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Commentary

What is the future of ribavirin therapy for hepatitis C?

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ABSTRACT

With the introduction of direct-acting antiviral (DAA) therapy against hepatitis C virus (HCV) infection, the field is rapidly evolving towards interferon-free regimens with high sustained virologic response (SVR) rates. The ultimate goal of therapy in chronic HCV infection should include an easily dosed all-oral regimen that is highly effective, inexpensive, pan-genotypic, safe and tolerable, with minimal to no resistance. Various investigational DAA regimens are currently under evaluation with and without ribavirin (Rbv). With the projected arrival of improved therapies over the next 5 years, the future role of Rbv comes into question. Despite being plagued by the lack of understanding of its mechanism of action and significant side effects such as anemia, Rbv has been a part of the standard-of-care therapies in chronic HCV infection for more than 10 years. As we look towards the future HCV therapy, Rbv may still have utility in the care of patients infected with HCV because of its low cost and potentially added value in combination with other DAAs. This article forms part of a symposium in *Antiviral Research* on "Hepatitis C: next steps toward global eradication."

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With the recent introduction of direct-acting antiviral (DAA) therapy for chronic hepatitis C (HCV) infection, the field is rapidly evolving towards interferon-free treatment regimens. Therapy including ribavirin (Rbv) has been a part of the standard-of-care for chronic HCV for more than a decade, and despite known toxicities and side effects, Rbv remains an essential component of approved DAA regimens. As we eagerly await for the arrival of highly efficacious DAA combination regimens that are easily administrated, with good safety and tolerability, the future role of Rbv in HCV therapy comes into question. This commentary forms part of a symposium in *Antiviral Research* on "Hepatitis C: next steps toward global eradication."

Rbv is a guanosine nucleoside analog that was first identified to have broad-spectrum antiviral activity against both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses in *in vitro* and *in vivo* models (Sidwell et al., 1972). In 1986, Rbv first obtained Food and Drug Administration (FDA) approval for the therapy of respiratory syncytial virus (RSV) infection (Hall et al., 1983). In various studies, Rbv has also been shown to be active against many other viruses (Kamar et al., 2010; Koren et al., 2003; McCormick et al., 1986; Huggins et al., 1991), including viruses similar to HCV (Sidwell et al., 1972; Patterson and Fernandez-Larsson, 1990). This initial observation led to anti-HCV pilot studies evaluating Rbv monotherapy in the early 1990's which showed little antiviral effect but improvement in markers of liver injury (ALT elevations) (Reichard et al., 1991; Bisceglie et al., 1992). Follow-up studies have confirmed that Rbv is inefficient at decreasing viral load *in vivo* (Dusheiko et al., 1996; Lee et al., 1998), but does result in a biochemical effect (Tong et al., 1994; Di Bisceglie et al., 1995). Rbv was then tested in combination with interferon-alpha and resulted in a substantial improvement in SVR rates (from 6–16% to 34–42% with 6 or 12 months of therapy) (Brillanti et al., 1994; Strader et al., 2004; Chemello et al., 1995). This regimen was more clinically effective than either drug alone (Buckwold, 2004), and thus became the standard of therapy of chronic HCV infection for more than 10 years (Brillanti et al., 1994; Strader et al., 2004; Ghany et al., 2009; EASL, 2011).

Since these and other landmark studies, Rbv has become an essential component of all HCV therapies. In patients with HCV genotype 1 or 4 infection, a weight-based Rbv regimen has been recommended (1000 mg/d in patients <75 kg and 1200 mg/d in patients ⩾ 75 kg) whereas a fixed dosage of Rbv (800 mg/d) is recommended in genotype 2 or 3 infection (Strader et al., 2004; Ghany

Abbreviations: Rbv, ribavirin; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; RSV, respiratory syncytial virus; FDA, Food and Drug Administration; HCV, hepatitis C; ALT, alanine aminotransferase; SVR, sustained virological response; DAA, direct-acting antiviral.

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et al., 2009; EASL, 2011). During the era of "dual therapy" with peginterferon and ribavirin, the expected SVR rate was approximately 50% in genotype 1 infection and 80% in genotype 2/3 infection.

