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Review

Ribavirin: Current role in the optimal clinical management of chronic hepatitis C☆

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Ribavirin in combination with peginterferon alfa shows strong clinical efficacy against chronic hepatitis C, and is now established as the standard of care. However, the precise role of ribavirin is still being defined, suggesting that optimal ribavirin dose should be maintained over the whole treatment period. Ribavirin dosage varies by bodyweight for genotype 1 disease (1000 mg/day in patients ⩽75 kg and 1200 mg/day in patients >75 kg), whereas 800 mg/day is sufficient to ensure optimal response in all genotype 2/3 patients. Similarly, genotype 1 patients benefit from 48 weeks of therapy, while 24 weeks is sufficient for genotype 2/3 disease.

Recent data suggest treatment success is dependent on cumulative ribavirin exposure, as patients who receive <60% of the planned dose have lower response rates, regardless of whether reductions are from temporary interruptions or premature cessation of therapy. All patients should be monitored for hemolytic anemia, as early diagnosis allows management through small dose reductions and stepwise return to the target dose, maximizing cumulative exposure. Despite these recent advances in our knowledge, many questions remain, such as whether the role of ribavirin will change or even be eliminated as new therapies are developed.

***Keywords*: Ribavirin; Chronic hepatitis C; Sustained virological response**

1. Introduction

Ribavirin has been studied for over 20 years as a potential therapy against a number of RNA and DNA viruses, including human immunodeficiency virus, respiratory syncytial virus, parainfluenza virus, lassa fever virus, herpes virus, measles virus and hepatitis C virus (HCV) [1]. Initial studies of ribavirin monotherapy showed limited direct antiviral activity against chronic HCV, with HCV RNA clearance seen in a small percentage (10%) of patients in one study [2] but no effect on viral levels in others [2–6], although improvement of alanine aminotransferase levels was commonly described. Pilot studies conducted around the same time showed much more promising results, when twice-daily ribavirin (1000/1200 mg/day) was added to interferon-alfa therapy (3 MU thrice weekly), resulting in improved end-of-treatment and end-of-follow-up responses [7]. Subsequent large clinical trials confirmed this finding, demonstrating significant improvements in sustained viral response (SVR; defined as undetectable HCV RNA 24 weeks after completion of therapy and reduced levels of relapse following ribavirin combination therapy [8–10].

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More recently, pegylated forms of interferon alfa, [pegylated interferon alfa-2a and pegylated interferon alfa-2b], with longer half-lives than the non-pegylated form allow for weekly dosing. Studies combining ribavirin with peginterferon alfa have consistently demonstrated further improvements in end-of-treatment response (ETR; defined as undetectable HCV RNA at end of therapy) and SVR, largely driven by a decrease in the rate of relapse (Fig. 1) [11–13]. Once-weekly subcutaneous peginterferon alfa plus twice-daily oral ribavirin is now regarded as the standard of care for the treatment of patients with chronic HCV infection.

It is clear that higher response rates are achieved in the majority of patients who are able to tolerate/adhere to ribavirin dosing, indicating the importance of cumulative ribavirin exposure [14]. For this reason, optimization of ribavirin dosing and duration of therapy, accompanied by careful clinical management, is crucial to ensure the best chance of a durable response to therapy. This review will focus on the clinical importance of ribavirin, in particular the selection and maintenance of the optimal ribavirin dosing strategy, to achieving the therapeutic goal of sustained viral suppression in patients with chronic HCV.

2. The impact of genotype on response to ribavirin plus peginterferon alfa in HCV

Combination therapy with peginterferon alfa and ribavirin has demonstrated high SVR rates and correspondingly low rates of virologic relapse in large clinical trials [11–13]. However, response to therapy varies according to HCV genotype. Genotype 2/3 HCV is more responsive to therapy than genotype 1 disease, with comparatively higher SVR rates observed with most therapeutic options studied to date [8,9]. Despite

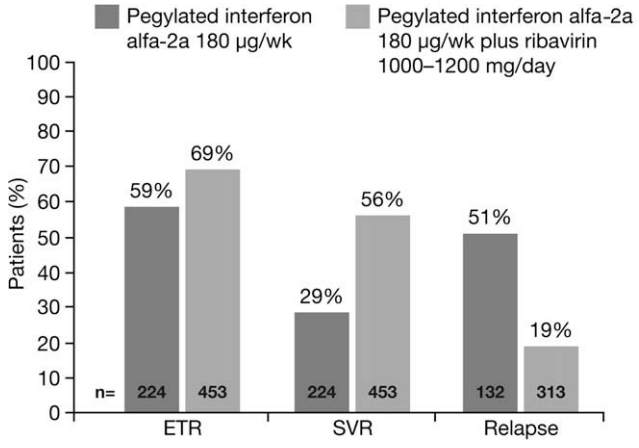

Fig. 1. Increased rates of SVR by prevention of relapse in patients with chronic HCV after the addition of ribavirin to 48 weeks' treatment with pegylated interferon alfa [12].

