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Future Treatment of Hepatitis C: What will be the Fate of Ribavirin?

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When I began my career as a hepatologist in 1988 there were no treatments for viral hepatitis. In fact, hepatitis C (HCV), then known as non-A, non-B (NANB) hepatitis, was not discovered until the following year. Almost a decade passed before treatment for HCV became available that resulted in acceptable Sustained Virologic Response (SVR) rates (now known to be consistent with virologic cure) - a combination of Interferon alpha (IFN) plus Ribavirin (RBV). Prior to this pairing, less than 10% of HCV patients achieved a SVR when treated with IFN alone. With combination therapy, SVR rates rose to approximately 40-50%. IFN plus RBV or PEGylated IFN (PIFN) plus RBV have been the backbone of HCV therapy since this time [1-4].

Identification of additional improved therapeutics with fewer Adverse Events (AEs), higher SVR rates and shorter treatment durations, was hampered by the inability to grow HCV in tissue culture and by the lack of robust small animal models. Development of a selectable HCV replicon cell culture system in 1999 significantly accelerated the drug discovery process [5]. Since this time, a plethora of small molecules capable of inhibiting HCV RNA replication have been identified and have advanced into phase II and III clinical trials.

We will soon be entering an exciting new era of therapy for HCV, one in which most patients can expect to be cured without the use of interferon. However, this gives rise to the question -"What role will ribavirin play in future treatment regimens?"

Ribavirin (1-beta-D-ribofuranosyl-1, 2,4-triazole-3-carboxamide) is a synthetic purine nucleoside analogue with antiviral activity that when administered as monotherapy to patients with HCV can normalize alanine aminotransferase (ALT) levels, improve liver histology, and temporarily decrease HCVRNA levels by approximately 1.0 $\log_{10}$IU/mL [6]. When combined with IFN or PIFN, SVRs significantly increase, primarily due to prevention of virologic relapse after treatment discontinuation [7-10].

The exact mechanism by which RBV increases SVRs remains unknown and the rationale for the use of RBV in HCV remains essentially empirical. Some suggested mechanisms of action include: inhibition of guanosine triphosphate synthesis by an effect on Inosine Monophosphate Dehydrogenase (IMDH) thereby inhibiting viral RNA production [11]; action as a lethal mutagen multiplying the incidence of viral mutations consequently reducing HCV replication via "error catastrophe [12]; and enhancement of T helper1 (TH1) immune responses which may promote viral clearance [13,14]. Finally, it has been postulated that RBV may have activity in extra-hepatic sites of HCV infection, thus explaining the marked decrease in relapse rates with combination therapy without an appreciable effect on initial antiviral response [15].

RBV is associated is many AEs, the most dose-limiting of which is hemolytic anemia. While the mechanism of action by which RBV enhances SVR rates are not totally understood, the mechanism by which RBV leads to hemolytic anemia is better understood. After entering the circulation, a significant portion of RBV is transported into RBCs and metabolized into phosphorylated derivatives [16]. Owing to the lack of phosphatase activity in RBCs, these phosphorylated metabolites of RBV are trapped intracellularly and build up over time, resulting in depletion of intracellular adenosine triphosphate, impaired adenosine triphosphate–dependent oxidative respiration and impaired membrane integrity, resulting in hemolysis [17]. Anemia is a common side effect of RBV therapy. Most patients have a rapid decline of 2-3 g/dL in hemoglobin over the first 4 weeks of initiating RBV therapy [6,7,18] and approximately 50% of patients on combination PIFN/RBV experience a hemoglobin decline of 4 g/dL [19]. RBV-associated hemolytic anemia is the main reason for dose reductions and treatment termination in patients taking PIFN/RBV [20]. 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 incidence of anemia. In clinical trials of BOC triple therapy *vs.* a control group 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 controls. Thus, elimination of RBV from future HCV treatment regimens would significantly decrease the incidence of severe anemia, which has complicated standard HCV treatment.

