Review

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Ideal oral combinations to eradicate HCV: The role of ribavirin

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Summary

Current all-oral interferon-free regimens offer sustained virological response (SVR) rates above 90% as well as 12-week treatment durations for the majority of patients with chronic hepatitis C virus (HCV), including treatment-naïve and -experienced patients with or without cirrhosis. There are multiple direct-acting antiviral (DAA) combinations that can be selected to optimize efficacy and safety outcomes. Each of them can be tailored according to different parameters including the use of ribarivin (RBV). For sofosbuvir (SOF)-based combinations, RBV is useful in the following situations: HCV genotype 1, treatment-experienced, cirrhotic patients, or patients with decompensated cirrhosis, and HCV genotype 3, cirrhotic patients. In these situations the addition of RBV allows to shorten the treatment to 12 weeks in the majority of cases and therefore decreases the cost of the treatment. The need of RBV remains to be determined in cirrhotic patients with a SOF plus simeprevir regimen. RBV-containing regimens are recommended in all HCV genotype 1a patients who receive the 3-DAA combination: paritaprevir/r, ombitasvir, dasabuvir. Globally, the addition of RBV to the different combinations of DAA increases slightly the risk of anaemia. However severe anaemia was rare and easily manageable with RBV dose reduction without any impact on SVR.

In practice, because RBV is cheap and well tolerated when combined with interferon-free regimen, it remains a useful tool to fine tune anti-HCV treatment regimens and optimize their results.

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Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; RBV, ribavirin; IFN, interferon; Peg-IFN, pegylated interferon; DAA, direct-acting antiviral; ALT, alanine transaminase; GTP, guanosine triphosphate; IMPDH, inosine monophosphate dehydrogenase; APRI, aspartate aminotransferase: platelet ratio index; SOF, sofosbuvir; SMV, simeprevir; DCV, daclatasvir; LDV, ledipasvir; ASV, asunaprevir; RAVs, resistance-associated variants; BMS, Bristol-Myers Squibb.

Introduction

Chronic hepatitis C virus (HCV) infection is associated with a progressive liver disease that can lead to cirrhosis, and hepatocellular carcinoma. Current estimates indicate that 130–150 million people worldwide are chronically infected with HCV, resulting in up to 350,000 deaths annually [1,2]. Seven HCV genotypes have been identified, with genotype 1 being the most prevalent worldwide [3].

Current treatment options include sofosbuvir (SOF), a uridine nucleotide analogue which inhibits the nonstructural protein 5B (NS5B) polymerase enzyme, [4,5] in combination with other compounds including pegylated interferon (Peg-IFN), ribavirin (RBV), and direct-acting antivirals (DAAs) from different families. Interferon (IFN)-free, SOF-based therapies result in an increase in sustained virologic response (SVR) rates above 90% with short treatment duration (12 weeks or less). In 2015, other IFN-free regimens without SOF will be approved related to phase III programs showing similar efficacy outcomes compared to those reported with IFN-free, SOF-based options.

Combination therapy with RBV has improved markedly the response to Peg-IFN by preventing relapse [6]. RBV was an important component of Peg-IFN based therapy with first generation protease inhibitor, preventing virologic breakthrough or relapse [7], but phase II clinical trials of IFN-free regimens based on DAAs suggested that RBV may not always be required [8,9]. Although RBV appears to have less toxicity in the absence of Peg-IFN, RBV is teratogenic and is associated with haemolytic anaemia. Thus, the objective of this review is to identify the groups of patients in whom the use of RBV remains recommended according to the different IFN-free regimens, currently approved, or approved in the near future.

Mechanism of action of RBV

The loss/cure of infected cells (second-phase slope) upon antiviral therapy is under the control of multiple parameters, some of which can be modified to optimize treatment responses, including the antiviral effectiveness of the drug combination, treatment duration, and the use of RBV. Thus, patients with a slow second-phase decline, such as patients with an unfavourable IL28B genotype, cirrhotic patients, and patients infected with HCV genotype 3 or 1a, etc., need a potent antiviral effectiveness of the drug

regimen and adapted treatment duration. Moreover, RBV could be a useful tool to either reduce treatment duration or improve SVR rates with a given duration. This is related to the acceleration of the second-slope of viral decline induced by RBV in patients in whom virus production is efficiently blocked by IFN-free drug combinations, through mechanisms that remain debated [10,11].

It has been shown that RBV exerts a significant, moderate, and transient antiviral effect in a significant proportion of patients receiving RBV monotherapy [10,12–14]. Moreover, a decrease in serum alanine transaminase (ALT), which was independent of the antiviral effect of RBV, has been reported during RBV monotherapy [12–14]. A number of putative mechanisms have been proposed as a direct inhibition of the viral RNA polymerase. However, the modest antiviral effect of RBV monotherapy *in vivo*, makes this hypothesis unlikely. It has been suggested that RBV antiviral activity was related to a depletion of intracellular guanosine triphosphate (GTP) pools caused by inhibition of the inosine monophosphate dehydrogenase (IMPDH) enzyme by RBV. However, other potent specific IMPDH inhibitors, used alone or in combination with RBV or IFN, do not exert a significant effect on HCV replication in patients with HCV infection suggesting that the inhibition of IMPDH does not influence RBV antiviral activity [15]. The concept of mutagenic properties of RBV leading to "error catastrophe", i.e., disorganization of the mutant distribution of quasispecies and the generation of nonviable viral population, has been studied with conflicting results obtained with HCV patients receiving RBV. However, a recent study has analysed RBV-induced mutations with high sensitivity, using deep sequencing. It revealed that RBV exerts a mutagenic effect on HCV by inducing nucleotide transitions, suggesting that this effect could be a relevant factor explaining the antiviral activity of RBV [12]. RBV-induced mutagenesis does not explain biochemical response. Finally, the hypothesis that RBV may act as a potentiator of IFN signalling by increasing interferon-stimulated genes induction was not demonstrated *in vivo* [14]. In summary, the dissociation between the antiviral and biochemical responses to RBV suggests that RBV may act through different mechanisms, a direct antiviral effect partly explained by mutagenic properties, and an indirect biochemical effect through an unknown mechanism.

