

Effect of Ribavirin Trough Concentration on Early Virological Response (EVR) According to HCV Genotype and on Early Haemoglobin (Hb) Decrease in HCV/HIV co-infected Patients Treated with RBV+Pegylated Interferon (PegIFN).

D Gonzalez de Requena, A Ibañez, D Aguilar Marucco, L Veronese, S Bonora, A D'Avolio, M Sciandra, A Sinicco, G Di Perri.

Department of Infectious Diseases, University of Torino, Torino, Italy

Background. RBV concentration was shown to correlate with Hb decrease and overall EVR in HIV+HCV+ pts. However, relationship between EVR and RBV plasma exposure according to HCV genotype has not been yet analysed. Therefore, our aim was to study the effect of RBV C_{trough} on both EVR according to HCV genotype and on early Hb decrease.

Patients and methods. HIV+HCV+ pts placed on association RBV + PegIFN alpha-2a or -2b in 2004 were prospectively evaluated. Qualitative and quantitative HCV-RNA, Hb levels, and RBV C_{trough} were measured at BL and week 2, 4, 8, and 12. HCV genotype was determined at BL. EVR was considered as a negative qualitative HCV-RNA and/or quantitative HCV-RNA decrease >2 log at week 12. Linear and logistic regression analyses were used as needed. RBV effective (EC) and toxic concentration (TC) were considered as the values associated with 50% or 90% probability of detecting EVR or Hb decrease by logistic regression. Values were given as median [IQR].

Results. Forty-one consecutive pts were included, of whom 21 (51.21%) with genotype 1 or 4. PegIFN-2a (180 ug) and -2b (1.5 ug/kg) were used in 31 and 10 pts, respectively. RBV weight-adjusted dose was 12.3 mg/kg [11.5-13.3]. HCV-RNA and Hb at BL were 6.3 log [5.94-6.64] and 15 g/dl [14-16], respectively. Overall, 31 pts (75.6%) showed EVR, with an HCV-RNA decrease of 5.44 log [-6.3; -2.06]. EVR was observed in 20/20 pts with genotype 3 as compared to 11/21 pts with genotype 1 or 4 (X²=12.59, p<0.0001). Overall, no correlation between Hb and RBV C_{trough} was found. Nevertheless, RBV C_{trough} was an independent predictor of EVR in subgroup of pts with genotype 1 or 4 (p<0.039). In the latter, RBV EC50% and EC90% were 1600 ng/ml and 2500 ng/ml, respectively. Overall maximum Hb decrease was 2.7 g/dl [-3.65; -4.5], and the lowest Hb value reached was 12.4 g/dl [11.4-13.3]. Mean RBV C_{trough} correlated with maximum Hb decrease (R=-0.358, p=0.02). Moreover, maximum Hb decrease >3 g/dl was predicted by higher RBV C_{trough} at logistic regression analysis (p=0.01). TC50% and TC90% for maximum Hb decrease >3 g/dl were 1700 ng/ml and 3000 ng/ml, respectively.

Conclusions. Our study confirmed an overall relationship between Hb decrease and RBV exposure, while, as opposite to previous reports, showed a C_{trough}-related EVR of RBV only in patients with genotype 1 or 4. Further studies are warranted in order to define the role of TDM as a tool to optimise RBV efficacy and/or tolerability according to the HCV genotype.

PATIENTS AND METHODS

HIV+HCV+ pts placed on association RBV + PegIFN alpha-2a or -2b in 2004 were prospectively evaluated at BL and weeks 2, 4, and 12.

Qualitative and quantitative HCV-RNA were performed at each study point.

Hb serum levels were also determined at BL and at weeks 2, 4, and 12 weeks. Maximum Hb decrease and minimum Hb serum levels along the 12 weeks study period were recorded.

RBV C_{trough} was measured at weeks 2, 4, 8, and 12 (when possible) by a validated HPLC method with UV detection. At least one RBV C_{trough} measurement was available for each subject.

Mean RBV C_{trough} was calculated as the mean of all available C_{trough} determinations for each subject. Results are reported in ng/ml.

EVR was considered as a negative qualitative HCV-RNA and/or quantitative HCV-RNA decrease >2 log at week 12.

Linear and logistic regression analyses were used as needed.

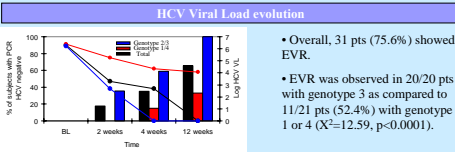
RBV effective (EC) and toxic concentrations (TC) were considered as the values associated with 50% or 90% probability of detecting EVR or Hb decrease >3 g/dl, by graphic representation of predicted probability (by logistic regression analysis) and mean RBV C_{trough}.

Values are given as median [IQR] unless other units are specified.

