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RIBAVIRIN DOSAGE IN HCV GENOTYPES 2 AND 3 PATIENTS COMPLETING SHORT THERAPY WITH PEG-INTERFERON ALFA- 2B AND RIBAVIRIN

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Key words: ribavirin, peginterferon, HCV, antiviral therapy, chronic hepatitis C

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3 **Background.** The optimal dose of ribavirin to be used in combination with Peg-IFN in HCV genotype
4 2 and 3 patients undergoing short treatment has not been established.

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7 **Aim.** To explore the relationship between starting ribavirin doses, expressed as mg/kg body weight and
8 both rapid viral response at treatment week 4 [RVR] and sustained virological response [SVR] in
9 patients treated for 12-14 weeks with peg-interferon alfa-2b and ribavirin.

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12 **Methods.** A post-hoc analysis of data collected from two multicenter clinical trials was performed.
13 Multiple regression analyses were employed to identify independent baseline and on-treatment
14 predictors of RVR and SVR. For each dose of ribavirin, the empirical estimated probability of response
15 was computed and the continuous exposure index was dichotomized by using a recursive partitioning
16 and amalgamation method.

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21 **Results.** A non-linear relationship was ascertained between ribavirin dose and RVR but not SVR. A
22 dose of 15.2 mg/kg was selected as the best splitting value for discriminating RVR versus non RVR.
23 Regression analysis identified low baseline viremia, genotype 2, and high ribavirin dose as independent
24 prognostic factors for RVR. The likelihood of an SVR was not correlated with baseline ribavirin dose,
25 but was independently predicted by adherence to the full dose throughout treatment and normal
26 platelet counts.

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31 **Conclusions.** Starting high ribavirin doses appeared capable to increase the rate of RVR in HCV
32 genotype 2 and 3 patients undergoing short treatment. Maintenance of the full planned dose throughout
33 treatment was essential for achieving optimal SVR rates.

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INTRODUCTION

The benefit of short (12 or 14 weeks) therapy with Peg-Interferon (Peg-IFN) in combination with ribavirin for patients with chronic HCV genotypes 2 or 3 infection has been documented in recent clinical investigations [1-6]. Patients who will benefit the most by short therapy are lean, non-cirrhotic individuals capable to clear the virus at treatment week 4 [7]. This experimental evidence has been incorporated in some, but not all, treatment guidelines issued by scientific societies [8-10], so that uncertainties still remain about implementing short therapy in everyday clinical practice. Indeed, a clear-cut benefit of short therapy in comparison with the standard 24 week treatment did not emerge in some other clinical trials [11,12].

A controversial issue in genotypes 2 and 3 therapy, that might explain part of previous inconsistencies across trials, is the optimal dose of ribavirin to be used in combination with Peg-IFN: whenever ribavirin was given at higher dosage (800-1400 mg daily, according to body weight) than the one currently recommended (800 mg daily), the benefit of short therapy appeared evident [1-4]; contrariwise, when administered dosage was the fixed 800 mg daily dosage [11-12], the benefit waned off.

The predominant mechanism(s) of ribavirin action against HCV are yet to be established. Although ribavirin monotherapy imposes a transient HCV decline early on therapy, the drug has no apparent long term effect on serum HCV RNA levels [13,14]; however, in combination with interferon, it dramatically improves the success of therapy. In naïve patients undergoing treatment with conventional interferon and ribavirin, higher ribavirin concentrations were associated with a higher likelihood of response [15]. Plasma ribavirin concentrations have been shown to correlate with the starting dose of the drug [15], so that selecting appropriate starting dose and maintaining it throughout treatment impact positively on therapeutic outcome. In genotype 1 patients, the probability of achieving a sustained virological response (SVR) increased as a function of the ribavirin dose (mg/kg of body weight), with a 40-50% increase for a 12-16 mg/kg dose [16]. Data are less clear for genotypes 2 and 3 infection, as a single study failed to prove a correlation between probability of SVR after 24 weeks of treatment and the ribavirin dose [16]. Although debate is ongoing as to which ribavirin dosage should be administered in combination with Peg-IFN, it is clear that ribavirin activity is dose/exposure dependent [15,16], and selecting and maintaining the optimal dose of the drug might be crucial for a successful therapy. This concept might apply particularly when considering short treatment duration.

Objective of this analysis was to explore the relationship between starting ribavirin and both rapid viral response at treatment week 4 (RVR) and SVR in patients with genotypes 2 and 3 undergoing short (12 or 14 weeks) therapy with ribavirin and Peg-IFN alfa-2b.

