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Commentary

What is the future of ribavirin therapy for hepatitis C?

Christopher Koh *, T. Jake Liang *

Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, United States

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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.

* Address: Liver Diseases Branch, National Institutes of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bldg. 10, Room 9B16, 10 Center Drive, MSC 1800, Bethesda, MD 20892-1800, United States. Tel.: +1 301 496 1721; fax: +1 301 402 0491.

E-mail addresses: Christopher.Koh@nih.gov (C. Koh), JakeL@bdg10.niddk.nih.gov (T.J. Liang).

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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.

and Rbv can be further improved. Additionally, with the potency demonstrated in current investigational therapies, there may not be a need for Rbv analogues or alternative forms of interferon.

In 2011, the first direct-acting antivirals (DAAs), boceprevir and telaprevir, were approved by the FDA for use as "triple therapy" in combination with peginterferon and ribavirin in patients with chronic HCV genotype 1 infection (Poordad et al., 2011; McHutchison et al., 2009; Hezode et al., 2009; Bacon et al., 2011). These DAAs target the HCV NS3/NS4A protease and significantly increase SVR rates to 69–75% when used as "triple therapy" (Poordad et al., 2011; Jacobson et al., 2011). Thus, triple therapy is currently the recommended therapy for chronic HCV genotype 1 infection (Ghany et al., 2011; Liang and Ghany, 2013). However, despite these improved SVR rates, there is still much room for improvement as the current therapy is poorly tolerated given the additional side effects of the first-generation DAAs and the low response rates in prior null responders to dual therapy. In retrospective analysis of these pivotal trials, it is interesting to note that Rbv dose can be significantly reduced (as low as 600 mg per day) without compromising the treatment response to the triple therapy (Sulkowski et al., 2011a; Sulkowski et al., 2011b). This observation raises the intriguing possibility that in combination with more potent anti-HCV drugs, the maximal dose of Rbv may not be necessary.

As we look towards the future, the field of HCV therapy will explode with various investigational DAAs targeting viral enzymes and proteins involved in essential functions of the HCV lifecycle. Various DAAs under investigation include NS3/4A protease inhibitors, nucleoside/nucleotide and non-nucleoside inhibitors of the RNA-dependent RNA polymerase, and NS5A inhibitors (Liang and Ghany, 2013).

In the immediate future, as evidenced by ongoing and published clinical trials, the goal of therapy appears to be interferon-free regimens. However, the use of Rbv in combination with DAAs may still be necessary in the next round of DAA regimens. Many of the recently published all-oral regimen studies still utilize Rbv in combination with one to three DAAs. In the various phase II & III trials with a single DAA (the polymerase inhibitor sofosbuvir) and ribavirin (Gane et al., 2013; Osinusi et al., 2013; Jacobson et al., 2013; Lawitz and Gane, 2013; Zeuzem et al., 2013) (Table 1), investigators have shown that not only is an interferon-free regimen possible, but in the treatment of HCV genotype 2/3, a single DAA plus Rbv for 16 weeks is not inferior to current standard of care peginterferon and Rbv therapy. Additionally, one study demonstrated the continued importance of Rbv in DAA regimens as only 60% of genotype 2/3 infected patients achieved an SVR with sofosbuvir monotherapy versus the 100% SVR seen with sofosbuvir plus ribavirin (Gane et al., 2013). Thus for the near future, therapy of genotype 2/3 will still require Rbv.

Although a single DAA plus Rbv regimen appears possible for chronic HCV genotype 2/3 infection, it may not be feasible for the more difficult-to-treat genotype 1 infection. Currently, a multitude of two and three DAA plus ribavirin regimens for 12–24 weeks are being investigated in genotype 1 patients. Various two DAA plus ribavirin phase 2 clinical trials (Jacobson et al., 2012; Poordad et al., 2013; Lawitz et al., 2013; Zeuzem et al., 2013; Lawitz et al., 2013) have shown high rates of SVR in

Table 2
Two direct-acting antiviral plus ribavirin studies.