RBV has traditionally been administered twice daily (BID) in divided doses. However, the pharmacokinetics of RBV supports once daily (qd) dosing. The elimination half-life (t½) of RBV following a single oral dose administration is approximately 120 to 170 hours in healthy adults [21]. The single dose pharmacokinetics and bioavailability of RBV has been shown to be independent of hepatic function [22]. After BID dosing of RBV the t½ is approximately 270 hours. The long washout t½ of RBV reflects its accumulation in red blood cells, in addition to other tissue compartments.

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 [23]. Waizmann and Ackermann demonstrated that RBV administered up to 1200 mg qd resulted in SVR rates equivalent to or better than that of studies using traditional BID RBV dosing [24]. Importantly, comparable safety profiles between the RBV qd and bid regimens were shown in these trials. RBV in qd dosing is being studied in at least one new Direct-Acting Antiviral (DAA) clinical trial [25]. Sixty G1 treatment-naïve patients were enrolled 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 bid) for 24 weeks. Preliminary results showed that SVR4 rates were not statistically different between the once-daily and twice-daily RBV regimens. Twenty-five patients participated in a 36 hour viral kinetic sub-analysis, which demonstrated that the rate of early viral decay was independent of once-daily or twice-daily RBV. Finally, comparable safety was found with both dosing regimens.

Once-daily *vs.* twice-daily or more frequent medication dosing

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intervals enhances adherence to medication across a variety of disease states, as demonstrated in a meta-analysis of 52 studies reported by Coleman et al. [26]. The single most reliable predictor of treatment adherence among organ transplant recipients was found to be the simplicity of the medication regimen [27]. In patients with chronic conditions such as human immunodeficiency virus, hypertension, cardiovascular disease, type 2 diabetes, osteoporosis and ulcerative colitis, the number and frequency of tablets ingested (pill burden) has been shown to have a significant effect on adherence and Quality of Life (QOL), as well as morbidity and mortality [28-34]. Indeed, in CHC, higher rates of adherence are associated with increased SVR rates [35,36].

The effect of simplifying RBV pill burden among HCV patients was evaluated in two trials comparing adherence rates treated with fewer, higher-dose RBV tablets - a 400 mg or 600 mg RBV tablet available in a unit dose blister pack - *vs*. the same total dose of the traditional bottled 200 mg RBV tablets. Results from a single-center observational study of 92 patients demonstrated that those taking PIFN plus the more compact formulation of RBV- which gave rise to a reduced pill burden, experienced less AEs, better QOL, improved medication adherence, and a trend toward higher SVR rates compared with patients taking PIFN plus the standard 200 mg RBV tablets [37]. In a multicenter comparative study of fewer high -dose RBV tablets *vs.* standard 200 mg dose RBV, those taking fewer total RBV tablets were less likely to prematurely discontinue treatment and more likely to adhere to prescribed therapy at Weeks 12 and 24 compared with patients taking the standard higher pill burden 200 mg dose RBV [38]. Streamlining RBV dosing regimens by reducing pill count will likely become an even more crucial factor contributing to enhanced adherence and better outcomes when all oral once-daily DAA regimens become a mainstay of HCV treatment.

As of this date, many new DAA - based regimens in U. S. Phase III trials include RBV, due to its effects on enhancing SVR rates and preventing relapse as demonstrated in Phase II trials [39-47]. In addition, many new DAAs in development have qd dosing and there is a trend toward co-formulated medications to reduce pill burden [48]. However, there are also some trials that have shown compelling data that HCV patients can be cured with 2 or more DAAs without the use of RBV [49,50].

The future looks bright for HCV patients as well as for the HCPs caring for them. Cure rates not only will soar, but treatment regimens will be simpler. It is becoming apparent that RBV will remain an important component to future therapies for many patients, while others may be cured without its use. Finally, in patients who continue to require the use of RBV, simpler RBV dosing regimens will likely improve adherence and contribute to optimal outcomes.

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