PATIENTS AND METHODS

Study subjects

Data used in this analysis were collected from two multicenter clinical trials, run in Italy and Scandinavia, in naïve patients with genotypes 2 and 3. The complete inclusion and exclusion criteria, study design and primary results of which are available elsewhere [5,7]. The primary efficacy objective of these trials was to compare SVR following Peg-IFN alfa-2b (Peg-Intron; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin administered for short (12 or 14 weeks, respectively) or standard (24 weeks) duration. All patients received Peg-IFN alfa-2b 1.5 µg/kg subcutaneously weekly together with ribavirin administered orally. In the study by Mangia et al. [7], 718 patients were treated with Peg-IFN alfa-2b plus ribavirin 1000 or 1200 mg/day on the basis of body weight higher or lower than 75 kg; 496 patients with week 4 viral clearance (labelled as rapid virological responders, RVR) were allocated to 12 week treatment duration, whereas those without RVR were given therapy for 24 weeks. Italian patients with missing serum creatinine values at baseline were not included in the present analysis. In the 428 patients enrolled in the trial by Dalgard et al [5], ribavirin dose varied according to body weight, as follows: 800 mg for body weight <65 kg, 1000 mg for body weight ranging from 65 to 85 kg, 1200 for body weight ranging from 85 and 105 kg, and 1400 for body weight >105 kg. For sake of homogeneity with the design of the Italian study, of the original 428 Scandinavian patients only 148 individuals with RVR who were treated for 14 weeks, and 130 non-RVR patients whose treatment lasted for 24 weeks were considered eligible for the present investigation; the remaining 150 patients with RVR who were treated for the standard 24 weeks were excluded. **Among Scandinavian patients considered eligible, only 10 had body weight > 105 kg and required 1400 mg, therefore the combined database allowed us to evaluate a large series of patients, including a comparable number of genotype 2 and 3, who received similar dosages of ribavirin.**

Per protocol, the ribavirin dose had to be reduced by 200 mg daily in patients who experienced a decrease in haemoglobin level of more than 2 g/dl during treatment, and by 400 mg daily if haemoglobin levels decreased to less than 10 g/dl. Ribavirin was discontinued if haemoglobin levels decreased to less than 8.5 g/dl. The use of erythropoietin was not allowed. Anaemia was defined as

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3 haemoglobin concentration <10 g/dl documented on at least one occasion during the studies. For
4 patients who were intolerant to Peg-IFN alfa-2b, dose reductions in decrements of 12% of the assigned
5 dose were allowed.
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10 **Analytic Methods**

11 Definitions. The HCV RNA level was measured using the COBAS AMPLICOR HCV Test [(Roche
12 Molecular Systems, Branchburg, NJ, USA), version 2.0; limit of detection 50 IU/ml]. Rapid virologic
13 response (RVR) was defined as undetectable serum HCV RNA at treatment week 4. End-of-treatment
14 response (ETR) was defined as undetectable HCV RNA at weeks 12, 14 or 24 according to the
15 different therapeutic regimens, and SVR was defined as undetectable HCV RNA at the end of a 24
16 week follow-up period.
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24 **Statistical analysis**

25 As the primary objective of the present study was to explore the impact of ribavirin dose on both RVR
26 and SVR, only patients who could tolerate antiviral drugs for the planned length of therapy were
27 retained in the analysis. Patients who had reduction of ribavirin and/or Peg-IFN at some point during
28 treatment but completed the planned treatment duration were retained. Consequently, of the total 905
29 eligible patients enrolled in the two previous trials, only 673 patients (405 from the Italian cohort and
30 268 from the Scandinavian cohort) were retained. Of the 232 excluded patients, 120 had no serum
31 creatinine available for glomerular filtration (GFR) rate calculation, and 112 (10 among patients
32 treated for 12-14 weeks and 102 among those treated for 24 weeks) had a premature treatment
33 discontinuation for major side effects or were lost to follow up.
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42 Baseline patients' characteristics were reported as frequencies and groups were compared with Pearson
43 chi-square. Multiple logistic regression analyses were employed to identify independent baseline and
44 on-treatment predictors of RVR and SVR, with age, sex, body mass index, genotype, baseline viremia,
45 platelet count, aspartate aminotransferase-to-platelet ratio index (APRI) score [17,18], and starting
46 ribavirin dose as dependent variables. An exploratory analysis was made in order to assess the nature of
47 the relationship between dose of ribavirin adjusted for GFR and response probability: for each dose, the
48 empirical estimated probability of response was computed. Moreover, the continuous exposure index
49 was dichotomized using the best splitting value by using a Recursive Partitioning and Amalgamation
50 (RECPAM) method [19]. All analyses were performed using SAS® release 9.1. Two-tailed P-values
51 <0.05 were considered significant.
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RESULTS