the good response to therapy in genotype 2/3 patients, there is still a clear benefit of adding ribavirin to therapy with peginterferon alfa, and SVR rates of approximately 80% have been described with this combination [11–13,15–18]. The impact of peginterferon plus ribavirin on response in other HCV genotypes (4, 5 and 6) is less well understood, as these genotypes are less common and tend to be pooled for analysis or excluded from larger trials.

Although patients with genotype 1 disease are generally less responsive to therapy, a sustained response to ribavirin plus peginterferon therapy is still seen in approximately 50% of patients with genotype 1 [11–13,19]. A large, randomized, controlled study, comparing peginterferon alfa-2a alone (180 µg/week) with peginterferon alfa-2a plus ribavirin (1000/1200 mg/day) or interferon alfa-2b (3 MU thrice weekly) plus ribavirin over 48 weeks clearly demonstrated that ribavirin significantly improves outcomes in genotype 1 patients [12]. In this study, SVR rates in genotype 1 patients were highest in the peginterferon alfa-2a plus ribavirin arm (46%), compared with the interferon alfa-2b plus ribavirin arm (36%; $p = 0.01$) or the peginterferon alfa-2a alone arm (21%; $p < 0.001$). Other clinically important endpoints such as rate of relapse and ETR are also favorable when ribavirin is included as part of standard therapy [11,12].

3. Mechanism of action, pharmacokinetics and viral kinetics

A range of mechanisms have been proposed, any or all of which may contribute to the strong antiviral effect observed in clinical practice. Ribavirin is a guanosine analog, which is rapidly absorbed and distributed following oral administration with maximum plasma concentrations reached within approximately 1.5 h. Due to extensive distribution to non-plasma compartments, the apparent volume of distribution is greater than 2000 L. Following multiple dosing, steady state is achieved in approximately 4 weeks with a terminal half-life of approximately 12 days [20]. The main route of elimination is via the kidneys, and it has been suggested that the optimal dosing strategy may be based on renal function, as measured by creatinine clearance, rather than bodyweight, as used currently [21]. Ribavirin alone has a relatively minor antiviral effect in HCV-infected patients, but in combination with peginterferon alfa it appears to enhance the second and third phases of viral decay, thereby reducing the chance of relapse, particularly in patients with low responses to the interferon component of therapy [22–24].

The proposed mechanisms of ribavirin antiviral activity have been reviewed elsewhere [25–27], and suggested mechanisms include error catastrophe resulting from

mutagenesis via incorporation of ribavirin into HCV RNA during replication [28,29], direct inhibition of HCV RNA replication [30,31], inosine-monophospate-dehydrogenase (IMPDH) inhibition [32], and immunomodulation [33,34]. Most attention has been given to the theory that ribavirin acts as a mutagen, and a number of studies have described a significant but in some cases transient increase in mutation rate with ribavirin monotherapy both *in vitro* and *in vivo* [35–37].

However, it is important to note that, while much of the evidence regarding the mode of action of ribavirin is derived from studies of ribavirin monotherapy, strong antiviral activity is only seen when used as combination therapy; indeed synergism between ribavirin and interferon alfa has been demonstrated *in vitro* [38,39], although the mechanism of action driving this synergism has yet to be defined.

Of note, the mutagenic effect of ribavirin appears to be abolished *in vivo* when administered in combination with peginterferon alfa, although this may be due to the activity of peginterferon alfa masking a mutagenic effect [36]. Although debate is ongoing as to which of these modalities are responsible for the antiviral effect of ribavirin in combination with peginterferon alfa, it is clear that ribavirin activity is dose/exposure dependent [14,22,40–42], and selecting and maintaining the optimal starting dose is crucial to the successful management of chronic HCV.

