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Ribavirin revisited in the era of direct-acting antiviral therapy for hepatitis C virus infection

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Abstract

Over the past two decades, ribavirin has been an integral component of treatment for hepatitis C virus (HCV) infection, where it has been shown to improve the efficacy of (pegylated) interferon. However, because of treatment-limiting side effects and its additive toxicity with interferon, the search for interferon- and ribavirin-free regimens has been underway. The recent approvals of all-oral direct acting antivirals (DAAs) have revolutionized the HCV therapeutic landscape, and initially it was expected that the role of ribavirin with DAA regimens would be eliminated. On the contrary, what we have witnessed is that ribavirin retains an important role in the optimal treatment of some subgroups of patients, particularly those that historically have been considered the most difficult to cure. Fortunately, it has also been recognized that the safety profile of ribavirin is improved when co-administered with all-oral DAA combinations in the absence of interferon. Despite the antiviral mechanism of action of ribavirin being poorly understood, we now have a range of novel insights into the potential role of ribavirin in all-oral DAA HCV treatment and greater insight into the antiviral mechanism by which it continues to provide clinical benefit for defined patient groups.

KEYWORDS

direct-acting antiviral, hepatitis C virus, interferon-free, ribavirin

1 | INTRODUCTION: THE ROLE OF RIBAVIRIN IN THE ERA OF INTERFERON

The guanosine analogue ribavirin has been an important component of interferon-based regimens for hepatitis C virus (HCV) infection since the 1990s, when it was shown that adding it to conventional interferon significantly increased treatment efficacy by decreasing the risk of post-treatment viral relapse.[1] Similarly, the combination of ribavirin and pegylated interferon (peginterferon) was shown to be superior to peginterferon alone (Table 1),[2] because of higher on-treatment responses and, more importantly, lower rates of relapse following therapy.

The introduction of the first-generation HCV protease inhibitors boceprevir and telaprevir to peginterferon/ribavirin regimens boosted sustained virological response (SVR) rates even further.[3–7] With these new potent agents, it was hoped that ribavirin would no longer be necessary; however, eliminating ribavirin from the regimen altogether significantly reduced response rates and increased rates of breakthrough with virus resistance-associated substitutions (RASs). Ribavirin dosage reduction was shown to be safe and did not negatively impact SVR rates unless dosage was reduced by more than 50% of the recommended ribavirin dosage.[8]

Despite improving the efficacy of interferon-based therapy, ribavirin is associated with a number of treatment-limiting adverse events (AEs), particularly haemolytic anaemia.[9–11] Other ribavirin-related AEs include pruritus, rash, insomnia, mild abdominal discomfort, and upper respiratory tract symptoms.[9–11] Furthermore, the combination

with interferon or peginterferon results in higher rates of some AEs, compared with either agent alone (Fig. 1A, B).[1,2] Finally, because of a teratogenic effect in animals,[12] ribavirin is contraindicated during pregnancy, warranting a Category X designation, and contraception is required in all women of child-bearing potential, including those with male partners taking the medication.[13, 14]

Ribavirin is not metabolized via a cytochrome P450-mediated mechanism and, therefore, has a low potential for drug–drug interactions.[13] However, there are issues with a small number of agents with additive toxicity, e.g. the nucleoside reverse transcriptase inhibitors zidovudine and didanosine as well as the immunosuppressant drug azathioprine. No issues have been identified with ribavirin and any approved direct-acting antiviral (DAA) therapies for HCV.

Key points

- Ribavirin has been an integral component of treatment for hepatitis C virus (HCV) infection for the past two decades.
- In the interferon-free era of HCV treatment, ribavirin has retained an important role in the optimal treatment of some difficult-to-cure subgroups of patients.
- The safety profile of ribavirin is improved when co-administered with all-oral direct-acting antiviral (DAA) combinations in the absence of interferon.
- Recently, new insights have been gained into the antiviral mechanism by which ribavirin delays or prevents the emergence of resistance-associated substitutions (RASs).

2 | THE ROLE OF RIBAVIRIN IN THE INTERFERON-FREE ERA

In the interferon-free era of HCV treatment, most clinical trials have been designed to systematically evaluate DAA regimens with or without ribavirin. Ribavirin's role was expected to diminish or even be eliminated over time, but pivotal trial data indicate that, for certain regimens, it remains an important component for the optimal treatment of some patients. Deciding whether to include ribavirin as a therapy component, and how best to manage its use, largely depends on HCV genotype (GT), GT subtype, fibrosis stage, and the treatment regimen itself (Table 1).

2.1 | Optimizing therapy by maximizing SVR rates in HCV GT1-infected patients

Clinical trial data for interferon-free DAA combinations have shown that adding ribavirin results in higher SVR rates in select GT1-infected patients. However, it should be recognized that, even without ribavirin, highly potent DAA combinations that target multiple components of the HCV lifecycle have a high barrier to resistance and achieve nearly universal on-treatment rates of undetectable HCV ribonucleic acid (RNA). Therefore, in most cases, adding ribavirin maximizes SVR rates by reducing post-treatment viral relapse, presumably through action within hepatocytes.

Sofosbuvir, a nucleotide analogue NS5B inhibitor, has been evaluated in combination with the NS5A inhibitor ledipasvir with and without ribavirin in patients with GT1 infection in the phase 3 trials, ION-1, ION-2 and ION-3.[15–17] Among treatment-naive patients recruited in ION-1 (N=865) and ION-3 (N=647), SVR rates in all treatment arms were high and adding ribavirin did not appear to confer additional benefit over that observed with ledipasvir/sofosbuvir.[15, 17] However, among treatment-experienced patients recruited in ION-2 (N=440), the addition of ribavirin was shown to increase SVR rates compared with ledipasvir/sofosbuvir in certain patient subsets.[16] For example, 4/87 (4.6%) patients without cirrhosis treated for 12 weeks with ledipasvir/sofosbuvir and no ribavirin experienced post-treatment viral relapse, compared with 0/89 of their counterparts treated with ribavirin. Furthermore, the relatively few patients infected with the HCV GT1b subtype, with or without cirrhosis, tended to achieve a numerically lower SVR rate when treated for 12 weeks without ribavirin (20/23 [87.0%]), compared with those treated for 12 weeks with ribavirin (23/23 [100%]).[16] However, it is difficult to draw conclusions from study samples that were not powered to detect differences within subpopulations, and may explain why the approval for 12-week treatment with ledipasvir/sofosbuvir in treatment-experienced patients without cirrhosis does not include the use of ribavirin for either GT1 subtype.[18, 19] Conversely, the lack of benefit with ribavirin seemed clear in GT1-infected treatment-experienced cirrhotic patients treated for 24 weeks. Treatment with ledipasvir/sofosbuvir with or without ribavirin for 24 weeks achieved SVR rates of 100% (n=22 in each), while treatment for 12 weeks with or without ribavirin achieved SVR rates of 82% and 86% respectively (n=22 in each).[16] This led to what seemed like the incontrovertible recommendation that 24-week ledipasvir/sofosbuvir treatment in patients with compensated cirrhosis be administered without ribavirin.[18, 19] However, in the SIRIUS study (N=155) of GT1-infected patients with cirrhosis who had failed therapy with peginterferon/ribavirin and a protease inhibitor, treatment with ledipasvir/sofosbuvir with ribavirin for 12 weeks achieved a similar SVR rate to treatment with ledipasvir/sofosbuvir alone for 24 weeks (96% and 97%, respectively).[20] This again highlights the need to ensure that studies are adequately powered to evaluate important sub-groups. Inclusion of only 22 treatment-experienced patients with cirrhosis in each arm of ION-2 led to the incorrect conclusion that ribavirin was of no benefit.

