Original article

The ARRIBA concept: adequate resorption of ribavirin

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Background: Adequate ribavirin exposure is essential for optimal sustained virological response (SVR) rates in chronic HCV treatment. It has been proposed that the area under the concentration-time curve up to 4 h after intake of ribavirin ($AUC_{0-4\,h}$) of the first weight-based ribavirin dose should be ≥1.755 mg•h/l to guarantee the highest chance of SVR. Our ARRIBA concept comprises a test dose of ribavirin to select the optimal starting dose to achieve adequate exposure. This study aims to evaluate whether adequate exposure can be achieved after dose advice based on the $AUC_{0-4\,h}$ of a single weight-based ribavirin test dose.

Methods: (Formerly) HCV-infected subjects received a single weight-based ribavirin test dose (<75 kg: 400 mg; ≥75 kg: 600 mg) and the $AUC_{0-4\,h}$ was calculated. If ribavirin $AUC_{0-4\,h}$ was ≥1.755 mg•h/l, subjects received the same dose 4 weeks later; if the $AUC_{0-4\,h}$ was <1.755 mg•h/l, an adjusted dose was administered. The ribavirin $AUC_{0-4\,h}$ was recorded again. The primary outcome was the proportion of subjects with an $AUC_{0-4\,h}$ ≥1.755 mg•h/l after the second dose.

Results: A total of 26 subjects were included. The geometric mean (95% CI) ribavirin $AUC_{0-4\,h}$ was 1.67 (1.44–1.92) mg•h/l with 9 subjects (35%) reaching the target AUC on day 1. Thus, on day 29, 17 subjects (65%) received an adjusted dose. The geometric mean (95% CI) $AUC_{0-4\,h}$ increased to 1.90 (1.62–2.21) mg•h/l and then 16 subjects (62%) had an $AUC_{0-4\,h}$ ≥1.755 mg•h/l, which is significantly higher than day 1 (P<0.05).

Conclusions: Our ARRIBA concept of a ribavirin test dose, with dose adjustment if necessary, leads to an increased proportion of patients with an AUC≥1.755 mg•h/l compared to traditional weight-based ribavirin dosing.

Introduction

Ribavirin is a synthetic nucleoside (guanosine) analogue [1] and is used in combination with pegylated interferon for chronic HCV infections, but is also a component of various treatment options with newer direct-acting antivirals (DAAs) [2–8]. In particular the combination of sofosbuvir and ribavirin has become the first interferon-free gold standard therapy for patients with an HCV genotype-2 infection. An advantage of ribavirin is that physicians and nurses are familiar with the drug, including its side effects. Adverse events can therefore be recognized quickly and adequately managed. Ribavirin, when administered without pegylated interferon, results in fewer and less severe side effects [3]. Finally, ribavirin is cheap and generically available.

Adequate exposure to ribavirin in dual therapy consisting of ribavirin and pegylated interferon is essential for optimal sustained virological response (SVR) rates [9–15]. Studies have shown that ribavirin pharmacokinetics display small intra- but large inter-patient variability [11,16]. For this reason, therapeutic drug monitoring of ribavirin has been suggested in the literature [17–19]. Usually, therapeutic drug monitoring is performed at steady-state. However, due to the long elimination half-life of ribavirin, steady-state is not

reached before week 8 of treatment [16] and therefore interventions based on measuring ribavirin concentrations at this point in treatment may come too late to influence treatment outcome. Loustaud-Ratti *et al*. [20] have proposed that the area under the concentration–time curve up to 4 h after intake of ribavirin ($AUC_{0–4\ h}$) of the very first weight-based dose of ribavirin should be ≥1.755 mg•h/l to guarantee the highest chance of SVR in patients treated with pegylated interferon and ribavirin. Here, we introduce the ARRIBA concept: Adequate Resorption of RIBAvirin. It comprises a test dose of ribavirin to select the optimal starting dose for each individual HCV-infected patient (Figure 1). The objective of this study is to evaluate whether adequate ribavirin exposure ($AUC_{0–4\ h}$ ≥1.755 mg•h/l) can be achieved after dose advice based on the $AUC_{0–4\ h}$ of a single weight-based dose of ribavirin.