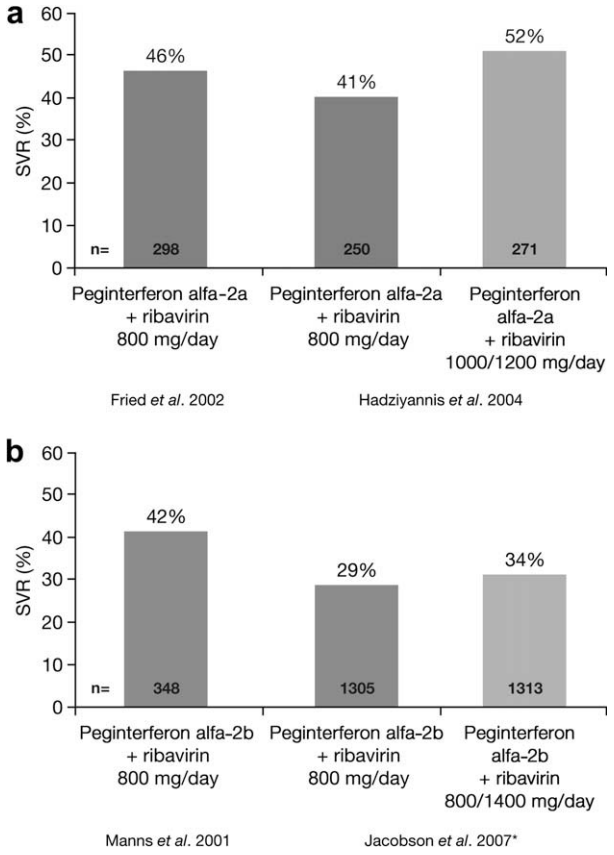

Fig. 2. SVR rates in patients with genotype 1 chronic HCV in pivotal trials of peginterferon alfa plus ribavirin. (a) SVR rates following 48 weeks of peginterferon alfa-2a plus 800 mg/day ribavirin [12] and 48 weeks of peginterferon alfa-2a plus 800 mg/day or standard dose ribavirin at 1000/1200 mg/day [13]. (b) SVR rates following 48 weeks of peginterferon alfa-2b plus 800 mg/day ribavirin [11] and 48 weeks of peginterferon alfa-2b plus ribavirin at 800 mg/day or weight-based dosing at 800–1400 mg/day [43].

4. Clinical considerations in ribavirin dosing

There are several important considerations that a physician must make when prescribing ribavirin, including selecting the appropriate starting dose, maintaining this dose by careful clinical management of any ribavirin-related side effects by incrementally decreasing the ribavirin dose, and determining when to return to the indicated dose following successful side effect management. It is also crucial to continue ribavirin to the end of therapy where possible, as even late discontinuation can have a strong negative impact on clinical outcomes.

4.1. Selecting the appropriate starting dose

A relationship between ribavirin dose and response to therapy with both interferon alfa-2a and −2b has been established in genotype 1 patients, who benefit from doses >800 mg/day [11–13,43]. When ribavirin is combined with peginterferon alfa-2a, relatively small reductions to 800 mg/day lead to significantly lower rates of SVR (odds ratio [OR] standard versus low dose: 1.55, 95% confidence interval [CI]: 1.14, 2.10; $p = 0.005$; Fig. 2a) [13]. Similarly, a large, comparative trial of fixed-dose ribavirin compared with weight-based dosing in combination with peginterferon alfa-2b, showed that stratifying patients of all genotypes to receive starting doses ranging from 800–1400 mg/day dependent on weight leads to a significantly higher SVR rate than using a fixed dose of 800 mg/day for all patients (44.2% versus 40.5%, respectively; $p = 0.008$; Fig. 2b) [43]. Of note, this effect was most profound in patients with genotype 1 disease (34.0% versus 28.9%, respectively; $p = 0.005$) [43].

A detailed analysis of the relationship between bodyweight and SVR suggests that the dose per kilogram may be the determining factor of response in genotype 1 patients (Fig. 3a), with a 40–50% increase in probability of SVR for a 12–16 mg/kg dose ribavirin increase [40]. Ribavirin dosage by weight may impact plasma concentration of the drug, which has also been shown to correlate with response [41]. While this relationship has been well documented in genotype 1 patients, data are less clear for other genotypes. A plasma concentration–response relationship has been suggested for non-genotype 1 patients [41], but another study showed no