A pooled analysis of phase 2 and 3 studies, including the SIRIUS study, provided additional evidence that ribavirin may enhance SVR rates in a 12-week ledipasvir/sofosbuvir regimen in the subset of treatment-experienced HCV GT1-infected patients with compensated cirrhosis.[21] With 12 weeks of treatment, SVR rates were numerically higher with ribavirin than without (95.6% [152/159] vs 90.1% [64/71]), whereas there was no evidence of a ribavirin-related efficacy boost in those treated for 24 weeks.[21] Subsequently, prescribing information has been updated to include an alternative recommendation of 12 weeks ledipasvir/sofosbuvir with ribavirin for patients with compensated

TABLE 1 Comparative data evaluating the role of ribavirin in the treatment of GT1 HCV

Patient characteristics			Treatment regimen			
Prior treatment	**Genotype**	**Cirrhosis, Y/N (%)**	**First author/study name**	**Treatment**	**Duration**	**SVR, n/N (%)**
Naive	1	Y (5)[a,b]	McHutchinson et al. (1998)[1]	IFN vs IFN + RBV	24 wks 48 wks	3/167 (2) vs 26/164 (16) 11/162 (7) vs 46/166 (28)
Naive	1, 4, 5, 6	Y (4)[a,b]	Poynard et al. (1998)[77]	IFN vs IFN + RBV	48 wks	20/179 (11) vs 56/180 (31)
Naive	1	Y (13)[b,c]	Fried et al. (2002)[2]	PegIFN vs PegIFN + RBV	48 wks	30/145 (21) vs 138/297 (46)
Naive	1	Y (16)	ION-1[15]	LDV/SOF vs LDV/SOF + RBV	12 wks 24 wks	211/214 (99) vs 211/217 (97) 212/217 (98) vs 215/217 (99)
Naive	1	N	ION-3[17]	LDV/SOF vs LDV/SOF + RBV	8 wks	202/215 (94) vs 201/216 (93)
PegIFN ± NS3/4A PI	1	Y (20)	ION-2[16]	LDV/SOF vs LDV/SOF + RBV	12 wks 24 wks	102/109 (94) vs 107/111 (96) 108/109 (99) vs 110/111 (99)
PegIFN ± RBV or naive	1	Y (100)[b]	Reddy et al. (2015)[21]	LDV/SOF vs LDV/SOF + RBV	12 wks 24 wks	109/118 (92) vs 196/204 (96) 103/133 (98) vs 58/58 (100)
PegIFN/RBV; PegIFN/RBV + PI or naive	1 or 4	Y (67)	SOLAR-1[42,a]	LDV/SOF + RBV	12 wks 24 wks	152/168 (90) 151/163 (93)
Experienced or naive	1 or 4	Y	SOLAR-2[43]	LDV/SOF + RBV	12 wks post-transplant[d] 24 wks post-transplant[d] 12 wks pre/post-transplant[e] 24 wks pre/post-transplant[e]	82/86 (95) 64/65 (98) 61/72 (85) 60/68 (88)
Experienced or naive	1, 4	Y (50)	Reddy et al. (2014)[92]	LDV/SOF + RBV	12 wks 24 wks	103/112 (92) 96/102 (94)
PegIFN/RBV + PI	1	Y (100)	SIRIUS[20]	LDV/SOF vs LDV/SOF + RBV	12 wks 24 wks	74/77 (96) 75/77 (97)
PegIFN/RBV	1	N	COSMOS[34]	SMV + SOF vs SMV + SOF + RBV	12 wks 24 wks	13/14 (93) vs 26/27 (96) 14/15 (93) vs 19/24 (79)
Experienced or naive	1a	N	OPTIMIST-1[35]	SMV + SOF	8 wks 12 wks	92/116 (79) 112/116 (97)
Experienced or naive	1b	N	OPTIMIST-1[35]	SMV + SOF	8 wks 12 wks	36/39 (92) 38/39 (97)
Naive	1	N	AVIATOR[93]	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	12 wks	70/79 (89)[f] vs 76/79 (96)[f]
Naive	1a	N	PEARL-IV[30]	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	12 wks	185/205 (90) vs 97/100 (97)
Naive	1b	N	PEARL-III[28–30]	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	12 wks	209/209 (100) vs 209/210 (99.5)
PegIFN/RBV	1b	N	PEARL-II[28,29,31]	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	12 wks	91/91 (100) vs 86/88 (98)
Naive	1a	N	SAPPHIRE-I[26, 28, 29]	OBV/PTV/r + DSV + RBV	12 wks	308/322 (96)

(continues)

TABLE 1 (continued)

Patient characteristics			Treatment regimen			
Prior treatment	**Genotype**	**Cirrhosis, Y/N (%)**	**First author/study name**	**Treatment**	**Duration**	**SVR, n/N (%)**
Naive	1b	N	SAPPHIRE-I[26]	OBV/PTV/r + DSV + RBV	12 wks	148/151 (98)
PegIFN/RBV	1a	N	SAPPHIRE-II[27]	OBV/PTV/r + DSV + RBV	12 wks	166/173 (96)
PegIFN/RBV	1b	N	SAPPHIRE-II[27]	OBV/PTV/r + DSV + RBV	12 wks	119/123 (97)
PegIFN/RBV or naive	1a	Y (100)	TURQUOISE-II[28, 29, 32]	OBV/PTV/r + DSV + RBV	12 wks 24 wks	124/140 (89) 115/121 (95)
PegIFN/RBV or naive	1b	Y (100)	TURQUOISE-II[32]	OBV/PTV/r + DSV + RBV	12 wks 24 wks	67/68 (99) 51/51 (100)
PegIFN/RBV or naive	1b	Y (100)	TURQUOISE-III[33]	OBV/PTV/r + DSV	12 wks	60/60 (100)
PegIFN/RBV + telaprevir or boceprevir or naive	1	N	Sulkowski et al. (2014)[67]	DCV + SOF vs DCV + SOF + RBV	12 wks 24 wks	41/41 (100) vs 39/41 (95) 35/35 (100) vs 34/35 (97)
Experienced or naive	1–6	Y (30)	ALLY-1[94]	DCV + SOF + RBV	12 wks	100/113 (88)
PegIFN/RBV or naive	1a	Y (67)[b]	C-WORTHY[58]	GZR + EBR vs GZR + EBR + RBV	12 + 18 wks combined	76/82 (93) vs 76/81 (94)
PegIFN/RBV or naive	1b	Y (67)[b]	C-WORTHY[58]	GZR + EBR vs GZR + EBR + RBV	12 + 18 wks combined	40/41 (98) vs 46/46 (100)
PegIFN/RBV (non-responder)	1	Y[a]	Jacobson et al. (2015)[37]	GZR + EBR vs GZR + EBR + RBV	12 wks 16 + 18 wks combined	34/37 (92) 33/33 (100)
PegIFN/RBV ± telaprevir or bocerprevir (prior on-treatment failure)	1a	Y (36)[b]	Thompson et al. (2015)[38]	GZR + EBR vs GZR + EBR + RBV	12 wks 16 + 18 wks combined	62/69 (90) vs 75/80 (94) 49/52 (94) vs 54/54 (100)
Naive	1b	N	Serfaty et al. (2015)[40]	GZR + EBR vs GZR + EBR + RBV	8 wks	29/31 (94) vs 27/30 (90)
Experienced or naive	1a	Y (100)	C-SALT[45]	GZR + EBR	12 wks	24/27 (89)
Experienced or naive	1b	Y (100)	C-SALT[45]	GZR + EBR	12 wks	3/3 (100)

DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; NR, not reported; OBV, ombitasvir; PegIFN, pegylated interferon; PI, protease inhibitor; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

[a]Excludes decompensated cirrhosis.

[b]Proportion of cirrhotic patients across the whole study population (data are not provided for subgroups presented here).

[c]Cirrhosis or bridging fibrosis.

[d]Patients with METAVIR score F0–F3 or Child-Pugh score A.

[e]Patients with Child-Pugh score B or C.

[f]Sustained virological response at 24 wks (SVR24).

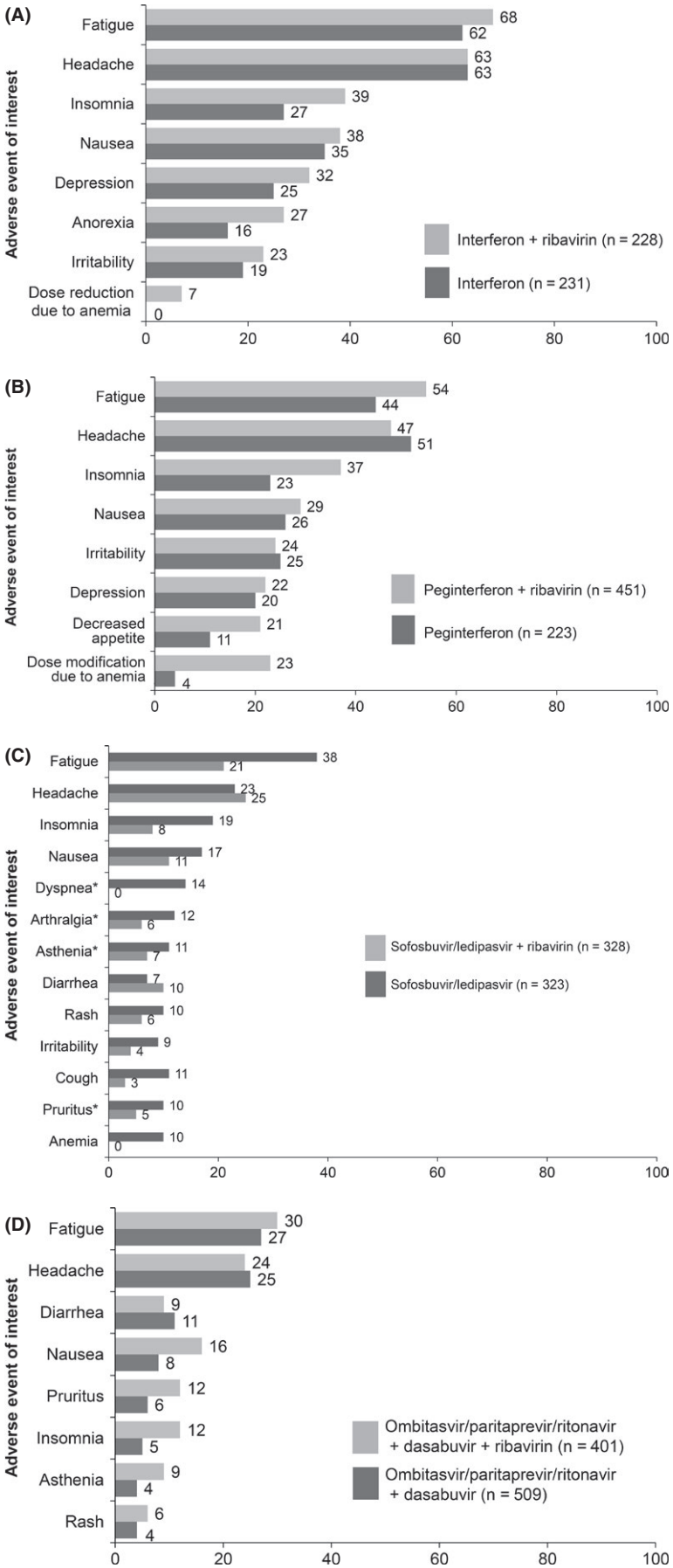

FIGURE 1 Incidence of AEs of interest with ribavirin-containing and ribavirin-free regimens (% of patients). (A) Interferon with or without ribavirin for 24 wks in patients with all HCV GTs.[1] (B) Pegylated interferon with or without ribavirin for 48 wks in patients with all HCV GTs.[2] (C) Ledipasvir/sofosbuvir with or without ribavirin for 12 wks in treatment-naive or treatment-experienced patients with GT1 HCV (pooled data from two phase 3 studies).[15,16] (D) Ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin for 12 wks in treatment-naive or treatment-experienced patients with GT1 HCV (pooled data from eight phase 2 or 3 studies)[79] *Data only reported from one of the two studies pooled in this analysis. AE, adverse event; GT, genotype; HCV, hepatitis C virus.

cirrhosis who have failed a prior course of therapy.[18, 19] Among patients with compensated cirrhosis, European Association for the Study of the Liver (EASL) guidelines recommend treatment with ledipasvir/sofosbuvir with ribavirin for 12 weeks in both treatment-naive and treatment-experienced patients,[22] whereas American Association for the Study of Liver Diseases (AASLD) guidelines recommend ledipasvir/sofosbuvir for 12 weeks without ribavirin in treatment-naive patients and ledipasvir/sofosbuvir for 12 weeks with ribavirin or 24 weeks without ribavirin in treatment-experienced patients.[23]

