) or full-dose RBV (1000-1200 mg administered BID) for 24 weeks. Preliminary results demonstrated that SVR4 rates were not statistically different between the QD and the BID RBV dosing regimens and pharmacodynamics modeling demonstrated similar effectiveness with both arms. Figure 5.

Furthermore, a sub-analysis of 25 patients who participated in a 36-hour viral kinetic study revealed that the rate of early viral decay was rapid and independent of the RBV dosing schedule. Figure 6. Finally, safety was found to be comparable with both regimens.

Several DAAs at various stages of development have QD dosing. In addition, there appears to be a growing trend toward co-formulation of agents in order to decrease pill burden. Many Phase III clinical trials of new antiviral agents include RBV since it enhances SVR rates and prevents relapse as demonstrated in Phase II trials. However, there are also clinical trials that have demonstrated that some HCV patients can be cured with two or more DAAs without the use of RBV.

Current Ribavirin Prescribing Practices Among HCPs

Off-label use of a drug is defined as any use of a medication for a condition or in a manner not appearing on the drug’s approved label. Off-label use of medication occurs frequently among HCPs, especially in an outpatient setting, and it accounts for approximately 21% of prescriptions among leading drugs. The off-label use of RBV in the treatment of HCV is not well described in the literature.

A survey of HCPs examined the current prescribing regimens and the potential future prescribing trends related to RBV dosing schedules of HCV patients. A 5-question questionnaire (Table 1) was sent to 123 HCPs who regularly treat a high-volume of HCV patients. 65 HCPs anonymously completed the questionnaire.

Guidelines according to the ribavirin package insert recommend dose reduction to 600 mg to be administered BID in two doses – a 200 mg pill and two 200 mg pills (400 mg). However, there are no publications addressing the rationale for BID as opposed to QD dose reduction. Furthermore, after a comprehensive literature search, only two clinical trials could be identified that utilized a
RBV dose reduction regimen of 600 mg QD as opposed to BID.\textsuperscript{69,70} Thus, when asked their dose reduction recommendations, surprisingly 86% of HCPs (n =56 HCPs) stated that they advise their patients to dose reduce to 600 mg once daily (QD) instead of BID. HCPs were then asked if there are specific patient populations to whom they are more likely to recommend once daily instead of twice daily RBV. Responses showed a tendency to recommend once daily RBV to patients not experiencing any gastrointestinal disturbances due to RBV, noncompliant patients, patients with genotypes 2 and 3, patients on 800mg or less, patients with anemia, patients who are dose reduced, dialysis patients or those with renal insufficiency, patients without cirrhosis, patients with insomnia (total dose QAM), and patients who take multiple medications.

**Table 1. High-Volume HCP Questionnaire Concerning RBV- Dosing Practices**\textsuperscript{68}

1. For your patients who have been dose reduced to 600 mg, have you ever recommended they take the full dose once daily?

2. Are there specific patient populations to whom you are more likely to recommend once daily ribavirin?

3. Have you ever recommended that your patients on higher doses take the entire dose once daily?

4. If future regimens include once-daily DAAs, would you want and/or use a once daily ribavirin formulation?

5. Why or when would you recommend ribavirin be taken once daily?

**Future Trends in RBV Prescribing Practices**

While most HCPs, 77 % (n=50), stated that they currently are more likely to prescribe full-dose RBV BID as compared to QD, only 3% of HCPs responded that when future regimens consist of DAAs dosed QD, that they would continue to dose RBV BID. Finally, HCPs stated that they would change their current prescribing practices from BID to QD RBV dosing regimens if data were published demonstrating comparable efficacy, AEs and cost. There was a consistent overall trend that emphasized that QD dosing would foster ease of use and adherence, especially if and when future treatment regimens include PIFN-free, all-oral, once-daily DAAs.

**CONCLUSION**

The future is optimistic for HCV patients. Cure will be a reality for most patients, and treatment regimens will be easier than ever. The elimination of RBV would significantly simplify therapy and reduce the incidence of severe anemia that has historically complicated and reduced the efficacy of HCV treatment. However, while some patients may be cured without its use, RBV will likely remain an important component to therapy for many patients. Finally, in patients who continue to require the use of RBV, simpler RBV dosing regimens will improve adherence and contribute to optimal outcomes.

**References**


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