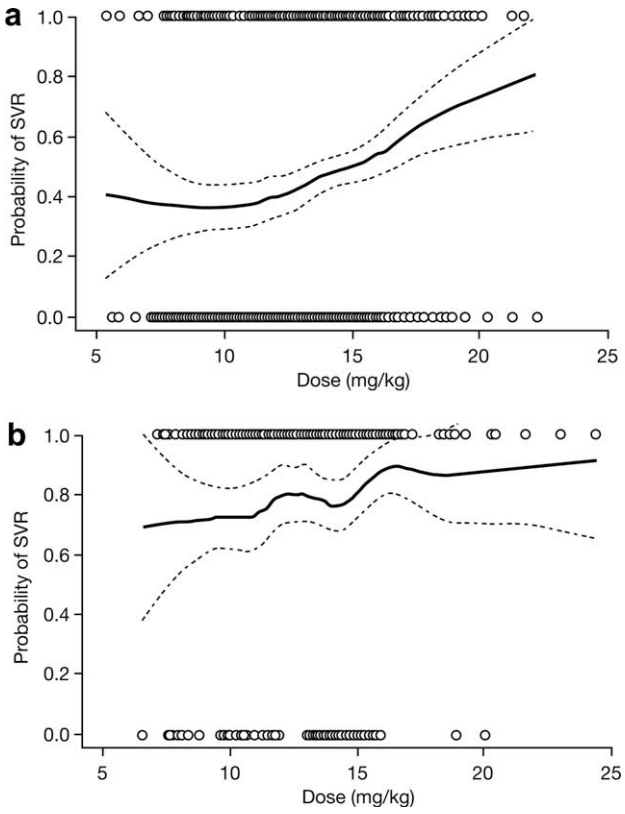

Fig. 3. The relationship between ribavirin dose and probability of an SVR in patients with chronic HCV treated with peginterferon alfa-2a plus ribavirin. (a) In genotype 1 patients. (b) In genotype 2/3 patients [40].

effect of dose per kilogram of bodyweight on SVR in genotype 2/3 patients (Fig. 3b) [40].

Based on these data, weight-based dosing has been utilized more extensively in patients with genotype 1 HCV, and is required in order to achieve maximum efficacy. The standard initial ribavirin dose in patients with HCV genotype 1 is 1000/1200 mg/day (1000 mg/day $\leqslant$75 kg; 1200 mg/day >75 kg) over a 48-week treatment course, although higher ribavirin doses are considered for patients >85 kg. A large population pharmacokinetic analysis involving 380 patients has shown that the pharmacokinetics of ribavirin are highly variable, with lean body weight emerging as the only factor that influences clearance, supporting the use of these two distinct weight-based doses in patients with genotype 1 disease [44]. However, caution must be exercised with weight-based dosing above 1200–1400 mg. Although data modeling from patients who received this standard starting dose suggests that SVR increases linearly with ribavirin doses that equate to >10 mg/kg, there is also a simultaneous linear increase in the rate of anemia (<10 g/dL hemoglobin) [40]. A ribavirin dose of 15 mg/kg/day might achieve the best balance between efficacy and a manageable safety profile.

In some patient groups, such as genotype 2/3 patients or those with a very high sensitivity to peginterferon alfa, ribavirin dose reductions are being assessed. Interim analysis of a randomized study of peginterferon alfa plus ribavirin for 24 weeks at doses of either 400 or 800 mg suggests no decrease in SVR rates in the lower-dose group [45]. Lower doses of ribavirin may also be appropriate in certain patient groups who could not otherwise tolerate ribavirin therapy, such as those with renal impairment. With careful monitoring of plasma concentrations to avoid over dosing, ribavirin doses of 200–800 mg/day have been successfully administered in a small cohort of renally impaired patients [46]. Although five of these seven patients required treatment for ribavirin-induced hemolytic anemia, virologic and renal remission were achieved and maintained in four patients [46]. Similarly, patients in dialysis with end-stage renal disease may also benefit from peginterferon alfa plus ribavirin, with SVRs described in three of six patients who received carefully monitored ribavirin doses of 170–300 mg/day [47]. Although ribavirin is not recommended for use in patients with renal impairment [48,49], these reports suggest that reduced ribavirin at 200–400 mg/day can be safely dosed and may allow for more successful treatment [46,47,50].