Similar observations have recently been made in real-world clinical practice. Results from a sub-analysis of the TRIO Network that evaluated the efficacy of ledipasvir/sofosbuvir with or without ribavirin in treatment-experienced cirrhotic patients, albeit with low patient numbers, showed numerically higher SVR rates in those receiving ledipasvir/sofosbuvir with ribavirin for 12 weeks (96%, 25/26) compared with those receiving ledipasvir/sofosbuvir without ribavirin for 12 (84%, 102/121) or 24 weeks (92%, 303/329).[24]

Closer inspection of pooled ledipasvir/sofosbuvir data suggests that the benefit of ribavirin seems to be greatest in those with RASs detectable at baseline. In a pooled analysis of GT1-infected treatment-naive and treatment-experienced patients with compensated cirrhosis and detectable NS5A RASs at baseline, the addition of ribavirin resulted in numerically higher SVR rates (12 weeks: 88% [without ribavirin] vs 94% [with ribavirin]; 24 weeks: 85% vs 100%), by reducing rates of relapse.[25] The impact on the rate of SVR12 was predominantly observed in HCV GT1a-infected treatment-experienced cirrhotic patients with baseline NS5A RASs that conferred >100-fold shift in EC_{50}. Conversely, in patients without detectable NS5A RASs at baseline, SVR rates were unaffected by treatment extension or addition of ribavirin.[25] These data suggest that ribavirin may improve DAA efficacy in patients infected with a detectable proportion of resistant HCV, but the mechanism of this effect remains poorly understood.

The possible benefit of ribavirin addition in patients with GT1a infection has also been demonstrated in those receiving the approved combination of ombitasvir (an NS5A inhibitor), paritaprevir (an NS3/4A protease inhibitor, pharmacokinetically enhanced by ritonavir co-administration) and dasabuvir (a non-nucleoside NS5B inhibitor). In the randomized, placebo-controlled SAPPHIRE trials, overall SVR rates of 96% were demonstrated in GT1a treatment-naive and -experienced patients without cirrhosis who received 12 weeks of ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin.[26–29] Subsequently, a set of randomized, regimen-controlled trials examined the efficacy and safety of this 12-week regimen with and without ribavirin in treatment-naive patients without cirrhosis, infected with either HCV GT1a (PEARL-IV)[30] or HCV GT1b (PEARL-III),[30] or treatment-experienced, GT1b-infected patients (PEARL-II).[31] These trials showed that ribavirin confers a possible benefit in treatment-naive, GT1a-infected patients without cirrhosis, in whom it numerically increased SVR rates from 90% to 97%.[30] In contrast, in GT1b-infected patients without cirrhosis, 100% (300/300) SVR rates were achieved without ribavirin, even among those with a null response to prior peginterferon plus ribavirin therapy.[28–31] In the TURQUOISE-II study (N=380), which enrolled HCV GT1-infected, treatment-naive and -experienced patients with cirrhosis, SVR12 rates were high in both GT1b- (99.2% [118/119]) and GT1a-infected (91.6% [239/261]) individuals treated with ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin for 12 or 24 weeks.[28, 29, 32] The longer therapy duration improved the SVR rate in GT1a-infected patients with a prior null response to peginterferon plus ribavirin, but conferred no additional benefit in the rest of the patient population. The high response in HCV GT1b patients with ribavirin led to the TURQUOISE-III study, a single-arm (N=60) trial, to evaluate whether HCV GT1b-infected patients with cirrhosis could be effectively treated with the 12-week ribavirin-free ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen. All 60 patients achieved SVR12; however, because of the small number of patients enrolled into the study, 95% confidence intervals were 94%–100%.[33] Collectively, these data for ombitasvir/paritaprevir/ritonavir plus dasabuvir show that adding ribavirin is useful for HCV GT1a but does not confer additional benefit in HCV GT1b-infected patients, even those with compensated cirrhosis.

These examples demonstrate that, with multiple DAA regimens, ribavirin may maximize SVR rates through reducing relapse rates in select HCV GT1-infected patients, particularly those with GT1a, in which a lower barrier to resistance has been demonstrated with the protease, NS5A, and non-nucleotide polymerase inhibitor classes compared. In combination with GT1b agents with a higher barrier to resistance, particularly nucleotide polymerase inhibitors, the ribavirin effect is less clear.

However, small studies may be misleading. Ribavirin did not appear to affect the SVR12 rates in the COSMOS trial (N=167), which randomized HCV GT1-infected, treatment-naive or -experienced patients to receive sofosbuvir and the NS3/4A protease inhibitor simeprevir, with and without ribavirin, for 12 or 24 weeks.[34] The high SVR rates in all groups suggested that ribavirin was of no benefit and that the Q80K substitution, which affects the response of HCV GT1a-infected patients to simeprevir, did not have a major impact in this trial (although four of the six relapsers in this study had this polymorphism).[34] However, the larger phase 3 OPTIMIST-1[35] and OPTIMIST-2 trials[36] showed that, with sofosbuvir and simeprevir, the presence of the Q80K substitution at baseline was associated with lower SVR rates with 12 weeks of therapy in patients with cirrhosis and lower SVR rates when treatment was shortened to 8 weeks in non-cirrhotic patients. Extending therapy to 12 weeks in the non-cirrhotic group overcame the effect of the baseline Q80K polymorphism. Based on the COSMOS results, neither addition of ribavirin nor extended treatment duration to 24 weeks were evaluated in the OPTIMIST trials.[35,36] Both of these strategies have proven useful to overcome resistance in other studies, and one wonders whether either approach would have improved SVR rates with this regimen.

Recently, pooled analyses of phase 2 and 3 trials of the second-wave NS5A inhibitor, elbasvir, and the second-generation protease inhibitor, grazoprevir, have demonstrated a role for ribavirin in select HCV GT1-infected populations. A pooled analysis of HCV GT1-infected patients with compensated cirrhosis demonstrated that including ribavirin and extending therapy from 12 to 16/18 weeks increased the SVR rate from 92% to 100% in the

subset of non-responders to prior peginterferon plus ribavirin therapy (Table 1).[37] A similar numerical increase in SVR rate was observed when ribavirin was included and therapy was extended from 12 to 16/18 weeks in HCV GT1a-infected patients with on-treatment failure to prior therapy with peginterferon plus ribavirin with or without a first-generation protease inhibitor (90% vs 100%; Table 1).[38] Closer analysis shows again that the effect of ribavirin relates to overcoming the impact of baseline RASs. In both treatment-naive and treatment-experienced patients with GT1a infection, baseline NS5A RASs significantly reduced the likelihood of SVR. In the treatment-experienced population, extension of grazoprevir/elbasvir therapy from 12 to 16/18 weeks with the addition of ribavirin overcame the effect of baseline RASs, with 100% of patients achieving SVR, compared with 76% of those who received 12 weeks of therapy without ribavirin.[39] Extension of treatment was unnecessary in those without baseline RASs, with similar response rates with 12 or 16/18 weeks of therapy with or without ribavirin (96% vs 100%).[39] The effect of adding ribavirin in treatment-naive patients was not analysed; however, the U.S. Food and Drug Administration (FDA) has recommended baseline NS5A RAS testing prior to starting grazoprevir/elbasvir in all patients with GT1a infection, with the recommendation to extend therapy to 16 weeks and add ribavirin in those who test positive. Notably, in a pooled analysis of non-cirrhotic, treatment-naive patients with GT1b infection, baseline RASs had no effect on response rates for 8 weeks of grazoprevir/elbasvir therapy with or without ribavirin (90% vs 94%; Table 1).[40] Collectively, these data suggest that ribavirin increases the barrier to resistance, which is particularly relevant for patients with GT1a infection receiving regimens that include DAAs with low barriers to resistance such as NS5A inhibitors, protease inhibitors and non-nucleoside NS5B inhibitors.

