

Ribavirin: Past, present and future

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Abstract

Before the advent of direct acting antiviral agents (DAAs) ribavirin, associated to pegylated-interferon played a crucial role in the treatment of chronic hepatitis C, preventing relapses and breakthroughs. In the present era of new potent DAAs, a place is still devoted to the drug. Ribavirin associated with sofosbuvir alone is efficient in the treatment of most cases of G2 infected patients. All options currently available for the last difficult-to-treat cirrhotic G3 patients contain ribavirin. Reducing treatment duration to 12 wk in G1 or G4 cirrhotic compensated patients is feasible thanks to ribavirin. Retreating patients with acquired anti NS5A resistance-associated variants using ribavirin-based strategies could be useful. The addition of ribavirin with DAAs combinations however, leads to more frequent but mild adverse events especially in cirrhotic patients. Preliminary data with interferon-free second generation DAAs combinations without ribavirin suggest that future of the drug is jeopardized even in difficult-to-treat patients: The optimization of ribavirin dosage according to an early monitoring of blood levels has been suggested to be relevant in double therapy with peginterferon or sofosbuvir but not with very potent combinations of more than two DAAs.

Key words: Ribavirin; Hepatitis C; Peginterferon; Direct acting antiviral agents

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Core tip: Ribavirin plays a crucial role when associated with peginterferon, preventing relapses and

breakthroughs and doubling the support vector regression rate. Its antiviral effect is weak and ribavirin could enhance the response of interferon-stimulated genes in the combination. Ribavirin is still useful in the era of approved new direct acting antiviral agents (DAAs), in order to shorter treatment duration in genotype 1 or 4 cirrhotic patients, in all options available for genotype 3 cirrhotic patients, and as the only drug associated with sofosbuvir in genotype 2. Preliminary data with interferon-free second generation DAAs combinations without ribavirin suggest that future of the drug is jeopardized.

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INTRODUCTION

Before the advent of direct acting antiviral agents (DAAs) ribavirin played a crucial role in the treatment of chronic hepatitis C associated to pegylated interferon^[1]. This combination is still relevant in many parts of the world which do not have access to new therapies because of cost issues^[2]. Although the role of ribavirin in the era of DAAs will probably decrease in the future with the arrival of second generation drugs, it remains essential in strategies decreasing treatment duration or in some difficult situations. The goal of this review is to briefly recall the recent past of ribavirin and consider its present and potential future.

RIBAVIRIN: MECHANISMS OF ACTION

So far, multiple mechanisms of action of ribavirin have been described. The antiviral mechanism is probably the best documented, the erroneous incorporation of ribavirin triphosphate into replicating RNA strands inhibiting chain elongation^[3]. *In vitro*, in the hepatitis C virus (HCV) RNA replication system, ribavirin reduces HCV replicon colony-forming efficiency in a dose-dependent manner, reinforcing this hypothesis^[4]. The inhibition *via* inosine monophosphate dehydrogenase of the *de novo* synthesis of GTP, required for the synthesis of viral RNA, is another but probably weak potential mechanism of action^[5]. However, the mutagenesis hypothesis remains controversial^[6]. The last most attractive mechanism of action is that ribavirin could enhance the response of interferon-stimulated genes making cells more sensitive to exogenous interferon and increasing the production of endogenous interferon^[7].

Two phases of plasma HCV RNA decline in patients treated with peginterferon and ribavirin have been described: A rapid first phase in the first two days^[8] reflecting the genesis and release of new virions and a slower second phase corresponding to the elimination

of infected cells. The impact of the first-phase decline is weak (0.5 log) and goes unnoticed during double therapy, but is enhanced in patients treated with ribavirin alone^[9]. The second slope probably reflects the interferon-stimulated genes' response and the production of endogenous interferon.

Multiscale models recently considered the possible effects of DAAs on intracellular HCV RNA production, degradation, assembly and secretion as virus into the circulation^[10]. The first-phase decline represents the viral clearance. The second represents the loss of intracellular viral RNA by export and degradation as well as the elimination of infected cells. The third represents a combination of the reduction in intracellular viral RNA production and the elimination of infected cells. Nowadays, there are no data available on the role of ribavirin in this setting, but we may imagine that ribavirin might impact the second- and the third-phase decline.