Methods

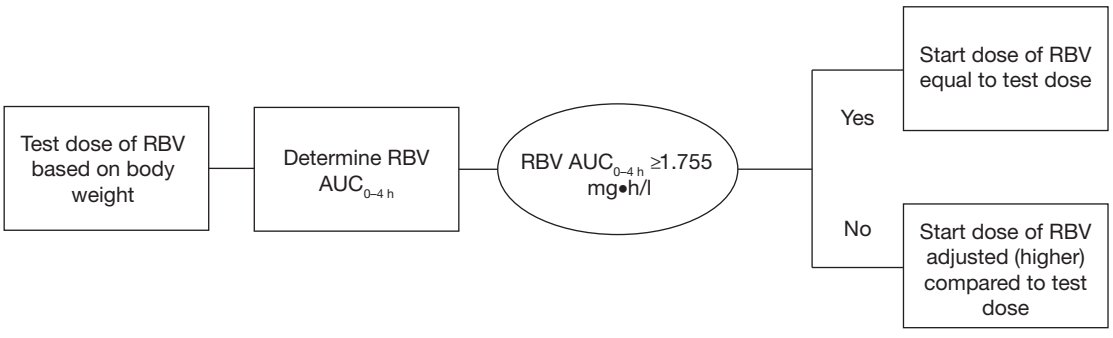
This open-label, prospective, multicentre, Phase IIa trial was conducted at Radboud University Medical Center, Nijmegen, and Erasmus University Medical Center, Rotterdam, both in the Netherlands, and at University Hospital Bonn, Bonn, Germany. The trial was approved by the Investigational Review Boards of the study sites and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study was registered at The European Union Clinical Trials Register (EudraCT Number 2010-020371-22). All participants signed informed consent prior to screening evaluations.

The study was designed to determine whether adequate exposure to ribavirin, that is ribavirin $AUC_{0–4\ h}$ ≥1.755 mg•h/l can be achieved after dose advice based on the $AUC_{0–4\ h}$ of a single weight-based dose of ribavirin. The primary outcome was the proportion of subjects with an $AUC_{0–4\ h}$ ≥1.755 mg•h/l after the second dose of ribavirin. Secondary objectives were to evaluate the number of patients that need a dose adjustment, if there are subgroups of HCV-infected patients who more often need a dose adjustment to achieve sufficient exposure to ribavirin and to evaluate the safety and tolerability of an adjusted dose of ribavirin in (formerly) HCV-infected individuals.

HCV-treatment experienced patients were selected who were at least 18 years at screening, had tolerated ribavirin in the past and who were either cured or not yet eligible for subsequent HCV treatment. Main exclusion criteria were ribavirin use within 90 days prior to the first dose, pregnancy or breastfeeding, haemoglobinopathies, severe pre-existing cardiac disease, severe psychiatric condition, haemoglobin <7.5 mmol/l (female) or <8.5 mmol/l (male), $CD4^+$ T-cell count <200 cells/mm^3 within 3 months prior to screening for HIV-positive patients, creatinine clearance <50 ml/min or signs of progressive liver disease.

On day 1 of the study, participants received a single dose of ribavirin based on their body weight (<75 kg: 400 mg ribavirin [two tablets of 200 mg Copegus®; Roche, Woerden, the Netherlands], ≥75 kg: 600 mg ribavirin [three tablets of 200 mg Copegus®; Roche]). Medication was taken at the study centre with a standardized breakfast (two pieces of brown bread, one slice of cheese and one slice of meat, one cup of custard and one cup of water [200 ml]). Blood samples were taken before and at 0.5, 1, 1.5, 2, 3 and 4 h after ribavirin intake to measure plasma ribavirin concentrations and to calculate $AUC_{0–4\ h}$. If ribavirin $AUC_{0–4\ h}$ was adequate, that is ≥1.755 mg•h/l, subjects received the same dose on day 29. If exposure to ribavirin was too low, that is an $AUC_{0–4\ h}$ <1.755 mg•h/l, an adjusted dose of ribavirin was administered on day 29, based on a predefined algorithm (Table 1). On day 29, after the second dose

Figure 1. The ARRIBA concept



$AUC_{0–4\ h}$, area under the concentration–time curve up to 4 h after intake of ribavirin (RBV).