2.2 | Optimizing therapy by shortening treatment duration in HCV GT1-infected patients

Recent data, particularly in patients with cirrhosis, have shown that adding ribavirin to DAA regimens may allow for shortened treatment durations without reducing SVR rates. As discussed above, a pooled analysis of phase 2 and 3 trials in HCV GT1-infected patients with cirrhosis receiving ledipasvir/sofosbuvir for 12 or 24 weeks showed that ribavirin can boost SVR rates in patients treated for 12 weeks, while ribavirin confers little additional benefit in those treated for 24 weeks, suggesting that ribavirin compensates for reducing the length of treatment.[21] Combined with the results from the SIRIUS study,[20] also discussed above, these data suggest a role for ribavirin in reducing the treatment duration of ledipasvir/sofosbuvir in treatment-experienced patients with cirrhosis.[20,21]

Further insight into ribavirin's potential to shorten DAA treatment duration will come from the multitude of "real-world" studies currently underway. Interim results from the HEPATHER French cohort study support trial data. The addition of ribavirin to 24 weeks of daclatasvir and sofosbuvir for HCV GT1-infected patients was of no clear benefit (SVR12 98% [61/62] with and 93% [172/184] without); however, with a 12-week course of treatment, the addition of ribavirin increased SVR rates from 85% (45/53) to 100% (11/11). Although these data support the concept that ribavirin may allow shorter treatment duration, the small number of patients and the non-randomized nature of this study limit interpretation of results.[41]

2.3 | Optimizing therapy in other HCV GT1-infected patient populations

In the interferon era, patients with very advanced liver disease were highly challenging to treat because of poor efficacy and increased toxicity. Consequently, there has been an urgent medical need for safer and more effective treatment options. Well-tolerated oral DAA therapies have changed the options for these patients dramatically, but results from clinical trials of DAA regimens have shown that, in many cases, ribavirin is still of benefit.

2.3.1 | Decompensated liver disease and preliver transplant

Until recently, few data existed for patients with decompensated cirrhosis. Initial trials of ledipasvir/sofosbuvir (SOLAR-1/SOLAR-2) and daclatasvir and sofosbuvir (ALLY-1) included low-dose ribavirin and have shown SVR rates of >85% or >55% in patients with Child-Pugh B or C cirrhosis, respectively.[42–44] It is unknown whether excluding ribavirin would have changed treatment outcomes. The phase 2 C-SALT study evaluated the efficacy and safety of elbasvir/grazoprevir without ribavirin in 30 patients with HCV GT1 and Child-Pugh B cirrhosis, and showed an overall SVR rate of 90%.[45] Whether adding ribavirin would confer additional benefit is unclear. The only study to look at the role of ribavirin in decompensated patients was the recently completed phase 3, ASTRAL-4 study that investigated the efficacy and safety of the DAA combination sofosbuvir/velpatasvir (pan-genotypic NS5A inhibitor) with or without ribavirin in patients classified with Child-Pugh B cirrhosis.[46] Numerically higher SVR12 rates were achieved in HCV GT1-infected patients receiving 12 weeks of sofosbuvir/velpatasvir with ribavirin (96%; 65/68) vs those without ribavirin (88%; 60/68).[46] Moreover, the study suggested that extending treatment duration to 24 weeks in the absence of ribavirin (92%; 65/71) may be less effective than addition of ribavirin to 12 weeks of sofosbuvir/velpatasvir treatment in patients with decompensated cirrhosis.[46] These results may retrospectively vindicate the decision to perform the earlier SOLAR-1, -2, and ALLY-1 studies in decompensated patients only with ribavirin. Patients with decompensated cirrhosis tend to be more difficult to treat and have lower SVR rates compared with patients with compensated cirrhosis.[47] The reasons for this are unclear; however, addition of ribavirin may be important to maximize SVR rates in this patient population. Of note, in ASTRAL-4, a weight-based ribavirin dose of 1000–1200 mg/day was used compared with a lower ribavirin starting dose of 600 mg in the SOLAR and ALLY-1 studies (increased doses as tolerated were used in SOLAR-1 and -2).[42–44,46]

For patients with detectable HCV at the time of transplant, posttransplant recurrence of HCV in the graft is universal[48] and, therefore, HCV-infected patients on liver transplant waiting lists remain a

population with high unmet medical need. Limited data are available for patients in the pretransplant setting; however, a small phase 2 study of sofosbuvir plus ribavirin for 12 weeks demonstrated prevention of HCV recurrence in 70% (30/43) of patients with HCV-related liver cancer who achieved an HCV RNA of <25 IU/mL prior to transplant.[49] Although addition of ribavirin is likely beneficial over sofosbuvir monotherapy, whether the use of a second DAA would achieve similar benefits is unknown. Ribavirin was again fairly well tolerated even in these patients with advanced cirrhosis.

2.3.2 | Post-liver transplant

Similar to trials in patients with decompensated liver disease, most studies in post-liver transplant recipients have not been designed to formally evaluate ribavirin's role. In the post-transplant setting, SVR rates of 70% (28/40 patients) have been described with sofosbuvir plus ribavirin.[50] Although these rates seem suboptimal compared to the non-transplant setting, it is important to remember that trials included patients with fibrosing cholestatic hepatitis and recurrent cirrhosis post-transplant. Trials of regimens that combine DAAs and ribavirin have shown higher SVR rates in transplant recipients, including ledipasvir/sofosbuvir plus ribavirin, which yielded SVR rates of 95%–98% (SOLAR-1 and SOLAR-2),[42,43] and daclatasvir and sofosbuvir plus ribavirin, which yielded SVR rates of 95% (ALLY-1).[44] To date, all trials of ledipasvir/sofosbuvir, and daclatasvir and sofosbuvir, have included ribavirin. Given concerns about tolerability, ribavirin has been started at a lower dose in the post-transplant setting (typically 600 mg daily) with no obvious clinical consequence; however, higher (or lower doses) have not been evaluated. In part 1 of the CORAL-1 study, an SVR rate of 97% was reported in 34 liver transplant recipients with HCV GT1 who received ombitasvir/paritaprevir/ritonavir and dasabuvir plus ribavirin for 24 weeks.[51] Whether ribavirin plays an important role for HCV GT1-infected liver transplant recipients without cirrhosis has been evaluated in part 2 of the CORAL-I study.[52] In part 2, HCV GT1b-infected patients who were either treatment-naive or prior relapsers to peginterferon/ribavirin were treated with 24 weeks of ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin. All 13 patients achieved SVR, reinforcing the high barrier to resistance in GT1b-infected patients that allows for the exclusion of ribavirin.[52] Patients with GT1a infection and those with GT1b infection who were prior non-responders were treated with 24 weeks of ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin; 26 of 27 (96%) achieved SVR.[52]

