PLASMA RIBAVIRIN CONCENTRATION IN HCV CIRRHOTIC PATIENTS TREATED WITH DIRECT ACTING ANTIVIRALS (DAAs)

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Background:

Ribavirin (RBV) may still be necessary in treating HCV cirrhosis with direct acting antivirals (DAAs) in spite of dose-limiting hemolytic anemia *(AISF Guidelines 2015, EASL Guidelines 2015, AASLD Guidelines 2015).*

Plasma RBV levels are reported to drive the intracellular phosphorylation rate of RBV *(Wu LS Antimicrob Agents Chemother 2015)*, however plasma RBV kinetics during DAA treatment have not been fully elucidated.

Aim:

The aim of the study was to examine RBV and Hemoglobin (Hb) kinetics in cirrhotic patients during DAA treatment.

Patients, materials and methods:

43 HCV consecutive cirrhotic patients treated with DAAs and weight-based RBV for 12 or 24 weeks have been enrolled.

Demographic, clinical, biochemical and virological characteristics of enrolled patients are shown in *Table 1*.

79% were HCV genotype 1 infected patients, 28% were naïve, 21% were diabetics, 23.3% had hypertension and 28% had esophageal varices.

Patients were treated with different interferon free regimens, 88% of which containing sofosbuvir *(Table 2)*.

Plasma samples were collected at week 1, 2, 3, 4, 6, 8, 10 and 12 to evaluate RBV and Hb plasma levels (RBV-L, Hb-L).

RBV dose was modified in patients with anemia. Anemia was defined as Hb loss of ≥ 2 g/dL as compared to baseline and/or Hb levels ≤ 10 g/dL.

RBV-L at week 4 were compared with values of 20 PEG-IFN and RBV treated controls.

The trend of RBV-L over 12 weeks was examined as a function of gender, renal function (e-GFR) and RBV dose; the trend of Hb-L was examined as a function of gender, e-GFR, RBV-L and RBV-dose.

We used a mixed effects model with random intercept, i.e. assuming that patients had different RBV-L at week 1. We also hypothesized that the trend of RBV-L over time would be non-linear.

Table 1: Demographic, clinical, biochemical and virological characteristics of HCV cirrhotic patients (N=43)

Characteristics (mean ± ds)	Patients (N=43)	Characteristics (mean ± ds)	Patients (N=43)
Sex (M/F)	26/17	**Hemoglobin (g/L)**	14.5 ± 1,6
Age (years)	60.5 ± 9.4	**Platelets/Ml**	126 ± 60
BMI	24.9 ± 3.6	**Tot bilirubin (mg/dL)**	1.2 ± 0,8
Diabetes	9/43 (20.9%)	**GOT (U/L)**	82.4 ± 38,6
Hypertension	10/43 (23.3%)	**GPT (U/L)**	87.8 ± 50,6
Liver Stiffness (KPa)	20.42 ± 7.41	**Albumin (g/L)**	4.1 ± 0,5
Child A5	40/43 (93%)	**INR**	1.2 ± 0,2
Esophageal varices	10/43 (23.3%)	**e-GFR (mL/min)**	92.6 ± 14
Naive	12/43 (27.9%)	**HCV Genotype 1**	34/43 (79%)
Previously treated	31/43 (72.1%)	**HCV Genotype 2, 3, 4**	9/43 (21%)
HCVRNA (UI/mL)	2.907.179 ± 2.249.249		

Table 2: Interferon free regimens

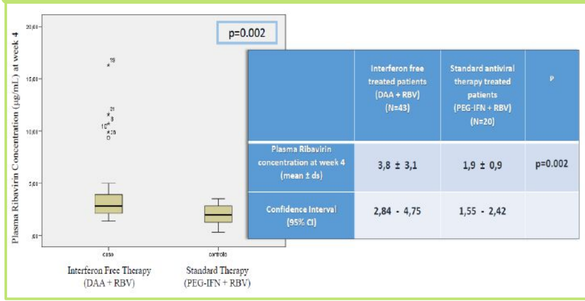
INTERFERON FREE REGIMENS	Patients N° (%)
Sofosbuvir + Simeprevir + Ribavirin	27 (62.8%)
Sofosbuvir + Daclatasvir + Ribavirin	9 (20.9%)
Sofosbuvir + Ribavirin	2 (4.7%)
Paritaprevir/Ritonavir + Dasabuvir + Ombitasvir + Ribavirin	5 (11.6%)

Results:

Sustained virologic response (SVR-12) was 95%.