4.2. Achieving the optimal duration of ribavirin therapy

The duration of combined therapy with peginterferon alfa plus ribavirin has a significant impact on therapeutic outcomes, and it is important to continue both therapies for the full treatment course to obtain the best response. The optimal duration of combined therapy is genotype specific; in genotype 1 patients, reducing the duration of treatment from the recommended 48 to 24 weeks results in a >10% reduction in SVR (OR 24 versus 48 weeks: 2.19; 95% CI: 1.52, 3.16; $p < 0.0001$) [13]. However, shorter treatment courses may be viable in select genotype 1 patient populations such as those who achieve a rapid virologic response and have a low pre-treatment HCV viral load [51,52]. In genotype 2/3 patients, a 24-week duration of treatment with a fixed 800 mg/day dose of ribavirin is sufficient to achieve an optimal response in the majority of patients [13]. As well as considering the total duration of treatment, it is also important to maintain the ribavirin component of therapy throughout the entire treatment course. Genotype 1 patients who discontinue ribavirin after 24 weeks while continuing on peginterferon alfa show significantly higher rates of breakthrough and relapse than those who continue on combined therapy for the full 48 weeks (SVR 52.8% versus 68.2%, respectively; $p = 0.004$) [19]. However, patients with an early response within 2 weeks of initiating therapy may not require the full 48 weeks of ribavirin to sustain this response [19]. This is supported by further evidence from the DITTO trial of dynamically

individualized treatment, which suggested that reducing the length of treatment in patients who achieve an early response may still allow for optimal virologic control. In this study, reducing the length of therapy from 48 to 24 weeks in rapid responders allowed for equivalent virologic efficacy, although no improvements in response were seen [53]. Similarly, assigning a 12- or 24-week course, depending on rapid viral response (RVR), to patients receiving peginterferon alfa-2b plus ribavirin is as effective as using a 24-week course for all patients [16].

4.3. The impact of cumulative ribavirin exposure on response to therapy

As data emerge to suggest that both the starting dose of ribavirin and duration of treatment affect response to therapy, it now seems increasingly likely that total cumulative exposure is critical to achieve an optimal SVR for all patient groups. In patients with genotype 1 HCV, as cumulative ribavirin exposure decreases, there is a concomitant decrease in SVR and increase in rates of relapse [14,19]. The effect on SVR is independent of peginterferon alfa exposure, as patients who received $\geqslant$97% of their intended peginterferon alfa dose but <60% of the target cumulative ribavirin dose had dramatically lower SVR rates than those who received $\geqslant$60% of the planned ribavirin dose (33% versus 64%, respectively; $p < 0.0001$; Fig. 4) [14]. The effect of cumulative ribavirin dose on response to therapy appears to be consistent whether the reduced exposure is mainly due to prolonged periods of drastic (>200 mg) dose reduction, temporary interruptions and/or premature cessation of ribavirin therapy [14]. Furthermore, reductions in SVR have also been described in patients who received >97% of the planned ribavirin dose during weeks 1–12 but reduced exposure during weeks 13–48, demonstrating that maintaining ribavirin exposure over the whole duration of therapy is crucial, not just up to week 12 [14]. Therefore, maintaining the patient on the starting dose for as long as possible, reducing it in small decrements in patients who do not tolerate their starting dose, and stepping back up to the starting dose once toxicities have been resolved are key to maximizing the chance of a successful response. The clinical importance of maintaining ribavirin exposure has also been confirmed in a real-world setting, using data from a large peginterferon alfa-2a expanded access program [42].

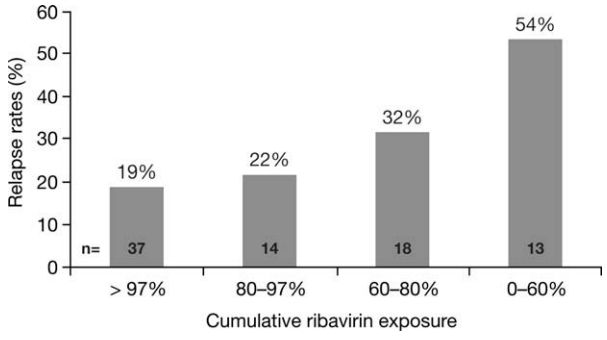

Fig. 4. The impact of ribavirin dose reductions on relapse rates in patients with genotype 1 chronic HCV treated with peginterferon alfa-2a plus ribavirin [14].