PAST OF RIBAVIRIN: COMBINATION THERAPY PEGINTERFERON AND RIBAVIRIN

Clinical history

Ribavirin, a guanosine analog is active against many DNA and RNA viruses and has clinical applications in respiratory syncytial infection in children, and Lassa Fever infection^[11,12]. Di Bisceglie *et al*^[13] first showed that ribavirin could double the efficiency of standard alfa interferon. A similar synergy was observed with the association of peginterferon and ribavirin^[14,15], ribavirin impacting favourably the number of relapses and breakthroughs^[16]. A total daily dose of ribavirin during the first three months > 10.6 mg/kg of body weight was predictive of sustained virological response (SVR)^[14,17] and ribavirin had to be administered for the total duration of treatment^[16]. A pilot study also showed, that the use of high doses of ribavirin early during treatment led to high sustained virological rates^[18]. The same team proposed to optimize the dose of ribavirin using a formula based on renal function and body weight^[19].

Pharmacokinetics of ribavirin

Ribavirin is a drug typically adapted for therapeutic drug monitoring: Long half-life, large inter-individual variability of the dose-concentration relationship, and narrow therapeutic zone. After the first oral dose, a rapid absorption phase is observed with a maximum concentration at 1.5 h, followed by a rapid distribution phase (half-life of 3.7 h), and a long elimination phase of about 100 h post-dose^[20]. The monitoring of ribavirin plasma concentrations during double therapy initially used trough concentrations at week 4 and week 8 of treatment^[21,22]. However, trough concentrations had a lower influence than the genotype and the viral load on SVR^[21].

We secondly showed that ribavirin plasma exposure

after the first dose [*i.e.*, measured by the interdose area under the concentration curve, area under the curve (AUC_{0-12h}) or abbreviated AUC_{0-4h}] was strongly linked to SVR and was probably a more relevant tool^[23]. Using receiver operating characteristic curve analysis, we defined an AUC_{0-4h} threshold of 1755 µg/h per litre at day 0 as a target for ribavirin early dose adjustment, AUC_{0-4h} being estimated using 3 blood samples (0.5, 1 and 2 h after the first dose) and Bayesian estimation. When comparing adapted and non-adapted patients with a suboptimal exposure to ribavirin at day 0 (*i.e.*, D0 AUC_{0-4h} < 1755 µg/h per litre), the difference of SVR reached nearly 30%, enhancing the benefit of adapted dose in this population (unpublished results).

Ribavirin and anemia during peginterferon and ribavirin treatment

Ribavirin-induced haemolytic anaemia is a frequent adverse event leading to drug discontinuation in 36% of the cases in real-life studies^[24], even if this anemia is reversible and dose-dependent. Medullar regeneration is partially prevented by various degrees of bone marrow suppression due to interferon impact. The prevalence of anaemia is high, with Hb level < 11 g/dL in 30% and < 10 g/dL in 9% to 13% of the patients^[14,15] with 10% to 15% of the patients presenting with an Hb decline of more than 5 g/dL. Erythropoietin has been shown to improve the ribavirin treatment maintenance and tolerance^[25,26] but did not prove its impact on SVR.

PRESENT OF RIBAVIRIN: TREATMENT WITH NEW DAAS

Interferon-free regimens DAAs currently approved by FDA and EMEA are used in combinations: Pangenotypic polymerase inhibitor sofosbuvir (Sovaldi®) associated with NS5A inhibitors ledipasvir (associated with sofosbuvir: Harvoni®) or daclatasvir (Daklinza®) (genotype 1, 3, 4), or with a protease inhibitor simeprevir (Olysio®) (genotype 1, 4); triple combination paritaprevir boosted with ritonavir (protease inhibitor), ombitasvir (NS5a inhibitor) (Viekirax®) and quadruple combination of paritaprevir, ritonavir, ombitasvir and dasabuvir (Exviera®) a polymerase inhibitor are also available for genotype 1, 4 patients.