Despite the success of Rbv in HCV therapy, the specific mechanism(s) of Rbv against HCV has yet to be elucidated. This knowledge gap has made it difficult to further improve on Rbv's action. Various mechanisms have been proposed, including: (1) RNA viral mutagenesis through incorporation of Rbv triphosphate into the HCV viral genome that can cause nucleotide transitions; (2) direct inhibition against HCV RNA dependent RNA polymerases leading to inhibition of genome replication; (3) inhibition of host inosine monophosphate dehydrogenase leading to decreased synthesis and lower levels of GTP with resultant decrease in viral replication; (4) alteration of the host adaptive immune response through Th2 response suppression and Th1 response induction leading to increased clearance of infected cells; (5) potentiation of interferon action by modulating genes involved in interferon signaling and/or an indirect mechanism that may act to reset interferon-responsiveness in an HCV-infected liver (Hofmann et al., 2007; Chevaliez et al., 2007; Chung et al., 2008; Feld et al., 2010; Thomas et al., 2011; Dietz et al., 2013; Rotman et al., 2014). Additionally, as a component of dual therapy, Rbv's side effects have prohibited many patients from successfully completing therapy. Such side effects include hemolytic anemia, fatigue, itching, rash, sinusitis and gout. Deaths from Rbv have also resulted from myocardial infarction in those with significant and/or unstable cardiac disease (Rebetol, 2013). Studies to increase SVR rates through higher doses (1400–3600 mg daily) of Rbv showed improved response rates but were associated with unacceptable side effects (hemolytic anemia) (Jacobson et al., 2007; Lindahl et al., 2005). Although these studies do not support the use of higher doses of Rbv in patients, they do provide an interesting scenario in which the maximal efficacy of Rbv has not been reached in HCV therapy.

Alternatively, viramidine (Taribavirin®), a nucleoside analogue and oral prodrug of Rbv that is converted to Rbv by adenosine deaminase, was designed with the hope of reducing the side effect of hemolytic anemia and increasing the efficacy of combination therapy (Wu et al., 2003; Lin et al., 2004). In two phase 3 clinical trials (ViSER1 and ViSER2), Taribavirin, although resulting in less anemia, proved to be less effective than Rbv in achieving a SVR (Benhamou et al., 2009; Marcellin et al., 2010). This was thought to be due to inadequate fixed dosing of Taribavirin in both studies, and a follow-up phase IIB study evaluating weight-based Taribavirin has demonstrated more promising results (Poordad et al., 2010). Alternative forms of interferon, such as consensus or lambda interferon, have been tested in HCV therapy, but it remains to be shown whether they are better than standard peginterferon (Ho et al., 2011; Meyer et al., 2010; Muir et al., 2010; Vierling et al., 2012; Izumi et al., 2012). Thus, without knowledge of the specific mechanisms of Rbv against HCV, along with the significant side effects of therapy, it is unclear whether dual therapy of peginterferon

Table 1
Single direct-acting antiviral plus ribavirin studies.

Year & trial acronym	Treatment regimen	Number of patients	Experience/genotype/ treatment duration (wks)	Sustained virologic response rate	Reference
2013 *ELECTRON*[a]	Sofosbuvir + Rbv	10	Naïve/ 2,3/ 12	100%	Gane et al., 2013
		25	Naïve/ 1/ 12	84%	
	Sofosbuvir	10	Naïve/ 2,3/ 12	60%	
	Sofosbuvir + Rbv	10	Null/ 1/ 24	10%	
2013 *NIH-SPARE*[a]	Sofosbuvir + Rbv	10 25	Naïve/ 1/ 24	68–90%	Osinusi et al., 2013
	Sofosbuvir + 0.6 g Rbv	25	Naïve/ 1/ 24	48%	
2013 *POSITRON*[a]	Sofosbuvir + Rbv	207	Naïve/ 2,3/ 12	78% (SVR12)	Jacobson et al., 2013
2013 *FISSION*[a]	Sofosbuvir + Rbv	253	Naïve/ 2,3/ 12	67% (SVR12)	Lawitz and Gane, 2013
2013 *FUSION*[a]	Sofosbuvir + Rbv	100	Null/ 2,3/ 12	50% (SVR12)	Jacobson et al., 2013
		95	Null/ 2,3/ 16	73% (SVR12)	
2013 *VALENCE*[b]	Sofosbuvir + Rbv	73	Naïve/ 2/ 12	93% (SVR12)	Zeuzem et al., 2013
		250	Naïve/ 3/ 24	85% (SVR12)	

The results from these studies demonstrate that the combination of sofosbuvir and ribavirin can be used in the treatment of HCV genotype 2/3 infection and does not appear to be inferior to the current standard of care.

Abbreviations: wks, weeks; Rbv, ribavirin; SVR, sustained virologic response.

[a] Sofosbuvir was administered at 400 mg/day with weight-based ribavirin (1000 mg/d in patients < 75 kg and 1200 mg/d in patients ⩾ 75 kg).

[b] Dosing not available.