Table 1. Predefined dosing algorithm for the second ribavirin dose based on the $AUC_{0-4\,h}$ after the first weight-based dose of ribavirin

$AUC_{0-4\,h}$ after first dose	Adjusted second dose
After 400 mg (that is, body weight <75 kg)	
≥1.755 mg•h/l	400 mg (no adjustment)
1.20–1.76 mg•h/l	600 mg
0.90–1.20 mg•h/l	800 mg
<0.90 mg•h/l	1,000 mg
After 600 mg (that is, body weight ≥75 kg)	
≥1.755 mg•h/l	600 mg (no adjustment)
1.35–1.76 mg•h/l	800 mg
1.10–1.35 mg•h/l	1,000 mg
0.90–1.10 mg•h/l	1,200 mg
<0.90 mg•h/l	1,400 mg

$AUC_{0-4\,h}$, area under the concentration–time curve up to 4 h after intake of ribavirin.

of ribavirin taken with the same standardized breakfast, blood samples were taken again at the same time points to measure plasma ribavirin concentrations and to calculate $AUC_{0-4\,h}$.

Blood samples for assessment of pharmacokinetic parameters of ribavirin were collected into heparinized tubes and centrifuged for 5 min at 2,500 *g* at 20°C within 5–6 h to obtain clear plasma. Plasma was transferred to polypropylene tubes and stored at -40°C until further bioanalysis. Plasma samples from all study sites were transported to the laboratory of the Pharmacy of the Radboud University Medical Center. Samples were prepared by a procedure previously described by Loregian *et al*. [21]. The concentrations of ribavirin in plasma were analysed by use of a validated reversed-phase high-pressure liquid chromatography (HPLC) method with UV detection [22]. The linear calibration ranges in plasma were from 0.03 mg/l to 12.0 mg/l.

Based on the individual plasma concentration–time data, the $AUC_{0-4\,h}$ was calculated by non-compartmental methods using the linear log trapezoidal rule in Winnonlin version 6.3. If a concentration of ribavirin was detected in the pre-dose sample on day 29, the $AUC_{0-4\,h}$ was corrected for this amount.

Since the primary outcome was the proportion of subjects with an adequate $AUC_{0-4\,h}$ ≥1.755 mg•h/l after the second dose, the percentage of patients with an $AUC_{0-4\,h}$ ≥1.755 mg•h/l was calculated on day 1 and day 29 and the McNemar test was carried out to compare day 1 and day 29 data using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA).

With a planned sample size of 50 subjects we would have sufficient power to demonstrate an increase in the proportion of subjects with an adequate AUC from 50% to 75%. We planned an interim analysis after 50% of the intended total number of patients had completed the study.

Results

We present the results from the planned interim analysis. A total of 26 patients (17 males) completed both pharmacokinetic days. Median (range) age and body mass index (BMI) were 50 (20–70) years and 23 (18–35) kg/m^2, respectively. All subjects were Caucasian, 14 were HIV-coinfected and 16 had achieved an SVR prior to the study.

In total, 12 subjects received an initial weight-based dose of 400 mg and 14 subjects received 600 mg on day 1. The geometric mean (95% CI) ribavirin $AUC_{0-4\,h}$ on day 1 was 1.67 (1.44–1.92) mg•h/l with only 9 out of 26 (35%) subjects reaching the AUC target. Therefore, at day 29, 17 subjects (65%) received an adjusted dose of ribavirin. The distribution of adjusted ribavirin doses was: 600 mg for six patients, 800 mg for six patients, 1,000 mg for four patients and one patient received 1,200 mg on day 29. On day 29 the geometric mean (95% CI) ribavirin $AUC_{0-4\,h}$ increased to 1.90 (1.62–2.21) mg•h/l and now 16 subjects (62%) had an $AUC_{0-4\,h}$ ≥1.755 mg•h/l, which is significantly higher than on day 1 (P<0.05, McNemar; Figures 2 and 3). In two patients ribavirin was detected in the pre-dose sample on day 29, their $AUC_{0-4\,h}$ was corrected for this. From the subjects with a dose intervention, eight (47%) had an adequate $AUC_{0-4\,h}$ on day 29. Eight patients with adequate exposure on day 1 were still on target after the second dose.