Most of the time, these regimens give more than 90% SVR rate without the addition of ribavirin. However, ribavirin is still relevant in some circumstances.

Ribavirin and sofosbuvir alone are efficient in the treatment of most cases of G2 infected patients

Sofosbuvir and ribavirin combination is recommended in both European Association for the Study of the Liver (EASL) and French guidelines in G2 patients for 12 wk mainly^[27] except for cirrhotic experienced-patients (24 wk)^[28]. In this particular population, the only way to reduce treatment duration to 12 wk with similar SVR (95% to 100%) is to add peginterferon^[29,30].

Nowadays, ribavirin remains essential for the last difficult-to-treat cirrhotic G3 patients

HCV G3 patients were first treated with sofosbuvir and ribavirin for 24 wk in phase III trials; response rates were 91% in patients without cirrhosis and only 68% in patients with cirrhosis, respectively^[27]. Recently, the Boson study showed the potential superiority of a peginterferon sofosbuvir and ribavirin regimen for 12 wk with a 91% to 86% SVR in naive and pre-treated cirrhotic patients respectively^[30]. Another strategy using sofosbuvir daclatasvir without ribavirin for 12 wk in G3 cirrhotic patients led to a weak 63% rate of SVR^[31]. Results of the French initial authorization for new DAAs are in favour of a 24-wk treatment but the sofosbuvir daclatasvir and ribavirin strategy for 12 wk was not available^[32]. This option could be a pertinent alternative to the 24-wk sofosbuvir daclatasvir association. Currently, EASL and French expert advices recommend treating patients with sofosbuvir daclatasvir for 24 wk, in the absence of the results of a new trial evaluating sofosbuvir daclatasvir ribavirin for 12 wk.

To sum up, all options currently available for cirrhotic G3 patients contain ribavirin and we have to wait for the results of new associations like sofosbuvir and the pangenotypic GS 5816 (astral 3 waiting results) or more sophisticated triple strategies like grazoprevir elbasvir and sofosbuvir^[33].

Ribavirin is still necessary for G1a patients treated with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

The approval of the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir in patients infected with G1 was supported by six phase III clinical trials. In PEARL-IV, in patients infected with subtype 1a, the SVR rates were 97% and 90% with and without ribavirin respectively, suggesting that, unlike for G1b, ribavirin is needed in the 12-wk regimen for this subtype^[34]. Moreover, considering treatment-experienced cirrhotic patients with subtype 1a infection a 24 wk-treatment duration with ribavirin was needed^[35].

Reducing treatment duration to 12 wk in G1 or G4 cirrhotic patients is feasible thanks to ribavirin

In compensated and decompensated cirrhosis:

Recent data suggest that the addition of ribavirin allows the treatment duration to be limited to 12 wk in patients with advanced liver disease, including patients with compensated cirrhosis (especially if they are treatment-experienced), patients with decompensated cirrhosis and subjects in pre- and post-liver transplant setting.

Twelve weeks with ribavirin or 24 wk without ribavirin are equivalent in compensated cirrhosis:

In the Sirius study^[36], ledipasvir-sofosbuvir plus ribavirin for 12 wk and ledipasvir-sofosbuvir for 24 wk provided similar high SVR12 rates in previous non-responders with HCV G1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore,

be useful to treat experienced patients with cirrhosis in case of no contra-indications to ribavirin.

Of note, in cirrhotic pre-treated patients with platelet count $< 75000/\text{mm}^3$, the SVR rate is suboptimal (84%)^[37] and EASL guidelines recommend to extend the ribavirin-associated regimen to 24 wk in this subgroup.

In a post-hoc analysis of data from seven clinical trials which evaluated the efficacy and safety of the fixed-dose combination of ledipasvir and sofosbuvir, with and without ribavirin in 513 treatment-naive and previously treated patients with G1 HCV compensated cirrhosis, Reddy *et al.*^[37] suggested the usefulness of ribavirin in the subpopulation of treatment-experienced patients receiving 12 wk of treatment (SVR12 rate of 90% vs 96% with ribavirin).