The real-world effectiveness of sofosbuvir-containing regimens in the post-transplant setting, with or without ribavirin, is being evaluated in the observational HCV-TARGET study[53] and the French prospective CUPILT study.[54] To date, an SVR4 rate of 91% (52/57 patients) has been described with simeprevir and sofosbuvir, compared with 82% (9/11 patients) with simeprevir and sofosbuvir plus ribavirin in the HCV-TARGET cohort.[53] In the CUPILT study, treatment with daclatasvir and sofosbuvir for 12 or 24 weeks has yielded SVR12 rates of 97% (73/75) without ribavirin and 95% (52/55) with ribavirin.[54] In both studies, the lack of randomization and the low patient numbers, particularly in the ribavirin-containing groups, limited any conclusions regarding whether there is a role for ribavirin in liver transplant patients as part of this regimen.

2.3.3 | Renal impairment

Currently patients with severe renal impairment have limited treatment options and there remains urgent medical need to evaluate DAA regimens in these patients. Using ribavirin in this setting is problematic because of the renal excretion of ribavirin and its metabolites resulting in an increase in drug exposure and potential toxicities.[55] However, a reduced daily dose of 200 mg of ribavirin can be administered to patients with severe renal impairment, including those who are undergoing haemodialysis.[14] The RUBY-I study investigated the efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with (HCV GT1a) and without (HCV GT1b) low-dose ribavirin for 12 weeks in patients with severe renal impairment or end-stage renal disease.[56, 57] Results show that 90% (18/20) of patients achieved an SVR. Of the two patients who failed to achieve an SVR, one GT1a-infected patient experienced virological relapse and one patient died after the end of treatment because of reasons not attributed to DAAs or ribavirin.[57] However, in patients with HCV GT1a infection and who received ribavirin, anaemia was responsible for nine out of 13 patients requiring ribavirin dose interruption, and four requiring erythropoietin.[57] No patient underwent a blood transfusion.[57] Given ribavirin's relatively poor tolerability in patients with chronic kidney disease, and the relatively high SVR rates without ribavirin in patients with normal renal function, even those patients with GT1a,[15, 16, 30, 58, 59] the role of ribavirin for GT1a-infected patients with chronic kidney disease is currently being evaluated in the ongoing RUBY-II study.[60]

The large C-SURFER study demonstrated that the DAA combination of elbasvir/grazoprevir without ribavirin was well tolerated and achieved an SVR rate of 94% in HCV GT1-infected patients with chronic kidney disease.[61] These data suggest that ribavirin is not needed with elbasvir/grazoprevir to optimize efficacy in HCV GT1a-infected patients with severe renal impairment. The reason for the apparent capacity to omit ribavirin in GT1a-infected patients with renal failure but not, as in C-EDGE, patients with normal renal function (in whom baseline RASs had an adverse impact)[59, 61] is unclear but may be related to the lower baseline HCV RNA levels seen in patients with advanced renal disease, somewhat mitigating the effect of baseline RASs in this population. Additional data focusing specifically on GT1a patients with renal failure and baseline RASs would be useful to definitively evaluate whether ribavirin is entirely dispensable in regimens lacking a nucleotide polymerase inhibitor in this setting.

2.3.4 | Human immunodeficiency virus/HCV co-infection

In patients co-infected with human immunodeficiency virus (HIV)/HCV, there is a general lack of head-to-head comparative data with and without ribavirin, and most ongoing clinical trials are currently evaluating ribavirin-free therapy.[62–65] Although the reluctance to use ribavirin in co-infected patients may stem from concerns about

additive drug toxicity with antiretroviral therapy, results in co-infected patients have been shown to be generally similar to those seen with HCV mono-infection, suggesting that ribavirin should play a similar clinical role in both populations. International guidelines recommend that HIV/HCV co-infected persons be treated and retreated the same as HCV-infected persons without HIV infection.[22, 23] Therefore, the addition of ribavirin may also be considered to maximize efficacy rates in specific subgroups of patients with HIV/HCV co-infection.

2.4 | Optimizing therapy in patients infected with HCV genotypes other than GT1

Results from clinical trials until now have shown that ribavirin confers benefit in select patients with HCV GT1. To date, many of the same insights into ribavirin's role seen with HCV GT1 have been seen in those with other genotypes.

2.4.1 | Genotype 2 or 3

Several phase 2 studies have provided insights into the importance of treating HCV GT2 and GT3 patients with ribavirin. The ELECTRON study evaluated the single DAA sofosbuvir plus ribavirin (weight-based [<75 kg, 1000 mg/day; ≥75 kg, 1200 mg/day] or reduced dose [800 mg/day]) for 8–12 weeks in treatment-naive and treatment-experienced patients.[66] SVR rates in this study showed that durations of less than 12 weeks (8 weeks [64%] vs 12 weeks [100%]) or 12 weeks with a reduced ribavirin dose (weight-based [100%] vs low dose [60%]) may adversely impact efficacy in patients with HCV GT2 or GT3.[66] One small, phase 2, open-label study evaluated the DAA combination of daclatasvir and sofosbuvir for 24 weeks with and without ribavirin in treatment-naive patients with HCV GT2 and GT3.[67] Although SVR rates were numerically higher in those who received ribavirin (100%) than in those who did not (93%), with only 14 patients per arm, it is difficult to evaluate the true value of ribavirin in this population.[67] The phase 3 ALLY-3 and ALLY-3+ trials in HCV GT3-infected patients evaluated daclatasvir and sofosbuvir for 12 weeks without ribavirin and for 12 or 16 weeks with ribavirin, respectively. Among patients with cirrhosis, numerically higher SVR rates were achieved in ALLY3+ with both the 12- and the 16-week regimens of daclatasvir and sofosbuvir plus ribavirin (83% [15/18] and 89% [16/18], respectively) vs the 12-week regimen without ribavirin (65% [22/34]) in ALLY-3.[68] Further analysis showed that the effect of ribavirin on SVR rates was related to overcoming the impact of baseline RASs. However, an interim analysis evaluating the efficacy of daclatasvir and sofosbuvir with and without ribavirin in clinical practice has shown that very high SVR rates are achieved without ribavirin, including in patients with GT3 infection and compensated cirrhosis, and the addition of ribavirin does not confer additional benefit.[69]

Furthermore, it appears that most ongoing trials investigating second-wave DAA combinations, such as the ASTRAL and SURVEYOR studies evaluating the efficacy and safety of sofosbuvir/velpatasvir and ABT-493 (NS3/4A protease inhibitor) plus ABT-530 (NS5A inhibitor), respectively, in patients with HCV GT2 and GT3 infection are doing so without the use of ribavirin.[70–72]