In a post hoc analysis there was no indication for a subgroup of patients not responding to the dose intervention, but numbers were small (Table 2). Overall, all subgroups demonstrated a 20–30% increase in adequate AUCs.

No serious adverse events were reported. In total, 46 adverse events were reported by 18 subjects. Sixteen adverse events were possibly related to the study drug. Two of these, headache in one patient and diarrhoea in another patient, were reported as grade 2 intensity. All other adverse events were reported grade 1.

Discussion

With our ARRIBA concept, we were able to increase the percentage of subjects with adequate exposure to ribavirin, that is $AUC_{0-4\,h}$ ≥1.755 mg•h/l, from 35% to 62% after the dose advice based on the $AUC_{0-4\,h}$ of the single weight-based dose of ribavirin. Higher exposure to ribavirin is associated with a better response to treatment and therefore this ARRIBA approach can help optimize treatment with ribavirin for an individual patient.

Figure 2. Mean ribavirin plasma concentrations versus time curve after a single dose based on body weight (day 1) and after a single dose based on individualized dose advice (day 29)

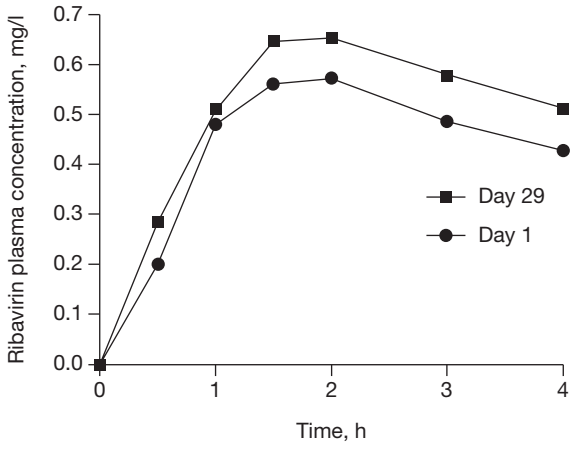
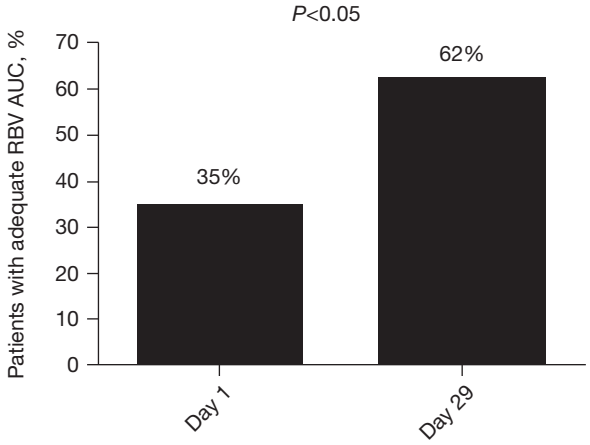


Figure 3. Percentage of patients with a ribavirin $AUC_{0-4\ h}$ ≥1.755 mg•h/l after a single dose based on body weight (day 1) and after a single dose based on individualized dose advice (day 29)



$AUC_{0-4\ h}$, area under the concentration–time curve up to 4 h after intake of ribavirin (RBV).

Table 2. Percentage of subjects with adequate $AUC_{0-4\ h}$ on day 1 (after weight-based dose of ribavirin) and on day 29 (after dose intervention)

Subgroup	*n*	Adequate AUC on day 1, %	Adequate AUC on day 29, %	Increase, %
HIV coinfection				
HIV-positive	14	43	71	28
HIV-negative	12	25	50	25
SVR status				
SVR	16	31	63	32
No SVR	10	40	60	20
Genotype				
Genotype-1	20	40	60	20
Non-genotype-1	6	17	67	50
Gender				
Male	17	41	65	24
Female	9	22	56	34
Ribavirin dose/kg body weight[a]				
<6.61 mg/kg	13	23	46	23
>6.61 mg/kg	13	46	77	31

[a]Median ribavirin dose/kg body weight was 6.61 mg/kg body weight. $AUC_{0-4\ h}$, area under the concentration–time curve up to 4 h after intake of ribavirin; SVR, sustained virological response.