Characteristics of patients

Baseline features of patients derived from the two studies are outlined in Table 1. There were differences in demographics, serum biochemistry, and virologic features of patients from the two cohorts: in the Scandinavian cohort, patients were as a mean 10 years younger, had a prevalent genotype 3 infection, and lower frequency of advanced liver damage, as indicated by the lower proportion of individuals with low platelet counts and APRI score >2. Conversely, a higher proportion of Italian patients received a high (≥ 15 mg/kg) dose of ribavirin, a finding that might be related to differences in the schedule of ribavirin administration between the two studies: a more stringent weight-related dosing in the Scandinavian trial, and a looser relation to body weight in the Italian study.

SVR rates and predictability of SVR by RVR in accordance with the different duration of treatment are reported in Table 2.

Impact of ribavirin dosing on rapid virologic response.

No patients had to reduce the ribavirin dose by treatment week 4, so that the relationship between starting ribavirin dose and the probability of RVR could be detailed. As shown in Figure 1, the dose of ribavirin, expressed in mg/kg of body weight, may be a determining factor of RVR in genotype 2 and 3 patients: the probability of RVR increased with increasing ribavirin dose. However, the relationship was a non-linear one and the probability increased from approximately 54% to 80% for a ribavirin dose increase from 13 to 15.2 mg/kg. The dose of 15.2 mg/kg was determined as the best splitting value for discriminating RVR versus non RVR: among the 147 patients receiving a dose of ribavirin higher than 15 mg/kg an 80% probability of achieving an RVR was observed, while for the 528 patients who received a lower dose, the RVR rate was 67%. At the univariate analysis of predictors of RVR, body mass index, genotype, viral load, and ribavirin dose were significantly associated with RVR [Table 3]. Multiple logistic regression analysis identified low baseline viremia ($< 400,000$ IU/ml) (OR = 2.5; 95% CI 1.6-3.8), genotype 2 (OR=1.7; 95% CI 1.2-2.5), and high ribavirin dose (15 mg/kg) (OR = 1.6; 95% CI 1.1-2.6) as independent prognostic factors.

Predictors of RVR at the univariate analysis are shown separately for HCV genotypes 2 and 3 in Table 4. At multivariate analysis, young age and low viremia were independent predictors of RVR in genotype 2 patients, OR =2.06, 95% CI 1.16-3.64 and OR= 2.01 (1.18-3.40), respectively. For

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3 genotype 3 patients independent predictors of RVR were low viremia (OR= 2.84, 95% CI 1.60-5.01)
4 high ribavirin dose (OR= 2.13, 95% CI 1.07-4.26) and young age (OR= 2.91, 95% CI 1.77-4.80).
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8 **Impact of ribavirin dosing on sustained virological response**

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10 As per protocol, antiviral therapy lasted 12-14 weeks in 473 patients with RVR, and 364 of them
11 (77.0%) attained an SVR. The likelihood of an SVR was not correlated with baseline ribavirin dose,
12 expressed in mg/kg of body weight but rather to the inability to adhere to the prescribed dose of the
13 drug. Low viral load (p=0.033), normal platelet count (p=0.0001) and maintenance of full dose of
14 ribavirin throughout treatment were associated with SVR (p=0.0001). Decreasing ribavirin dose
15 relative to target during treatment was a predictor of relapse: of patients who achieved an SVR, only
16 7% had to reduce the dose of ribavirin after the initial 4 weeks of therapy with a consequent 25% of
17 total amount of ribavirin reduction, whereas 19% of those who failed to clear the virus did so. At
18 multivariate analysis, independent predictors of SVR in patients with RVR were no ribavirin dose
19 reduction (OR =3.1; 95% CI 1.6-5.9) and normal platelet counts (OR = 2.75; 95% CI 1.6-4.7).
20 Two hundred patients without RVR were treated per protocol for the standard 24 weeks of therapy,
21 and 134 of them achieved an SVR (67%). At univariate analysis, female sex (p=0.09) and high baseline
22 ribavirin dose (p=0.05) emerged as the only two predictors of SVR. In particular, of 30 patients
23 without RVR who received ribavirin at dose of ≥ 15 mg/kg of body weight, 23 (78.7%) individuals
24 attained an SVR, as opposed to 110 of 170 patients in the lower ribavirin dose (64.7%). Dose
25 reduction of ribavirin only occurred in 2% of those without RVR and was not associated with response.
26 At the multivariate analysis no factor was independently associated with SVR.
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42 **Ribavirin-related side effects**