Year & trial acronym	Treatment regimen	Number of Patients	Experience/genotype/ treatment duration (wks)	Sustained virological response Rate	Reference
2012 *ZENITH*	Telaprevir (PI) + VX-222 (NNI) + Rbv	5	Naïve/ 1a/ 12	100%	Jacobson et al., 2012
		6	Naïve/ 1b/ 12	67%	
2013 *CO-PILOT*	250 mg ABT 450/r (PI) + ABT-333 (NNI) + Rbv	19	Naïve/ 1/ 12	95% (SVR12)	Poordad et al., 2013
	150 mg ABT 450/r (PI) + ABT-333 (NNI) + Rbv	14	Naïve/ 1/ 12	93% (SVR12)	
		17	Null & Partial/ 1/ 12	47% (SVR12)	
2013 *PILOT*	ABT 450/r (PI) + ABT-072 (NNI) + Rbv	11	Naïve/ 1/ 12	73% (SVR48)	Lawitz et al., 2013
2012 *SOUND-C2*	Faldaprevir (PI) + deleobuvir (TID)(NNI) + Rbv	81 80 77	Naïve/ 1/ 16, 28, or 40	52–59% (SVR12)	Zeuzem et al., 2013
	Faldaprevir (PI) + deleobuvir (BID)(NNI) + Rbv	78	Naïve/ 1/ 28	69% (SVR12)	
	Faldaprevir (PI) + deleobuvir (TID)(NNI)	46	Naïve/ 1/ 28	39% (SVR12)	
2013 *C-WORTHY*	MK-5172 (PI) + 20 mg MK-8742 (NS5A) + Rbv	25	Naïve/ 1/ 12	96% (SVR12)	Lawitz et al., 2013
	MK-5172 (PI) + 50 mg MK-8742 (NS5A) + Rbv	27	Naïve/ 1/ 12	89% (SVR12)	
2013	Daclatasvir (NS5a) + sofosbuvir (NI) + Rbv	21	TVR or BOC Failure/ 1/ 24	100% (SVR4)	Sulkowski, 2013

The results from these studies show that two DAA plus Rbv regimens can be used to treat genotype 1 treatment naïve patients.
Abbreviations: wks, weeks; PI, protease inhibitor; NNI, non-nucleoside inhibitor; r, ritonavir; BID, twice daily; TID, three times daily; Rbv, ribavirin; SVR, sustained virologic response; TVR, Telaprevir; BOC, boceprevir

genotype 1 treatment naïve patients (Table 2). In one study, the incorporation of Rbv resulted in a marked improvement in SVR in prior null responders (59% with Rbv vs. 39% without Rbv) (Zeuzem et al., 2013). Additionally, despite Rbv's known side effects, the use of Rbv in these regimens did not seem to significantly worsen the overall adverse event profiles or quality of life (Younossi et al., 2013). This suggests that Rbv may continue to have added value in interferon-free regimens without the observed side effects and toxicities seen in combination with interferon.

Currently, ribavirin-free regimens are being investigated. Initial evidence of this was described in one arm of a clinical trial (Gane et al., 2010) in which an all-oral DAA combination without RBV demonstrated antiviral activity. Subsequent follow-up phase 2 studies evaluating two DAAs (Lawitz et al., 2013; Sulkowski, 2013; Lok et al., 2012; Lok et al., 2012; Suzuki et al., 2013) and three DAAs (Kowdley et al., 2013; Everson et al., 2013) for 12–24 weeks have described that high rates of SVR are possible in genotype 1, 2 and 3 HCV infections without Rbv (Table 3). Although the subject numbers in these early phase Rbv-free clinical trials are small, there appear to be no significant differences in SVR rates comparing groups with or without Rbv in both dual and triple combination therapy (Sulkowski, 2013; Kowdley et al., 2013). As Rbv-free studies are still being tested, data on the feasibility of 12 weeks of therapy with dual DAAs and triple-DAA combinations in treatment-experienced populations are lacking. Taken together, we can anticipate that by combining DAAs with various modes of action, high SVR is attainable, particularly in genotype 1 and more difficult-to-treat populations, and a shortened course of therapy may be possible, and therapy without RBV is possible.

Table 3
Studies with ribavirin free direct-acting antiviral regimens.