Median RBV-L at week 4 were significantly higher in DAA compared to PEG-IFN/RBV treated patients (3.8 ± 3.1 vs 1.9 ± 0.9 mcg/ml; p=0.014) and a significant interpatient variability in the dose/RBV-L ratio was observed *(Figure 1)*.

Figure 1: Plasma Ribavirin Concentration at week 4 in patients treated with DAA compared to PEG-IFN/RBV



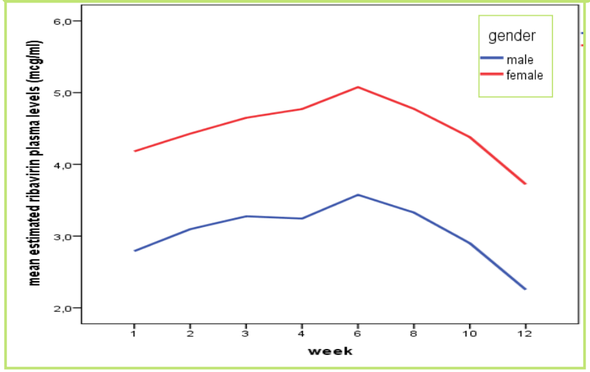
Results:

RBV dose was reduced in 25 pts (58%), 21 (84%) within 4 weeks of treatment, RBV-L remained above 2 mcg/ml in all and SVR was not affected.

RBV dose reduction was associated with age, gender, GFR and RBV-L at week 1 ($p<0.05$).

After controlling for the effect of e-GFR and RBV dose, RBV-L was on average higher in females, increased up to 6 weeks and declined thereafter *(Figure 2)*.

Figure 2: Ribavirin Level (RBV-L) kinetic during IFN free treatment according to gender

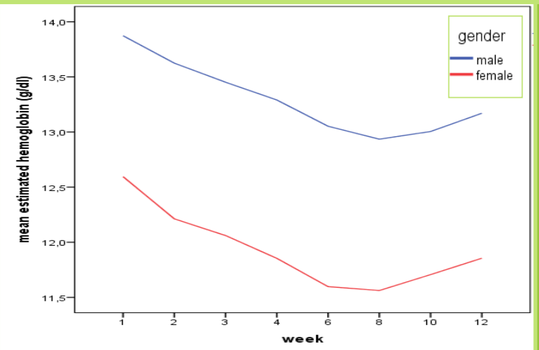


Results:

Accordingly, after controlling for the effect of e-GFR, RBV dose and RBV-L, Hb-L was significantly lower in females, reached the nadir value at week 8 and increased thereafter *(Figure 3)*.

Hb-L was significantly associated with RBV-L (p=0.001), but not with RBV dose (p=0.46) or e-GFR value (p=0.08).

Figure 3: Hemoglobin Level (Hb-L) kinetic during IFN free treatment according to gender



Conclusions:

A sharp, early rise of RBV-L with great inter-patient, gender-associated variability was observed in HCV cirrhotic patients treated with DAAs. Early (4 week) RBV dose reduction was often needed due to anemia, but did not affect SVR. After controlling for the effect of gender, e-GFR and RBV dose, RBV-L tended to spontaneously decrease after 6 weeks of treatment indicating a possible metabolic adaptation. Hb kinetic may safely guide individual adjustment of RBV dose.

References

1.AISF Guidelines 2015
(http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2015.aspx)

2. EASL Guidelines 2015
(http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015)

3.AASLD Guidelines 2015
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4.Wu LS, Rower JE, Burton JR et al. Population pharmacokinetic modeling of plasma and intracellular ribavirin concentrations in patients with chronic hepatitis C virus infection. Antomicrob Agents Chemother 2015; 59(4): 2179-88.

I certify that there is no conflict of interest in relation to this research