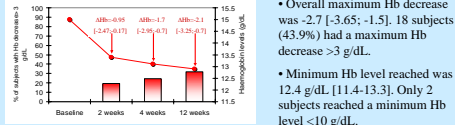
Population characteristics

Demographics and BL situation		Treatment	
N° of subjects	41	PegIFN n=2a 180 mg	31 (75.9%)
Sex (male)	28 (68.5%)	PegIFN n=2b 1.5 ug/kg	10 (24.8%)
Age (years)	41 [34-50]	RBV dose	1000 mg, 10 (24.4%)
Weight (kg)	67 [595-745]	800 mg, 27 (65.85%)	600 mg, 4 (9.75%)
Log HCV viral load at BL	6.3 [5.9-6.6]	RBV weight adjusted dose (mg/kg)	12.3 [11.5-13.4]
Genotype 1 or 4	21 (51.2%)	Concomitant antiretroviral therapy	5 (12.2%)
Haemoglobin at BL (g/dL)	15 [14-16]		
Log HIV VL at BL	2.47 [1.3-4.28]		
CD4+ at BL (cells/mm3)	499 [414-601]		

Clinical Evolution

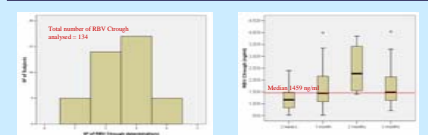


Haemoglobin evolution



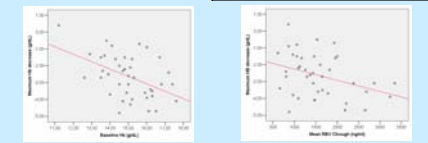
RESULTS

Pharmacokinetics



Linear Regression analysis

Δ HCV-VL at 12 weeks				Maximal Hb decrease		
Univariate	Total	Genotype 1/4	Genotype 2/3	Univariate	Univariate	Multivariate
IFN alpha type (2a=1)	-0.14 (p=0.38)	-0.252 (p=0.27)	-0.17 (p=0.48)	Hb at BL	-0.469 (p=0.002)	-0.469 (p=0.002)
RBV Dose	-0.154 (p=0.34)	-0.185 (p=0.27)	-0.14 (p=0.56)	RBV Dose	-0.326 (p=0.038)	
RBV weight adjusted dose	-0.181 (p=0.2)	-0.35 (p=0.11)	-0.26 (p=0.28)	RBV weight adjusted dose	0.11 (p=0.31)	
HCV Genotype (1/4=1)	0.656 (p<0.0001)	----	----	RBV Ctrough	-0.358 (p=0.021)	
RBV Ctrough	0.063 (p=0.7)	0.33 (p=0.1)	0.22 (p=0.37)			



PK/PD Analysis

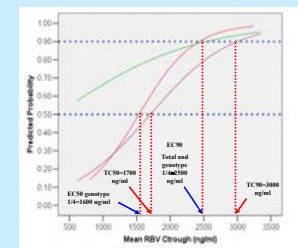
Logistic Regression analysis

Determinants of EVR				Determinants of HB decrease > 3 g/dL		
	Total	Genotype 1/4	Genotype 2/3	Univariate	Univariate	Multivariate
IFN alpha type (2a=1)	1.4 [0.3-7.2] p=0.63	-1.9 [0.25-14.8] p=0.33	----	Hb at BL	2.6 [1.3-5.1] p=0.006	2.45 [1.17-5.1] p=0.017
RBV Dose	1 [0.99-1.01] p=0.35	1.003 [0.99-1.01] p=0.43	----	RBV Dose	1.01 [1.003-1.02] p=0.009	Ns
RBV weight adjusted dose	1.28 [0.77-2.14] p=0.33	1.8 [0.83-3.9] p=0.13	----	RBV weight adjusted dose	0.77 [0.49-1.2] p=0.25	Ns
HCV Genotype (1/4=1)	na	----	----	RBV Ctrough	5.42 [1.5-19.5] p=0.01	4.95 [1.1-22.5] p=0.038
RBV Ctrough	2.8 [0.7-10.5] p=0.15	11.5 [1.13-117.2] p=0.039	----			

Graphic representation of the predicted probability of EVR and Hb decrease >3 g/dL against mean RBV C_{trough} gave an EC50 of 1600 ng/ml and a TC50 of 1700 ng/ml, respectively (see Figure).

In subjects with genotype 1/4, 8/10 (80%) subjects with RBV C_{trough} >1600 ng/ml had EVR, whereas the latter was observed in 3/11 (27.2%) subjects with <1600 ng/ml (X²=5.8, p=0.016).

In total population, 9/13 (69.2%) subjects with RBV C_{trough} >1700 ng/ml had a Hb decrease >3 g/dL, whereas such decrease was recorded in 9/28 (32.1%) subjects with <1700 ng/ml (X²=4.9, p=0.04).



CONCLUSIONS

- Our study confirmed an overall relationship between Hb decrease and RBV exposure. Nevertheless, as opposite to previous reports, in this study the correlation between RBV C_{trough} and EVR was showed only in patients infected with HCV genotype 1 or 4.
- This finding suggests that in subjects infected by HCV genotypes 2 or 3 EVR could be achieved with the standard RBV dosing, while in subjects with genotype 1 or 4 higher doses of RBV could be considered to increase the probability of EVR. In the latter, however, considering also the concentration-related risk of anemia, TDM-driven dose adjustment, associated with frequent monitoring of Hb, could allow to individualise RBV dosing.
- As observed, no therapeutic range for RBV concentrations could be defined due to the little differences between either EC50, or EC90 and TC90.
- Further studies are warranted in order to define the role of TDM as a tool to optimise RBV efficacy and/or tolerability according to the HCV genotype.

Contact Information

Daniel Gonzalez de Requena, Pharm D
e-mail: danifare@hotmail.com