Individualizing therapy with ribavirin based on targeting higher ribavirin plasma concentrations does lead to high SVR rates as several studies have shown [12,23,24]. Usually, therapeutic drug monitoring, measuring ribavirin concentrations to reach and maintain these concentrations in a therapeutic range, is performed at steady state. In the case of ribavirin, interventions at steady state are probably too late to affect treatment outcome. With this ARRIBA concept (Figure 1) we have shown that it is possible to increase the exposure to ribavirin with a dose adjustment, thereby increasing the number of patients who can start HCV treatment with adequate exposure to ribavirin. As Loustaud-Ratti *et al.* [20] showed, this exposure is associated with realizing a higher chance for achieving SVR when patients are treated with pegylated interferon and ribavirin. This individualized concept is also more favourable than treating all patients with higher ribavirin doses. No significant effect of non-individualized higher doses of ribavirin on SVR rates has been seen in trials [25–27] and some patients are probably over-treated which can lead to more anaemia and other adverse events.

Because no resistance to ribavirin in HCV patients is described, it is very unlikely that a single ribavirin test dose will lead to resistant virus.

In the study from Loustaud-Ratti *et al.* [20], the percentage of patients with an $AUC_{0-4\ h}$ ≤1.755 mg•h/l was 58%, which is comparable to the 65% found in this study. We expected to increase the percentage of patients with adequate ribavirin exposure by 25%, and we were able to increase this by 27%. On the other hand, there was still a proportion of patients who did not achieve adequate exposure to ribavirin and other dosing regimens should be explored. Our dosing algorithm was based on the linear relationship between the AUC from time zero to the last measurable concentration (AUC_{tf}) and single doses from 200 to 1,200 mg [28]. Even though the ribavirin AUCs increased in

13 of 17 (76%) subjects who received an increased dose, no more than 8 (47%) reached the target AUC. A possible explanation for this finding could be that although there is a linear relationship between AUC_{tf} and single doses, this linear relationship may not exist for $AUC_{0–4\ h}$. Ribavirin is a hydrophilic compound and requires nucleoside transporters for active transport into the cell [29,30]. The relationship between the ribavirin dose and the maximum plasma concentration is curvilinear, tending to asymptote above single doses of 800 mg, perhaps because of saturation of these nucleoside transporters [28]. It is possible that saturation of these transporters occurred with the doses used in our study. Therefore, other dosing algorithms or dosing frequencies should be explored and it was decided to terminate this study after the interim analysis.

A limitation of our study is that the threshold for the ribavirin AUC was determined in HCV treatment-naive patients treated with pegylated interferon and ribavirin [20]. The HCV landscape is changing rapidly and although ribavirin is still a component of various DAA-based treatment combinations, it remains to be determined whether the same threshold for ribavirin concentrations is valid. Preliminary studies from our group suggest, however, that a therapeutic range for ribavirin can also be defined when used as part of DAA-based HCV therapy [31].

In conclusion, our ARRIBA concept of a dose based on a test dose of ribavirin leads to an increased proportion of patients with an adequate AUC compared to the traditional weight-based dose of ribavirin. However, as there still remains a significant proportion of patients underdosed, alternative dosing algorithms should be explored.

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Disclosure statement

LK received honoraria for speaking at educational events from Gilead. JKR received honoraria for consulting or speaking at educational events from AbbVie, Bionor, BMS, Gilead, Janssen, Merck, Tibotec and ViiV. JPHD has received honoraria or research grants from Novartis, Zambon, Ipsen, Otsuka, Falk, Merck, Janssen, AbbVie and Norgine. DMB received honoraria or research grants from AbbVie, BMS, Gilead, Janssen/Tibotec, Merck and Roche. All other authors have no conflicts to disclose.

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