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44 Sixty four of 673 patients with RVR required modification of the ribavirin dose due to a drop in
45 haemoglobin levels below 10 g/dl. Anaemia was more frequently detected among patients treated with
46 ribavirin dose of ≥ 15 mg/kg than in those who were treated with lower doses (9.5 vs 4.4%), but the
47 difference was not significant (p=0.11). Other ribavirin related side effects as cutaneous rash, cough
48 and dry skin were not differently distributed among patients in the low and high ribavirin dosage: 3%
49 vs 2.4% (p=0.35).
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DISCUSSION

Current analysis evaluated the impact of ribavirin dosing on the therapeutic outcome in patients with genotype 2 and 3 infection who received Peg-IFN alfa-2b in combination with ribavirin for a short treatment duration. Original data were derived from two clinical trials where patients were allocated to short or standard treatment duration depending on whether or not they attained an RVR [5,7]. We could ascertain a relationship between the dose of ribavirin, expressed as mg/kg of body weight, and the likelihood of achieving an RVR. The relationship held true particularly for patients infected with HCV genotype 3. Furthermore, in RVR patients the SVR rate was higher among those who were compliant with the initially assigned ribavirin dose throughout treatment.

Weight-based dosing of ribavirin has been extensively utilized in patients with genotype 1, in whom a relationship between ribavirin dose and SVR has been established when the drug was administered in association with either Peg-IFN alfa-2a and alfa-2b [20-25]. Based on these data, the ribavirin dose of 15 mg/kg was selected as the best balance between efficacy and a manageable safety profile. Data are less clear for genotypes 2 and 3. When administered in combination with Peg-IFN alfa-2a for 48 weeks, ribavirin doses of 800 or 1000-1200 mg daily produced equivalent outcomes [22]. Similarly, a comparative trial of fixed- (800 mg daily) or weight-based doses of ribavirin (800-1400 mg daily) in combination with Peg-IFN alfa-2b showed equal SVR rates: 67.7% vs 65.0% [23]. This study also documented that responses were consistent across all body weight categories in the weight-based group, but lower SVR were attained with increasing weight [22]. However, a randomized study of Peg-IFN alfa-2a plus ribavirin for 24 weeks at doses of either 400 or 800 mg claimed no decrease in SVR rates in the lower dose group among genotype 3 infection, but SVR rates declined from the 67.5% rate in the 800 mg group to 63.9% in the 400 mg group [24].

It needs to be reminded that all previous trials administered therapy for at least 24 weeks. In principle, it might be conceivable that for the overall population of genotype 2 and 3 patients a fixed 800 mg/day dose of ribavirin could be enough to achieve optimal response rates after 24 weeks of therapy. However, as shorter treatment courses may be viable in select genotype 2 and 3 patients, such as those with RVR, it could be speculated that much more promising results could be obtained by weight adjustment of ribavirin dose when considering abbreviated treatment. Indirect evidences support this claim. In the NORDynamIC trial, patients who achieved SVR had significantly lower body weight

