Telaprevir Increases Ribavirin Toxicity Through eGFR Decrease in HIV-HCV Coinfected Patients

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Background

A significant hematological toxicity (HT) was observed during the retreatment of HIV-HCV genotype 1 coinfected patients in the **ANRS HC26 TelapreVIH study**. Alterations in renal function have been described with telaprevir (TVR). We examined the relationship between ribavirin (RBV) trough concentration, estimated glomerular filtration rate (eGFR) and hemoglobin (Hb) level, before and after introduction of TVR in the TelapreVIH study.

Methods

Patients

- Male and female patients, ≥ 18 years, Chronic HCV genotype 1 infection
- Controlled HIV-1 infection, stable cART ≥ 3 months.
- Previous virological failure after ≥ 12 weeks PegIFN + RBV
- eGFR ≥ 60 mL/mn
- Hb ≥ 130 g/L (male) or ≥ 120 g/L (female)

Treatment

- 4 weeks lead in PegIFN α-2a 180 µg sc / week + RBV 1000 mg/1200 mg /day
- 12 weeks Telaprevir 750 mg q8h (1125 mg q8h with Efavirenz), PegIFN + RBV
- 32/52 weeks PegIFN α-2a + RBV based on RVR_8 result

Measures

- RBV concentrations determined by HPLC at W4 and W8 (before and after TVR)
- eGFR determined by MDRD equation at baseline and monthly

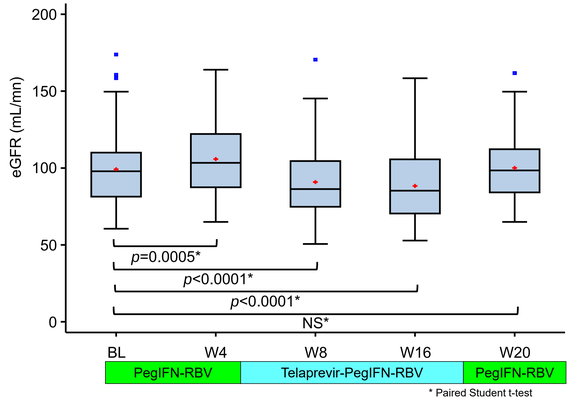
Hematological toxicity (HT) definition

- Hb < 70g/L, RBV dose reduction, prescription of EPO or blood transfusion
- Factors associated with HT were analyzed by uni- and multivariate analysis

Baseline characteristics

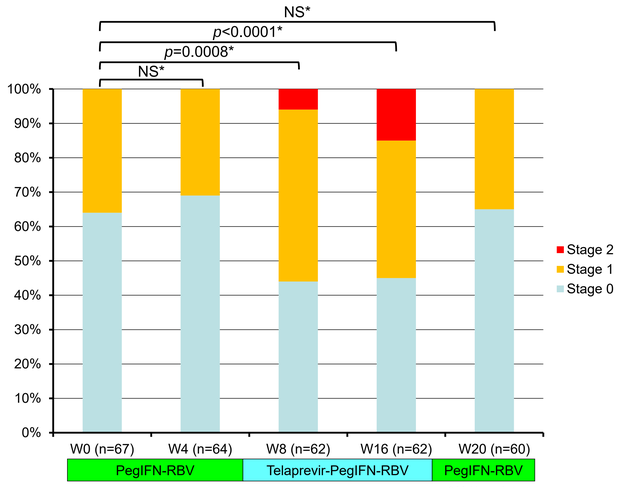
	N (%), n=67
Age, median [IQR]	50 years [47-52]
Male	53 (79 %)
Body weight <75 Kg	35 (52 %)
CDC stage C	11 (16 %)
CD4 cells/mm³, median [IQR]	630 [459-736]
HIV-RNA <50 copies/mL	66 (99 %)
Tenofovir based cART	65 (97 %)
Atazanavir based cART	42 (63%)
HCV genotype 1a / 1b	46 (69 %) / 21 (31%)
Log HCV-RNA, IU/mL, median [IQR]	6.2 [5.8-6.7]
Fibrosis score (METAVIR) F3/4	27 (40%)
ITPA - rs1127354	
AA/AC	13 (19%)
CC	54 (81%)
eGFR (mL/mn), median [IQR]	97.9 [81.4-110]
Hemoglobin (g/L), median [IQR]	15.4 [14.5 - 16.0]