Current treatment guidelines recommend discontinuation of therapy in patients who experience severe adverse events, such as hemoglobin levels <8.5 g/dL. For more moderate toxicities such as hemoglobin 8.5–10 g/dL, the labeling varies depending on whether peginterferon alfa-2a or -2b is being administered. In combination with peginterferon alfa-2a, both the US and EU labels recommend decreasing the ribavirin dose to 600 mg/day to combat moderate toxicities [54,55]. The advice is the same in the US for ribavirin when taken in combination with peginterferon alfa-2b [56]. However, the EU label is more complex, and indicates ribavirin dose reduction for some moderate adverse events such as hemoglobin <10 g/dL, but reduction of peginterferon alfa-2b dose only for the management of other adverse events such as low white blood cell, neutrophil or platelet counts [57]. Despite these recommendations, as described above, the majority of clinical data suggest that 200 mg stepwise decrements might be preferable to maintain exposure during treatment. This approach allows reduction in the dose per kg of bodyweight to approximately 80% of the starting dose across a broad weight range, whereas immediate reduction to 600 mg/day results in an effective 50–60% reduction in the ribavirin dose per kg (Table 1), therefore incremental dose reductions may help avoid the reduced SVRs described with cumulative exposure to <60% of the planned ribavirin dose [14]. Early and proactive management of adverse events may help reduce the need for further dose reductions and render this a viable approach to patient management; for example, epoetin therapy may be a suitable approach in some patients with moderately reduced hemoglobin levels, a strategy that will be discussed in detail in the next section.

In patients with difficult-to-cure characteristics, such as weight >85 kg or high viral load, higher ribavirin starting doses (>1200 mg/day) may help increase response rates. For example, patients with genotype 1 HCV, high viral load and weighing >85 kg have an increased SVR with 1600 mg/day ribavirin plus peginterferon alfa compared with the standard of care [58]. Body weight has a large impact on ribavirin clearance [41], and higher ribavirin doses may help ensure that a high enough serum concentration, and therefore sufficient cumulative exposure to ribavirin, is achieved and maintained in this patient population. Indeed, one small study has demonstrated that administering ribavirin at up to twofold higher than the recommended dose (mean

Table 1
Effect of ribavirin (RBV) starting doses and different RBV dose reduction strategies on administered dose and percentage dose reduction.

Patient weight (kg)	Ribavirin dosing according to peginterferon alfa-2a prescribing information [54,55]				Ribavirin dosing according to peginterferon alfa-2b prescribing information [56,57]		
	RBV dose at start of therapy[a]	RBV dose following first dose reduction mg/day[a]	Dose reduction from starting dose to after first dose reduction (%)		RBV dose at start of therapy[a]	RBV dose following first dose reduction[a]	Dose reduction from starting dose to after first dose reduction (%)[a]
			Based on prescribing information[a]	Based on fixed 200 mg dose reduction			
50	1000	600	60	80	800	600	75
60	1000	600	60	80	800	600	75
70	1000	600	60	80	1000	800	80
80	1200	600	50	83	1000	800	80
90	1200	600	50	83	1200	1000	83
100	1200	600	50	83	1200	1000	83
110	1200	600	50	83	1400	1200	86
120	1200	600	50	83	1400	1200	86

[a] Starting dose and dose reductions according to current prescribing information.

2540 mg/day at week 24) can achieve an SVR in 9 out of 10 genotype 1 patients [59]. However, careful patient management is required with high ribavirin dosing to minimize potential dose-related toxicities [58,59]. A large clinical trial is currently underway to determine whether induction doses (360 μg/week for the first 12 weeks of therapy) of peginterferon alfa and/or increased ribavirin (up to 1600 mg/day according to bodyweight) will increase response rates in difficult-to-cure patients with genotype 1 HCV.

5. Management of ribavirin-associated anemia

Successful management of ribavirin-associated toxicity is necessary to maintain the optimal ribavirin dose in all patients, and a particular emphasis be made on the diagnosis and management of hemolytic anemia, which is the most common reason for ribavirin dose reduction or treatment discontinuation [12,13,60]. The mechanism driving ribavirin-induced anemia is complex [61,62], however it has been observed that the concentration of ribavirin is up to 60-fold higher in erythrocytes than in blood serum [63].

Close monitoring of patients with increased risk factors for anemia is important, as early interventions such as modest reductions of ribavirin or prophylactic therapy could prevent a later more drastic reduction when a significant anemia has developed. Indeed, an early drop in hemoglobin of $\geqslant$1.5 g/dL after just 2 weeks of therapy is predictive of a larger drop by $\geqslant$2.5 g/dL by week 4 [64,65]. Other risk factors that may warrant closer monitoring for anemia include age (increased risk with every 10-year increase), low baseline hemoglobin (increased risk with every 1 g/dL decrease) and low creatinine clearance (increased risk with every 10 mL/min decrease) [65]. Although many clinical trials have used large dose reductions (600 mg) to manage side effects, consideration should be given to smaller dose reductions of 200 mg at a time, to help ensure that maximum ribavirin exposure is maintained and antiviral efficacy is not compromised.