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3 than those who did not; as a fixed dose of 800 mg of ribavirin was administered to all patients, it is
4 plausible that SVR patients had been exposed to higher dose of ribavirin than those who did not
5 achieve SVR [13]. A post-hoc analysis of the trial showed that the chance of achieving an SVR was
6 associated with higher median serum ribavirin concentrations at week 4 [25].
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10 In a study from Taiwan, a RVR rate of 86% was registered following therapy with Peg-IFN alpha-2a
11 and weight-based ribavirin (1000-1200 mg daily); considering that the mean body weight of patients
12 included into the study was 68 kg, a mean dose of 15 to 20 mg/kg was administered and could be one
13 factor that might have impacted on the pronounced RVR rate [4]. In opposition, the ACCELERATE
14 trial administered a fixed dose of 800 mg to patients whose mean body weight was 81.5 kg;
15 consequently, they received a low ribavirin dose (9.8 mg daily, as a mean) and attained an RVR at a
16 rate as low as 65.5% [12]. We acknowledge that, although suggestive, all mentioned evidences
17 should be interpreted with caution because they were derived from secondary analyses with potential
18 confounding variables.
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28 The present analysis has added new evidence to the ongoing debate on the optimal ribavirin dosage.
29 We found a relationship between body weight and RVR, an observation suggesting that the dose of
30 ribavirin per kilogram may contribute substantially to response to therapy in patients undergoing short
31 therapy. It is important to note that the type of the relationship was non-linear, but S-shaped, with a low
32 and a high threshold value for dosing of ribavirin. From our analysis it turned out that a threshold
33 value of ≥ 15.2 mg/kg was expected to result in better outcome of therapy when considering short
34 treatment. In previous studies [16] the concept that ribavirin clearance is linearly dependent on renal
35 function was not incorporated into the analysis, at variance in our patients as suggested by Bruchfeld
36 [25], the renal effect could be excluded after the adjustment for GFR. As a matter of fact, 80% of
37 patients given ribavirin dose ≥ 15.2 mg/kg achieve an RVR, as compared to 54% of those who were
38 given 13 mg/kg.
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48 Reddy et al reported that as long as patients achieved RVR, ribavirin dose reduction had minimal
49 impact on SVR after standard treatment duration [27]. Our findings on RVR patients who were treated
50 with only 12-14 weeks of therapy demonstrate lower SVR rates when the initial dosage of ribavirin had
51 to be reduced. Indeed, 46 of 473 patients with RVR required dose modification due to a drop in
52 haemoglobin levels below 10 g/dl, and 54% of them attained an SVR as opposed to a 79% rate in
53 those who could tolerate the starting dose of ribavirin throughout treatment. Although data modelling
54 suggests that RVR increases with ribavirin doses that equate to ≥ 15 mg/kg, there is also a simultaneous
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3 increase in the rate of anaemia. To contrast anaemia development, the use of off-label erythropoietin
4 has been implemented [28-30], but the drug was not allowed in our patients for cost-saving
5 considerations.
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8 In summary, the results of our study suggest that in patients with HCV genotypes 2 and 3 infection
9 completing short therapy with Peg-IFN alfa-2b in combination with weight-based doses of ribavirin,
10 a high starting dose of ribavirin appeared one of the factors influencing the rate of RVR. We would
11 recommend to administer ribavirin at a dose of ≥ 15 mg/kg when considering short treatment duration.
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14 **Larger prospective studies would be required to confirm the role of higher ribavirin doses on SVR as**
15 **both the need of maintaining the full planned dose of ribavirin throughout treatment to achieve an**
16 **optimal SVR rate or the improvement of SVR in patients still viremic at treatment week 4 after an**
17 **intensified ribavirin dosing suggest that higher ribavirin dosage affects SVR. Finally, the evidence that**
18 **genotype 3 may derive more benefit from high dosages of ribavirin warrant further confirmation of the**
19 **present post-hoc analysis.**
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11 Legend to Figure

12 Probability of rapid virologic response [RVR] in patients with hepatitis C virus genotype 2 and 3 as a
13 function of the ribavirin dose per kilogram of body weight after 12-14 weeks treatment. Observed
14 values are presented as circles. The dashed lines are the 95% point-wise confidence intervals.
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Table 1. Comparison of the demographic, biochemical, and virological profiles of 673 patients with genotype 2 and 3 infection, selected from the two original studies.

	Dalgard, 2008	Mangia, 2009
Total number of patients	268	405
Age:		
mean [years]	40.4 ±9.1	50.58±12.4
range	[19-63]	[19-75]
<45 years [no., %]	184(69)	146 (36)
Gender: male [no., %]	166 (62]	240 (59)
Body mass index:		
mean [kg/m ²]	25.7±4.3	25.9±3.6
range	(16-41)	(16-40)
<30 kg/m ² [no., %]	225 (84)	345 (85)
Body weight: [kg]		
<65 [no., %]	65 (24)	127 (31)
<65-85 [no., %]	125 (47)	230 (57)
>85-105 [no., %]	64 (24)	44 (11)
>105 [no., %]	14 (5)	4 (1)
Genotype 2 [no., %]	53 (20)	283 (70)
Genotype 3 [no., %]	215 (80)	122 (30)
Viral load:		
≥400.000 IU/ml [no., %]	204 (76)	247 (61)
Platelet count: *		
>140.000 mm ³ [no., %]	244 (92)	310 (78)
APRI : score >2 [no., %] **	32 (12)	89 (22)
Ribavirin dose:		
≥15 mg/kg [no., %]	19 (7)	128 (32)