Year & trial acronym	Treatment regimen	Numbers of patients	Experience/genotype/ treatment duration (wks)	Sustained virological response rate	Reference
2012	Asunaprevir (PI) + daclatasvir (NS5a)	Gt1a = 9 Gt1b = 2	Null/ 1a + 1b/ 24	1a = 22% 1b = 100%	Lok et al., 2012
2012	Asunaprevir (PI) + daclatasvir (NS5a)	18	Null/ 1b/ 24	83% (SVR12)	Lok et al., 2012
2013	Asunaprevir (PI) + daclatasvir (NS5a)	22	Naive/ 1b/ 24	64%	Suzuki et al., 2013
		21	Null/ 1b/ 24	90%	
2013	Sofosbuvir (NI) + daclatasvir (NS5a)	15 14	Naïve/ 1/ 24	100%	Sulkowski, 2013
		16 14	Naïve/ 2,3/ 24	88–100%	
		21	Null/ 1/ 24	100%	
2013 *AVIATOR*	ABT 450/r (PI) ± ABT 267 (NS5a) ± ABT 333 (NNI)	79	Naïve/ 1/ 12	87%	Kowdley et al., 2013
2013	Daclatasvir (NS5a) + asunaprevir (PI) + 75 mg BMS-791325 (NNI)	16	Naïve/ 1/ 12	94%	Everson et al., 2013
		16	Naïve/ 1/ 24		
	Daclatasvir (NS5a) + asunaprevir (PI) + 150 mg BMS-791325 (NNI)	24	Naïve/ 1/ 12	94% (SVR4)	
		12	Naïve/ 1/ 24	89% (SVR12)	
2013 *C-WORTHY*	MK-5172 (PI) + 50 mg MK-8742 (NS5A)	13	Naïve/ 1/ 12	100% (SVR12)	Lawitz et al., 2013
2013	Daclatasvir (NS5a) + asunaprevir (PI) + 75 mg BMS-791325 (NNI)	80	Naïve/ 1/	92% (SVR12)	Everson et al., 2013
	Daclatasvir (NS5a) + asunaprevir (PI) + 150 mg BMS-791325 (NNI)	86	12		
2013 *LONESTAR*	Sofosbuvir (NI) + ledipasvir (NS5A)	20	Naïve/ 1/ 12	95% (SVR12)	Lawitz et al., 2013
		20	Naïve/ 1/ 8	95% (SVR12)	
		20	Failed PI/ 1/ 12	100% (SVR12)	

The results from these studies demonstrate that treatment is possible without interferon or ribavirin with combination therapy utilizing direct-acting antivirals.
Abbreviations: wks, weeks; PI, protease inhibitor; NNI, non-nucleoside inhibitor; SVR, sustained virologic response; Gt, genotype; r, ritonavir

The "holy grail" of the future of HCV therapy appears to include an easily dosed all-oral regimen that is highly effective, inexpensive, pan-genotypic, safe and tolerable, with minimal to no resistance. The achievement of these goals in the next 5 years seems to be attainable. The question of whether Rbv will have a continued role in the future of chronic HCV therapy is an important one. As the next-generation DAAs become available, Rbv will probably continue to be part of combination therapy. In the more distant future, with increasingly potent DAAs to attack multiple HCV targets, the use of Rbv may not be necessary, especially because of the lack of understanding of its mechanism of action in chronic HCV infection. Future studies that may answer this question include: non-inferiority studies between regimens with and without Rbv; feasibility studies of lower doses of Rbv in Rbv + DAA combination regimens; and comparative studies of a shorter duration of DAA therapy with the addition of Rbv. However, with the demonstrated potency of current investigational DAAs, we suspect that the use of Rbv may be limited other than in resource-poor settings.

Alternatively, in the era of cost containment, affordable healthcare and accessibility, Rbv may still have significant appeal in HCV therapy. Rbv has been available in generic form since 2005 and a course of therapy with Rbv, as per current guidelines, ranges from approximately $4500 for genotype 2/3 infection to $13,500 for genotype 1 infection (48 weeks & >75 kg) (http://www.goodrx.com/ribavirin). The current cost of a treatment course with an FDA approved single DAA ranges from approximately $26,000–$49,000 (not including peginterferon and ribavirin) depending on response guided therapy (http://hepatitiscnewdrugs.blogspot.com/2011/09/telaprevir-incivekboceprevir-victrelis.html). As expected, the impending arrival of multiple DAA regimens may drive the cost of therapy to become prohibitively expensive, and therefore not affordable to people in resource-poor settings. For example, the recently FDA approved regimen containing sofosbuvir comes with a price tag of $80,000, which is only for sofosbuvir alone (http://www.sciencemag.org/content/342/6164/1302.full). As HCV is a worldwide health problem with global consequences, future DAA regimens containing Rbv may be more affordable and accessible on an international scale, especially for the developing regions of the world. Much of this scenario will depend on the comparability of future studies evaluating regimens with and without Rbv (pertaining to non-inferiority).

As therapies are rapidly advancing, the efforts to successfully treat the large majority of patients with chronic HCV infection appear promising. Clinicians will soon have multiple drugs in their armamentarium to eradicate HCV infection. This new frontier, either with or without RBV, offers a more personalized approach to medicine, with the ultimate goal of improving patient care.

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