Ribavirin dose reductions can help stabilize falling hemoglobin levels, but only tend to lead to modest improvements of ~1 g/dL [60]. Although the approaches taken to manage anemia vary widely, in some cases off-label use of epoetin alfa therapy may be considered to counteract anemia and help maintain the optimal ribavirin dose. Although this treatment option is expensive and not an approved form of therapy, the impact on hemoglobin levels is stronger than that of ribavirin dose reduction, with a mean change of +2.8 g/dL reported after 16 weeks of therapy, compared with +0.4 g/dL with the standard of care ($p < 0.0001$) [66]. This translates into a clinically important difference in the number of patients maintaining the desired ribavirin dose, which in this case was defined as $\geqslant$800 mg/day (83% versus 54%, respectively; $p = 0.022$) [66]. This finding was mirrored by a second study, in which patients with anemia during therapy with peginterferon alfa plus ribavirin were randomized to epoetin therapy or placebo and significantly more maintained their ribavirin dose in the epoetin group (88% versus 60%; $p < 0.001$) [67]. Epoetin is also generally well tolerated in this clinical context, and an improvement in quality of life accompanies these raised hemoglobin levels [67]. Despite these positive findings, a recent study has suggested that although epoetin use reduces the need for ribavirin dose reductions, this does not translate into an improvement in SVR [68]. However, it is worth noting that this study included a group of patients treated with a higher dose of ribavirin (15.2 mg/kg/day) plus epoetin, 93% of whom achieved $\geqslant$80% maximal cumulative ribavirin dose. Significantly higher rates of SVR were seen in this patient group than those randomized to a standard dose of ribavirin (13.3 mg/kg/day), with or without epoetin (49% with

high dose ribavirin + epoetin versus 29% with lower dose ribavirin + epoetin versus 19% with lower dose ribavirin alone; $p < 0.05$) [68]. Lastly, the potential benefit of epoetin must be balanced against the risks. Reports have emerged highlighting increased mortality and serious cardiovascular and thromboembolic events in patients who received erythropoiesis-stimulating agents to target higher hemoglobin levels, particularly in patients with renal failure and perisurgical patients [61]. In order to minimize this risk, the recommended target hemoglobin level is in the range of 10–12 g/dL [69]. Given these concerns, our own practice has been to consider off-label epoetin use in order to prevent ribavirin discontinuation and pay careful attention to maintaining hemoglobin levels <12 g/dL with epoetin therapy.

While the precise role of epoetin has yet to be defined, it is clear that careful patient management is warranted to monitor and pro-actively address ribavirin-associated hemolytic anemia, and the development of guidelines to help direct treatment strategies for the use of epoetin alongside ribavirin combination therapy is warranted. In cases of severe anemia, treatment discontinuation and transfusion may be considered as alternative therapeutic options, but with careful clinical management this scenario should rarely arise [61]. Given the relationship between anemia, ribavirin dose and SVR, one future consideration may be whether anemia itself could be regarded as a positive predictive factor for response to ribavirin combination therapy.

6. Alternatives to ribavirin

6.1. Ribavirin-like drugs

Peginterferon alfa plus ribavirin is currently the standard of care for patients with chronic HCV infection of all genotypes, however novel therapies that may be suitable for addition to this treatment paradigm or as replacements for ribavirin are constantly under development. In particular, there is a need for novel therapies with comparable efficacy to ribavirin, but improved tolerability. One such candidate, taribavirin, is an oral prodrug of ribavirin that is deaminated to ribavirin in the liver, and therefore accumulates less than standard ribavirin in red blood cells and may be associated with lower rates of anemia. It is being developed as an alternative to standard ribavirin with the objective of reducing ribavirin-related hemolytic anemia.

