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Paper Poster Session
Hepatitis C management focussing on new antivirals

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. Plasma levels are reported to drive the intracellular phosphorylation rate of RBV, however plasma RBV kinetics during DAA treatment have not been fully elucidated. We examined RBV and hemoglobin (Hb)kinetics in cirrhotic patients during DAA treatment.

Material/methods: 43 HCV cirrhotic pts (60%M,60.5 yrs,28% naives,79%G-1, 21% diabetes, 28% esophageal varices) treated with DAAs (88% SOF-based) and weight-based RBV for 12-24wks have been examined. 286 plasma samples were collected at wk 1,2,3,4,6,8,10,12 to evaluate RBV and Hb plasma levels (RBV-L, Hb-L). RBV-L at wk-4 were compared with values of 20 IFN-RBV treated controls. RBV dose was modified in pts with anemia. The trend of RBV-L over 12 wks was examined as a function of gender, renal function(GFR) and RBV dose; the trend of Hb-L was examined as a function of gender, GFR, RBV-L and 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.

Results: SVR-12 was 95%. Median RBV-L at wk 4 were significantly higher in DAA compared to IFN/RBV treated pts(3.8±3.1 vs 1.9±0.9mcg/ml;p=0.014)and a significant interpatient variability in the dose/RBV-L ratio was observed; RBV dose was reduced in 25 pts(58%), 21(84%) within 4 wks of treatment, RBV-L remained above 2mcg/ml in all and SVR was not affected. RBV dose reduction was associated with age, gender, GFR and RBV-L at wk1 ($p<0.05$). After controlling for the effect of GFR and RBV dose, RBV-L was on average higher in females, increased up to 6 wks and declined thereafter(Fig1). Accordingly, after controlling for the effect of GFR, RBV dose and RBV-L, Hb-L was

significantly lower in females, reached the nadir value at week 8 and increased thereafter (Fig1). Hb-L was significantly associated with RBV-L(p=0.001), but not with RBV dose(p=0.46)or GFR value(p=0.08).

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

FIGURE 1