Finally in the hepather cohort^[38], difficult-to treat G1 (88% cirrhotics) patients receiving sofosbuvir daclatasvir and ribavirin achieved a SVR4 of 100% not different from sofosbuvir daclatasvir for 24 wk (SVR4 95%). In a multivariate analysis, factors associated with SVR in cirrhotics were the addition of ribavirin (OR = 6.3; $P = 0.057$) and a treatment-duration of 24 wk (OR = 4.3; $P = 0.008$).

Similarly, results from the same cohort study showed a benefit in the pre-treated cirrhotic population infected with G4 and receiving sofosbuvir daclatasvir or sofosbuvir simeprevir, with ribavirin^[39].

Same results are observed in decompensated cirrhosis in the pre and post-transplant setting except for Child Pugh C patients: The association of sofosbuvir ledipasvir and ribavirin for 12 wk in the pre and post transplant setting led to more than 85% to 95% SVR in cirrhotic patients^[40,41]. However, in one study, the response rate was much lower (under 60%) in Child Pugh C patients suggesting a prolongation of treatment course to 24 wk^[42].

In non-cirrhotic G1 patients, ribavirin does not help to reduce treatment duration under 8 wk

Among previously untreated patients with HCV G1 infection and without cirrhosis in the phase III ION 3 study, the 8-wk ledipasvir-sofosbuvir regimen showed no inferiority to the 12-wk regimen^[43]. One interesting hypothesis could have been to further reduce the treatment duration by adding ribavirin to the combination.

However, in the electron study, among treatment-naive patients receiving 6 wk of sofosbuvir, ledipasvir and ribavirin, only 17 of 25 (68%) achieved an SVR12. The addition of ribavirin in this setting does not seem to be an appropriate strategy^[44].

Retreating patients with acquired anti NS5A resistance-associated variants using ribavirin-based strategies could be useful

In Reddy's study^[37], 91% of G1 cirrhotic patients with NS5A resistance-associated variants (RAVs) at baseline and treated with sofosbuvir-ledipasvir achieved SVR12 (95%CI: 84-96), as compared with 98% (407 of 417)

of those without baseline NS5A RAVs (95%CI: 96-99). This difference appeared to be mitigated by the addition of ribavirin to the regimen (88% of SVR without vs 94% with ribavirin).

The addition of ribavirin with DAAs combinations leads to more frequent but mild adverse events

In the main studies comparing interferon-free DAAs combinations with or without ribavirin for 12 wk, adverse events (AEs) were significantly higher (about 10%) when ribavirin was included in the strategy: Particularly fatigue, insomnia, pruritus, cough and of course all grades of anemia but only 5% of grade 3 and 4. Treatment discontinuation due to AEs (4%) was slightly more frequent. However, these AEs were not significantly higher in compensated cirrhotic patients when a 12-wk regimen with ribavirin was compared to a 24-wk regimen without ribavirin^[36]. Erythropoietin (EPO) was not used except in advanced cirrhotic disease and reduction of ribavirin dosage (9%) was most of the time sufficient with no impact on SVR^[45].

Of course, these AEs were more tolerable than in regimens including interferon, and even more than in triple therapy with first generation protease inhibitors.

There is probably no more place for ribavirin dose adjustment during treatment with DAAs

In the NIAID SPARE trial, Rower *et al.*^[46], showed that ribavirin-monophosphate concentrations in red blood cells at day 14 were related to anaemia and SVR. A therapeutic range was identified for ribavirin-monophosphate in persons with HCV G1 disease receiving 24 wk of sofosbuvir plus ribavirin, suggesting a potential pharmacological basis for individualized ribavirin dosing in this interferon-free regimen. However, Jacobson *et al.*^[45] showed in cirrhotic G1 patients, that ribavirin dose reduction due to anemia in the triple Abbvie combination (10% of the cohort) did not impact the SVR. One may hypothesize that the monitoring of ribavirin dose in G1 patients will not be useful when using at least two very potent new DAAs, unlike what was observed with the association of peginterferon and ribavirin or sofosbuvir and ribavirin.