* 8 missing values

** 16 missing values

Table 2. Rates of RVR, EOT and SVR according to RVR

Patients group by time point	All patients	Patients with RVR treated for 12 weeks	Patients without RVR treated for 24 weeks
Total	n=673	N=473	n=200
EOT	606 (90.0)	425 (89.9)	181 (90.5)
SVR	498 (74.0)	364 (77.0)	134 (67.0)

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Table 3. Univariate analysis of predictors of a rapid virological response (RVR) in 673 patients with HCV genotype 2 and 3 infection

	RVR	No RVR	P values
Total number of patients	473	200	
Age: <45 yrs [no., %]	233 (49)	97 (48)	0.84
Gender : male [no., %]	284 (60)	122 (61)	0.86
Body Mass Index:			
<30 kg/m ² [no., %]	410 (87)	160 (80)	0.035
>30 kg/m ² [no., %]	63 (13)	40 (20)	
Genotype 2 [no., %]	254 (54)	82 (41)	0.003
Genotype 3 [no., %]	219 (46)	118 (59)	
Viral load:			
≥ 400.000 IU/ml [no., %]	292 (62)	159 (79)	0.0001
<400.000 IU/ml [no., %]	181 (38)	41 (20)	
Platelet count:			
>140.000 mm ³ [no., %]	394 (83)	158 (79)	0.21
APRI score: <2 [no., %]	399 (84)	161 (80)	0.18
Ribavirin dose:			
≥15 mg/kg [no., %]	117 (25)	30 (15)	0.006
< 15 mg/kg [no., %]	356 (75)	170 (85)	

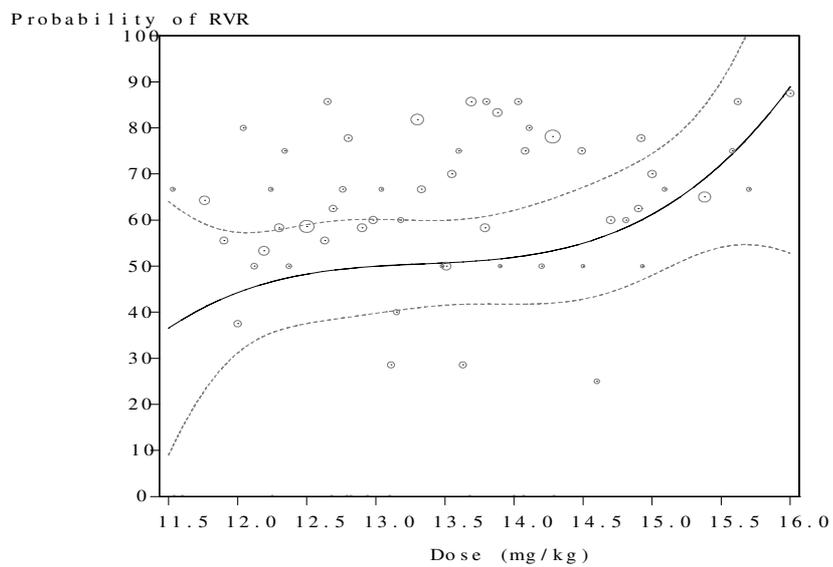
Table 4. Univariate analysis of predictors of rapid virological response (RVR) in patients sorted out by the HCV genotype

	Genotype 2		P	Genotype 3		P
	RVR	No RVR		RVR	No RVR	
Total number of patients	254	82		219	118	
Age: <45 yrs [no., %]	189 (74)	49 (60)	0.017	168 (77)	64 (54)	0.001
Gender : male [no., %]	137 (54)	50 (61)	0.30	147 (67)	72 (61)	0.28
Body Mass Index:						
<30 kg/m ² [no., %]	221 (87)	62 (76)	0.022	189 (86)	98 (83)	0.42
Viral load:						
>400.000 IU/ml [no., %]	100 (39)	20 (24)	0.017	138 (63)	97 (82)	0.0001
Platelet count:						
≥140.000 mm ³ [no., %]	204 (81)	58 (72)	0.08	190 (88)	102 (87)	0.86
APRI score:						
<2 [no., %]	217 (86)	60 (77)	0.06	182 (86)	103 (89)	0.60
Ribavirin dose:						
≥15 mg/kg [no., %]	69 (27)	17 (21)	0.30	48 (22)	13 (61)	0.017
< 15 mg/kg [no., %]	185 (73)	65 (79)		171 (78)	105 (89)	

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Figure 1



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