Evolution of eGFR



* Paired Student t-test

Progression in CKD stage

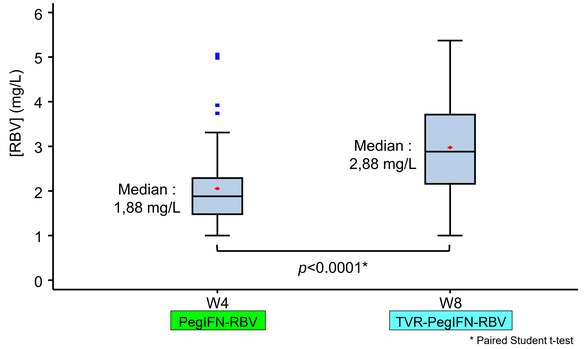


* McNemar's test

Chronic Kidney Disease stage definition :

- Stage 0 : eGFR ≥ 90mL/mn
- Stage 1 : 60 mL/mn ≤ eGFR < 90 mL/mn
- Stage 2 : 30 mL/mn ≤ eGFR < 60 mL/mn

RBV trough concentrations



* Paired Student t-test

[RBV]	W4 (n=67)	W8 (n=62)	*p**
< 3 mg/L	59 (88%)	34 (55%)	<0.0001
≥ 3 mg/L	8 (12%)	**28 (45%)**	

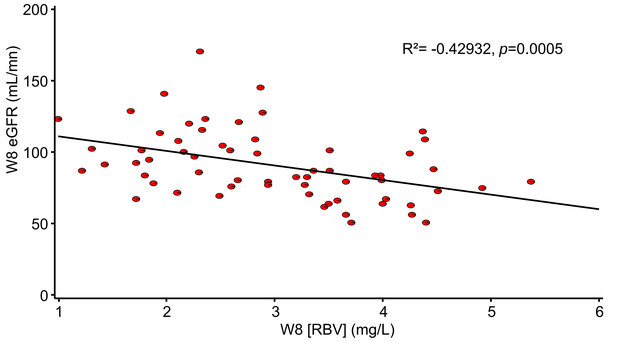
* McNemar's test

Factors associated with [RBV] ≥ 3 mg/L

	W4 [RBV] ≥ 3 mg/L (n (%))	*p**	**W8** [RBV] ≥ 3 mg/L (n (%))	*p**
Male Female	4 (8%) 4 (29%)	0.05	18 (38%) 10 (71%)	0.02
Body weight <75 Kg Body weight ≥ 75 Kg	6 (17%) 2 (6%)	-	16 (48%) 12 (41%)	-
ITPA AA/AC ITPA CC	2 (15%) 6 (11%)	-	6 (50%) 22 (44%)	-
Atazanavir No Atazanavir	4 (10% 4 (16%)	-	21 (54%) 7 (30%)	0.07
METAVIR F1/2 METAVIR F3/4	5 (13%) 3 (27%)	-	16 (44%) 12 (46%)	-
RVS_{24} No RVS_{24}	6 (11%) 2 (15%)	-	24 (47%) 4 (36%)	-
BL eGFR ≥ 90 mL/mn BL eGFR < 90 mL/mn	4 (9%) 4 (17%)	-	16 (40%) 12 (55%)	-
W4 eGFR ≥ 90 mL/mn W4 eGFR < 90 mL/mn	3 (7%) 4 (20%)	-		
W8 eGFR ≥ 90 mL/mn W8 eGFR < 90 mL/mn			4 (15%) 24 (37%)	0.0001

** Continuous variables: Student t-test; Discrete variables: Chi² or Fisher exact test

Correlation between eGFR and [RBV] at W8



Factors associated with W8 hematological toxicity

	Univariate analysis			**Multivariate analysis**	
	No (n=34)	Yes (n=27)	*p**	OR (95% CI)	*p***
Female (n (%))	3 (9%)	10 (37%)	0.007	-	-
BL Hb (g/L)	158 (152-161)	146 (137-155)	<0.0001	-	-
BL Hb <150 g/L (n (%))	6 (18%)	17 (63%)	0.0003	6.4 (1.7-23.8)	0.005
BL eGFR (mL/mn)	102 (85-122)	93(77-102)	0.03	-	-
W8 eGFR (mL/mn)	96 (79-113)	79 (64-88)	0.003	-	-
W8 eGFR <90 mL/mn (n (%))	14 (41%)	21 (78%)	0.004	-	
W8 [RBV] ≥ 3 mg/L	8 (24%)	20 (74%)	<0.0001	7.7 (2.2-27.4)	0.002
Atazanavir (n (%))	18 (53%)	20 (74%)	0.09	-	-

* Continuous variables: Student t-test; Discrete variables: Chi² or Fisher exact test
** Logistic regression

Conclusion

Addition of TVR to PegIFN+RBV was associated with a 8% decrease in eGFR, leading to a 55% increase in [RBV], which resulted in RBV over-exposure in 45% of the patients and in a significant hematological toxicity in the study.