Patients with HCV GT2 and GT3 infection were treated with sofosbuvir/velpatasvir for 12 weeks in the ASTRAL-2 and ASTRAL-3 studies, respectively.[70] Although the effect of ribavirin was not assessed in these studies, high SVR rates were achieved in HCV GT2-infected patients (99%; 133/134); however, relatively low SVR rates were observed in specific patient populations in the ASTRAL-3 study. Overall, 95% (264/277) of HCV GT3-infected patients achieved an SVR, with treatment-experienced patients with and without cirrhosis achieving numerically lower SVR rates of 89% (33/37) and 91% (31/34), respectively.[70] In a pooled analysis of the ASTRAL studies that included GT3-infected patients in ASTRAL-3, the SVR rate in patients with GT3 infection was numerically lower in those with baseline NS5A RASs vs those without (88% [28/32] vs 97% [235/242]).[73] Although the use of ribavirin has not yet been studied in this population, the AASLD/Infectious Diseases Society of America (IDSA) guidance document has recently recommended that ribavirin be added to sofosbuvir/velpatasvir for 12 weeks in all GT3 patients with cirrhosis and treatment-experienced non-cirrhotic patients who have baseline Y93 substitutions.[23]

2.4.2 | Genotype 4

A small number of HCV GT4-infected patients were included in the phase 3 studies of elbasvir/grazoprevir, C-EDGE[59] and C-SCAPE.[74] Initial observations suggest that ribavirin may confer benefit by maximizing SVR rates. C-EDGE enrolled treatment-experienced patients with and without cirrhosis, and irrespective of treatment duration, SVR rates were higher for patients treated with elbasvir/grazoprevir plus ribavirin compared with the same regimen without ribavirin (12 weeks, 93% [14/15] vs 78% [7/9]; 16 weeks, 100% [8/8] vs 60% [3/5] respectively).[59] Twenty further treatment-naive HCV GT4 patients without cirrhosis were enrolled in C-SCAPE, and treatment with elbasvir/grazoprevir plus ribavirin yielded similar SVR rates (100%, 10/10) compared with those treated without ribavirin (90%, 9/10).[74] Larger studies are needed to confirm ribavirin's role in reducing virological failure in HCV GT4-infected patients with elbasvir/grazoprevir and to evaluate whether specific patient subgroups are likely to require ribavirin (e.g. those with NS5A baseline resistance).

Combination therapy with ombitasvir/paritaprevir/ritonavir also benefits from the addition of ribavirin in patients with HCV GT4.[75] In the PEARL-I study, following treatment with 12 weeks of ombitasvir/paritaprevir/ritonavir, 91% (40/44) of treatment-naive non-cirrhotic patients achieved an SVR compared with 100% (42/42) in those treated with the addition of ribavirin.[75] These data suggest that ribavirin may reduce virological failure rates in HCV GT4-infected patients. Interestingly, all three patients who experienced virological failure were infected with subtype 4d and all had RASs present at the time of virological failure.[75] Adding ribavirin to ombitasvir/paritaprevir/ritonavir may act in preventing the emergence of RASs and removes HCV GT4 subtype-specific responses to therapy. Furthermore, 100% (49/49) of treatment-experienced, non-cirrhotic patients achieved

an SVR with 12 weeks of ombitasvir/paritaprevir/ritonavir plus ribavirin, leading to the recent approval of this regimen for HCV GT4; a ribavirin-free regimen was not explored.[75]

A recent study evaluating the efficacy and safety of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced HCV GT4-infected patients with and without cirrhosis reported SVR rates of 93%.[76] The role of ribavirin was not evaluated.[76]

2.5 | Improved safety and tolerability of ribavirin in combination with interferon-free regimens

A wealth of clinical experience has been amassed with ribavirin over the past 30 years. However, recent data from large, randomized trials of some DAA regimens with and without ribavirin have shown that the safety profile of ribavirin relies heavily on the medications with which it is co-administered. Thus, the AE profile of ribavirin warrants a full re-evaluation in the absence of interferon.

Interferon/peginterferon and ribavirin regimens for chronic HCV had poor tolerability profiles, with relatively high treatment discontinuation rates and declines in haemoglobin to <10 g/dL (Table 2).[1, 2, 77] The introduction of first-generation DAAs, boceprevir and telaprevir, to peginterferon plus ribavirin regimens boosted SVR rates, but was associated with even worse tolerability profiles.[3–7] Current interferon-free DAA regimens are relatively well-tolerated, and while adding ribavirin to these DAA regimens is generally associated with a slightly higher rate of some AEs than ribavirin-free regimens,[15, 16, 30, 31, 78] this does not appear to affect patients' ability to complete treatment. With the interferon-free, all-oral DAA regimens, discontinuation rates because of AEs are typically below 3%, both with and without ribavirin (Table 2).[15, 16, 30, 31, 67, 78] AEs (e.g. fatigue, headache, nausea, cough, rash, dyspepsia, insomnia and dyspnoea; Fig. 1C, D) and serious AEs (Table 2) generally occur much less frequently with interferon-free DAA regimens[15, 16, 30, 31, 67, 78] vs combined interferon/peginterferon and ribavirin regimens[1,2] and boceprevir- and telaprevir-based regimens with peginterferon.[3–7]

As with interferon-containing regimens plus ribavirin, the most common haematological AE in patients who received the newer DAAs plus ribavirin was anaemia. However, both the frequency and clinical severity of anaemia is greatly reduced compared with that observed in the interferon era, and also the frequency of anaemia appears to vary based on the DAA regimen (Table 2).

Data from trials of DAA regimens have demonstrated that patients receiving ribavirin that experienced haemoglobin declines have been able to undergo ribavirin dose modification or discontinuation without negatively impacting SVR rates. For example, ribavirin dose modifications occurred in 7.7% (n=2044) of patients in a safety analysis of ombitasvir/paritaprevir/ritonavir plus dasabuvir, but SVR rates were 98.5% and 96.0% in patients with and without ribavirin dose modifications respectively.[79] This finding is also consistent in patients with cirrhosis: an SVR rate of 100% was achieved in those who received a ribavirin dose modification in the TURQUOISE-II study.[32]

Recently, patient-reported outcomes (PROs), including health-related quality of life and work productivity, have been reported for the phase 3 ION-1, ION-2, and ION-3 trials of ledipasvir/sofosbuvir with or without ribavirin that are discussed above.[80] Although patients receiving ledipasvir/sofosbuvir without ribavirin showed significant improvements (P<.001) in PROs during treatment, those receiving treatment with ribavirin had significant (P<.001) declines in PROs during treatment; however, among patients who achieved SVR12, similar improvements in PROs were observed for both treatment groups post-SVR12.