Two Phase III trials of taribavirin versus ribavirin in combination with peginterferon alfa-2a have been performed to date, VISER 1 and 2. Both have indicated that while anemia rates are significantly lower among patients receiving taribavirin, rates of SVR are also lower (38% with taribavirin versus 52% with ribavirin across all genotypes with VISER 1, 40% versus 55%, respectively, in VISER 2) [70,71]. These results were disappointing and suggested that the dosing regimen of taribavirin will need to be increased to improve SVR, but this may also increase the anemia advantage seen at lower dosing. Specific inosine-monophosphate-dehydrogenase (IMPDH) inhibitors have also been developed and may show promise as alternative to ribavirin, such as merimepodib, mycophenolate mofetil and VX-497. Of these alternative agents, merimepodib has been studied for the treatment of HCV in most detail, and a Phase II trial in combination with peginterferon alfa and ribavirin showed undetectable HCV RNA at 24 weeks in 100% of patients on the higher 50 mg dose, compared with only 33% of patients who received peginterferon plus ribavirin alone [72].

6.2. The role of ribavirin in future STAT-C therapies

A number of specifically targeted antiviral therapies for HCV (STAT-Cs) are under development, with multiple protease and polymerase inhibitors entering into Phase I and II testing. Over the past year, we have learned a great deal about the role of ribavirin in these small molecule combination regimens. For example, the HCV protease inhibitors telaprevir (VX-950) and boceprevir are currently under investigation. Telepravir is being studied in combination with peginterferon alfa alone or with ribavirin in patients with genotype 1 disease, and preliminary data from Phase II trials suggest that adding telepravir leads to earlier viral responses in a higher proportion of patients [73,74]. In a Phase II study which included an arm where patients received only peginterferon alfa and telaprevir without ribavirin there was a dramatic impact on relapse rates and SVR, indicating that ribavirin will likely remain an essential part of newly emerging treatments [73].

Another promising group of novel therapeutics are the HCV polymerase inhibitors, which may be suitable candidates for addition to the current treatment regimen. The nucleoside analog R1626 is a pro-drug of the R1479 NS5B polymerase inhibitor, which is known to inhibit viral RNA replication via chain termination [75], a mechanism of action that has also been proposed for ribavirin [31]. A Phase I study of R1626 in combination with peginterferon alfa-2a and ribavirin has demonstrated promising antiviral activity compared with placebo and a favorable tolerability profile [76]. This study is ongoing to determine the optimal R1626 dose in chronic HCV, and Phase II trials have also been initiated to confirm these promising efficacy data and determine the optimal combination regimen. Importantly, *in vivo* synergy has also been observed between R1626 and peginterferon plus ribavirin or ribavirin alone, again suggesting that ribavirin will remain an important initial agent as we add small molecules to the current standard of care [77].

7. Conclusions

The addition of ribavirin to peginterferon alfa improves SVR rates and decreases the rate of relapse in patients with HCV infection, an effect that is consistent across genotypes. For this reason, peginterferon alfa plus ribavirin is the standard of care for the treatment of HCV. Tremendous advances have been made in our understanding of the role of ribavirin within this therapeutic regimen: the standard ribavirin dose is currently thought to be 1000 mg/day for genotype 1 patients <75 kg, 1200 mg/day for genotype 1 patients ⩾75 kg and 800 mg/day for all genotype 2/3 patients, although weight-based dosing at 15 mg/kg may yet prove to be the best approach. The ribavirin dose should be maintained over a period of 48 weeks for the majority of patients with genotype 1 disease and for 24 weeks for the majority of patients with genotype 2/3. Shorter durations of treatment may be appropriate for selected patients achieving an RVR with low baseline viral load. Doses of ribavirin above 1200 mg/day may be considered in difficult-to-cure patients infected with genotype 1 HCV. Alternatively, the ribavirin dose can be reduced or even stopped in patients with very high sensitivity to peginterferon alfa therapy.

Despite these advances in our knowledge, many questions still remain as to how we can further optimize therapy, for example should ribavirin dose be varied based on pre-treatment HCV viral load, and will the role of ribavirin alter as new therapies are developed. Importantly, cumulative ribavirin exposure is a crucial determinant of response to therapy, therefore achieving and maintaining the optimal dose throughout therapy is key to achieving high rates of SVR. Careful patient management is required to monitor the toxicities of therapy, in particular hemoglobin levels should be monitored in patients with risk factors for treatment-induced hemolytic anemia, and dose reductions or other therapeutic interventions should be administered in a timely manner. Dose reductions of ribavirin should be limited to the minimum required to address side effects, possibly using small decrements and avoiding reductions to below 60% of the target dose whenever possible. Consideration should then be given to stepping the ribavirin dose back up to the target dose on resolution of adverse events, to maximize total exposure. At present, there are no alternatives to ribavirin approved for the treatment of HCV, therefore maintaining patients on their indicated dose and length of therapy is crucial if the goal of a sustained response is to be achieved.

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