Impact of RBV on efficacy in genotype 1 non-cirrhotic patients

Sofosbuvir-based regimen

In vitro, SOF demonstrated potent pangenotypic activity across the HCV genotypes (1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a) at concentrations of SOF-inhibiting virus replication by 50% (EC values) of 0.014 to 0.11 μM. *In vitro* combination studies showed an additive interaction between SOF and IFN. A minor synergy was observed for the combination of SOF with RBV. However, in the phase II ELECTRON study, ten genotype 2 or 3 naïve patients were treated with SOF plus RBV for 12 weeks and all patients achieved a SVR24. Another ten genotype 2 or 3 naïve patients received SOF monotherapy for 12 weeks and only six patients reached SVR24. In this group, all ten patients had a rapid response and had undetectable levels of HCV RNA by week 4 of treatment, which was maintained for the duration of the treatment, four patients had a relapse after the end of treatment [16]. Although the significance of the study is limited due to small sample sizes, these results emphasize the important role of RBV in the prevention of relapse and maintenance of antiviral response.

Sofosbuvir and ribavirin

It is worthwhile to note that an independent study has assessed the efficacy of SOF in combination with RBV for 24 weeks in genotype 1 naïve patients. In the second part of the study, 50 patients were randomized to receive SOF with either weight-based or low-dose; 600 mg/day of RBV for 24 weeks. The SVR24 rates were 68% in the weight-based group and only 48% in the low-dose group [17]. However, because of its low effectiveness/cost ratio, this strategy is not recommended in HCV genotype 1 patients.

Sofosbuvir and ledipasvir

Three phase III trials have assessed the combination of SOF in combination with ledipasvir (LDV), an NS5A inhibitor, with or without RBV (1000 mg daily in patients with a body weight <75 kg and 1200 mg daily in patients with a body weight ⩾75 kg) in different genotype 1 populations (Table 1). It is important to note that these studies were not powered to compare responses to regimens with or without RBV or to 12 weeks and 24 weeks of treatment. In naïve, non-cirrhotic genotype 1 patients, SOF plus LDV for 8 weeks was as effective as SOF plus LDV with RBV for 8 weeks and SOF plus LDV for 12 weeks: 94% *vs.* 93% *vs.* 95%, respectively [18]. In naïve genotype 1 patients with or without cirrhosis, SOF plus LDV for 12 weeks was as effective as SOF plus LDV with RBV for 12 weeks and SOF plus LDV or SOF plus LDV with RBV for 24 weeks (99% *vs.* 97% *vs.* 98% *vs.* 99%, respectively). In non-cirrhotic patients, the addition of RBV had no impact on SVR [19]. The third study assessed the same four arms as the previous one in treatment-experienced patients with or without cirrhosis. The SVR were similar between the arms with (96% and 99% for 12 and 24 weeks, respectively) and without RBV (94% and 99% for 12 and 24 weeks, respectively). In non-cirrhotic patients, the use of RBV had no effect on SVR [20]. In summary, genotype 1 non cirrhotic patients can be treated with SOF and LDV without RBV.

Sofosbuvir and daclatasvir

Daclatasvir (DCV) is a potent, pangenotypic NS5A inhibitor with antiviral activity across HCV genotypes 1–6 *in vitro* [21], that has been combined with SOF for the treatment of chronic hepatitis C. This combination, SOF plus DCV, with or without RBV (1000 mg daily in patients with a body weight <75 kg and 1200 mg daily in patients with a body weight ⩾75 kg) was tested in mostly non-cirrhotic patients with genotype 1 infection who were randomly assigned to SOF plus DCV, with or without RBV, for 12 weeks (82 previously untreated patients) or 24 weeks (41 patients who had previous virologic failure with telaprevir or boceprevir plus Peg-IFN and RBV). In naïve patients, the SVR12 rates were 100% and 95% in SOF plus DCV and SOF plus DCV with RBV arms, respectively. In protease inhibitor failure patients, the SRV12 rates were 100% and 95% in SOF plus DCV and SOF plus DCV with RBV arms, respectively [22]. A non-controlled real-life cohort has shown that the SVR4 was 100% in 20 genotype 1 patients with severe fibrosis, but without cirrhosis (fibrosis stage based on non-invasive markers) who received SOF plus DCV without RBV for 12 weeks [23]. Due to a limited number of patients who receive the regimen, definite conclusions regarding the addition of RBV cannot be drawn;