2.6 | Insights into ribavirin's mechanism of action

Despite its long-standing use, the antiviral mechanism of action of ribavirin remains poorly understood. Multiple mechanisms have been proposed including inosine monophosphate dehydrogenase inhibition,[81, 82] promotion of a Th1 immune response,[81, 83–85] direct inhibition of the HCV polymerase,[86] stimulation of interferon-stimulated genes,[87] and mutagenesis leading to error catastrophe.[88] Although there is some experimental evidence supporting each hypothesis, definitive proof of one mechanism of action is lacking. The lack of experimental models of antiviral relapse, the main target of the clinical effect of ribavirin, makes studies challenging to perform. The clinical data with DAAs have shown that ribavirin delays or possibly prevents the emergence of antiviral resistance and reduces relapse after therapy. These two effects may be linked as most cases of relapse are associated with replication of HCV resistant to one or more of the DAAs used in a given regimen.

Of the proposed theories, mutagenesis by ribavirin is the most compatible with the clinical effects seen. Ribavirin is a guanosine analogue, but unlike most nucleoside/nucleotide analogues, insertion of ribavirin into a nascent HCV genome does not lead to chain termination. Elongation with incorporated ribavirin is able to proceed; however, rather than pair with the natural base, ribavirin incorporation leads to G to U and U to G transitions. These mutations may have fitness effects leading to negative selection of HCV virions able to incorporate ribavirin and, ultimately over time, limiting the quasispecies variability in the circulating virus. Reduced viral diversity may limit the escape capacity of the virus and hence the emergence of resistance in the setting of selective pressure from one or more DAAs. The restricted quasispecies variability may also limit compensatory mutations to overcome fitness deficits in resistant variants. Deep sequencing data support a mutagenic effect of ribavirin, as does mathematical modelling.[89, 90] Although ribavirin may act through multiple mechanisms, how the other proposed mechanisms of action would affect viral relapse and/or the emergence of resistance is less clear. The immunomodulatory functions of ribavirin have been recently comprehensively reviewed.[91]

3 | CONCLUSION

In the all-oral DAA era, there is still an important role for ribavirin in HCV treatment, particularly in the setting of DAAs with a low barrier to resistance, or in patients with features that make them hard to cure. Ribavirin delays or prevents the emergence of resistance, ultimately leading to a lower relapse rate and higher chance of

TABLE 2 Comparative data evaluating the tolerability of ribavirin in GT1 HCV patients treated with interferon-containing and interferon-free regimens

			Safety		
Study name	**Population**	**Regimen**	**SAEs (%)**	**Discontinued treatment because of AE (%)**	**Haemoglobin level (<10 g/dL) (%)**
McHutchinson et al. (1998)[1]	Naive, GT1–3, ±cirrhosis	24 or 48 wks IFN vs IFN + RBV	NR	9 (24 wks) 14 (48 wks) vs 8 (24 wks) 21 (48 wks)	0 (24 wks) 0 (48 wks) vs 7 (24 wks) 9 (48 wks)
Poynard et al. (1998)[77]	Naive, GT1–6, ±cirrhosis	24 or 48 wks IFN vs IFN + RBV	NR	NR (24 wks) 13 (48 wks) vs 8 (24 wks) 19 (48 wks)	NR
Fried et al. (2002)[2]	Naive, GT1–4, ±cirrhosis	PegIFN vs PegIFN + RBV	NR	6 vs 7	[Haemoglobin <12 g/dL in women; <13 g/dL in men] 4 vs 23
ION-1[15]	Naive, GT1, ±cirrhosis	12 or 24 wks LDV/SOF vs LDV/SOF + RBV	<1 (12 wks) 8 (24 wks) vs 3 (12 wks) 3 (24 wks)	0 (12 wks) 2 (24 wks) vs 0 (12 wks) 3 (24 wks)	0 (12 wks) 0 (24 wks) vs 9 (12 wks) 7 (24 wks)
ION-2[16]	PegIFN ± NS3/4A PI, GT1	12 or 24 wks LDV/SOF vs LDV/SOF + RBV	0 (12 wks) 6 (24 wks) vs 0 (12 wks) 3 (24 wks)	0 vs 0	0 (12 wks) 2 (24 wks) vs 2 (12 wks) 8 (24 wks)
ION-3[17]	Naive, GT1, no cirrhosis	8 or 12 wks LDV/SOF vs 8 wks LDV/SOF + RBV	2 (8 wks) 2 (12 wks) vs <1	0 (8 wks) 1 (12 wks) vs <1	0 (8 wks) <1 (12 wks) vs 5
PEARL-IV[30]	Naive, GT1a, no cirrhosis	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	0.5 vs 3	1 vs 0	0 vs 4
PEARL-III[30]	Naive, GT1b, no cirrhosis	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	2 vs 2	0 vs 0	0 vs 9
PEARL-II[31]	PegIFN/RBV, GT1b, no cirrhosis	OBV/PTV/r + DSV vs OBV/PTV/r + DSV + RBV	2 vs 2	0 vs 2	0 vs 1
SAPPHIRE-I[26]	Naive, GT1, no cirrhosis	Placebo vs OBV/PTV/r + DSV + RBV	0 vs 2	0.6 vs 0.6	0 vs 6
SAPPHIRE-II[27]	PegIFN/RBV, GT1, no cirrhosis	Placebo vs OBV/PTV/r + DSV + RBV	1 vs 2	0 vs 1	0 vs 5
TURQUOISE-II[32]	PegIFN/RBV or naive, GT1, with cirrhosis	OBV/PTV/r + DSV + RBV	6	2	9
ALLY-1[94]	Experienced or naive, GT1–6, with cirrhosis	DCV + SOF + RBV	13	2	[haemoglobin <9 g/dL] 6
C-EDGE[59]	PegIFN/RBV, GT1, ±cirrhosis	12 or 16 wks GZR + EBR vs GZR + EBR + RBV	4 (12 wks) 3 (16 wks) vs 3 (12 wks) 4 (16 wks)	1 (12 wks) 0 (16 wks) vs 1 (12 wks) 5 (16 wks)	0 (12 wks) 0 (16 wks) vs 9 (12 wks) 21 (16 wks)

DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; NR, not reported; OBV, ombitasvir; PegIFN, pegylated interferon; PI, protease inhibitor; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; wks, weeks.

SVR. Ribavirin also allows for shortening of therapy, particularly in patients with cirrhosis, without sacrificing efficacy. However, most data in support of a role for ribavirin in the all-oral DAA era are from small studies or subgroups that lack statistical significance. Ribavirin is relatively well tolerated as part of all-oral DAA regimens and the frequency and severity of anaemia is considerably reduced and easy to manage in the absence of interferon. While ribavirin's mechanism(s) of action remain elusive, it has proven harder to replace than expected and, for the time being, continues to play a useful role in HCV therapy.

CONFLICTS OF INTEREST

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ABBREVIATIONS

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; FDA, U.S. Food and Drug Administration; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; peginterferon, pegylated interferon; PRO, patient-reported outcome; RAS, resistance-associated substitution; RNA, ribonucleic acid; SVR, sustained virological response.

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