FUTURE

Preliminary data with second generation interferon-free DAAs combinations without ribavirin suggest that ribavirin future is jeopardized even in difficult-to-treat patients

New double combinations: Grazoprevir elbasvir without ribavirin for 12 wk is efficient in difficult-to-treat G1 and G4 patients. In a phase II study (C-Worthy), high SVR12 rates were achieved irrespective of the use of ribavirin or of the extension of treatment duration from 12 to 18 wk in two cohorts of G1 patients, *i.e.*, cohort 1, naive cirrhotic patients and cohort 2 previous null responders with or without cirrhosis. The SVR rate without ribavirin was 97% and 91% in the two

cohorts respectively^[29]. In the Edge study, considering G1 and 4 patients (35% cirrhosis), the association of grazoprevir elbasvir gave similar results with and without ribavirin for a 12- or 16-wk duration (92% to 97%). Interestingly however, SVR rates were higher for the 16 wk + ribavirin arm regardless the status of the patient, the presence of cirrhosis and the presence of NS5A mutation (97%)^[47] suggesting a small residual role of ribavirin. In a phase II preliminary study, the same combination without ribavirin was effective and well tolerated in G1 Child B-cirrhotic patients^[48] leading to a 90% SVR. The combination of grazoprevir and elbasvir was useless or suboptimal for G3 and G2 patients respectively even with the addition of ribavirin and G5 patients, interestingly, still needed ribavirin^[49,50].

The sofosbuvir GS-5816 (pangenotypic NS5a inhibitor) combination without ribavirin was clearly efficient in G3 non cirrhotic patients (100% SVR) and more efficient than other previous combinations in experienced cirrhotic patients (88%). However in the latter case, the addition of ribavirin seemed to bring a mild benefit (96% of SVR)^[51].

Multiple DAAs combinations without ribavirin in difficult-to-treat patients:

In G1 naive or pre-treated cirrhotic patients, the association of daclatasvir NS5A pangenotypic inhibitor, asunaprevir NS3 protease inhibitor and beclabuvir NS5B non nucleosidic polymerase inhibitor without ribavirin, gave high response rates in naive patients (93%). However, ribavirin could still be useful in pre-treated patients (93% vs 87% SVR with and without ribavirin, respectively)^[52].

In G3 cirrhotic patients, preliminary results showed that the association of grazoprevir elbasvir sofosbuvir without ribavirin gave a 91% SVR suggesting that this combination could be an ideal strategy for these difficult to treat population^[33]. Of course, these results have to be confirmed.

Renal insufficiency: It will be soon possible to avoid ribavirin

Ribavirin use is problematic in this setting due to the management of severe anemia and the delicate dose adjustment which is not standardized (200 mg × 3/wk to 200 mg/d) and requires ribavirin concentration measurement especially in hemodialysis.

Today, no DAA association is recommended in patients with estimated glomerular filtration rate < 30 mL/mn, especially because the key tool of the approved associations, sofosbuvir and its main metabolite are eliminated by the kidney and the appropriate dosing is not known. Preliminary studies however showed that the simeprevir sofosbuvir (200 mg/d) association without ribavirin gave a SVR rate of 88% to 100% with a quite good tolerance^[53,54].

The paritaprevir/ritonavir ombitasvir dasabuvir combination was also very efficient (100% response) but G1a subtype still needed ribavirin^[55].

Finally, in the largest study so far, out of 226 G1

patients with severe renal insufficiency, 191 with chronic kidney disease stage 5 and 179 hemodialysed showed a 99% SVR when treated with grazoprevir elbasvir for 12 wk without ribavirin with an excellent tolerance^[56].

These encouraging results will probably lead us to treat hemodialysed patients if no transplant perspective is envisaged, or before kidney transplantation, as HCV negatively impacts these patients' prognosis.

CONCLUSION

Even if new DAAs are cost-effective, at their current prices, they are not cost-saving, and the addition of ribavirin with approved DAAs interferon-free regimens is probably the best option to decrease treatment duration without impacting SVR. The next step of course is one pill of DAAs a day without ribavirin to treat all patients whatever the stage of the disease or the genotype, with no side effects and for the shortest treatment duration possible. Even if second generation drugs do not yet fulfil all the criteria and probably will not for the next 5 years, they dangerously jeopardize ribavirin future.

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