Defining the therapeutic range of ribavirin with telaprevir-based triple therapy for HCV infection: Is it possible?

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Disclosures

- **Klaartje de Kanter** has no disclosures
- **David Burger** has received honoraria or research grants from Abbvie, Gilead, Merck and Roche
- **Maria Buti** has received honoraria from Gilead, Janssen, MSD and Vertex
- **Stefan Zeuzem** has received honoraria from Abbott, Achillion, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Novartis, Roche, Santaris and Vertex
- **Ralph DeMasi**, **Sivi Ouwerkerk-Mahadevan** and **James Witek** are all employees of Janssen Pharmaceuticals

Introduction

- Dual therapy with pegylated interferon and ribavirin leads to variable degrees of sustained virological response (SVR) and anemia
- Many studies have shown that ribavirin pharmacokinetics display large inter-patient variability
- Some authors suggest that therapeutic drug monitoring of ribavirin is recommended

Morello J *et al*. J Antimicrob Chemother. 2008 Dec;62(6):1174-80
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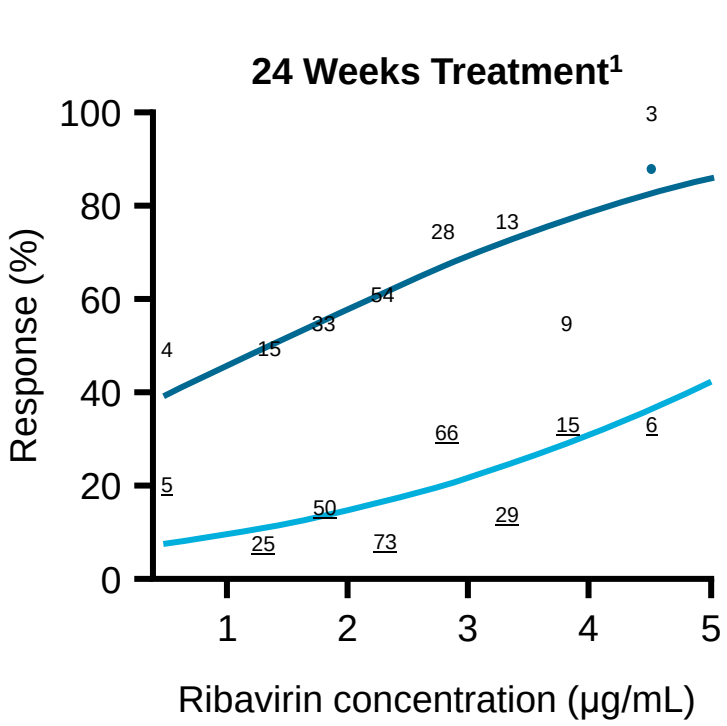
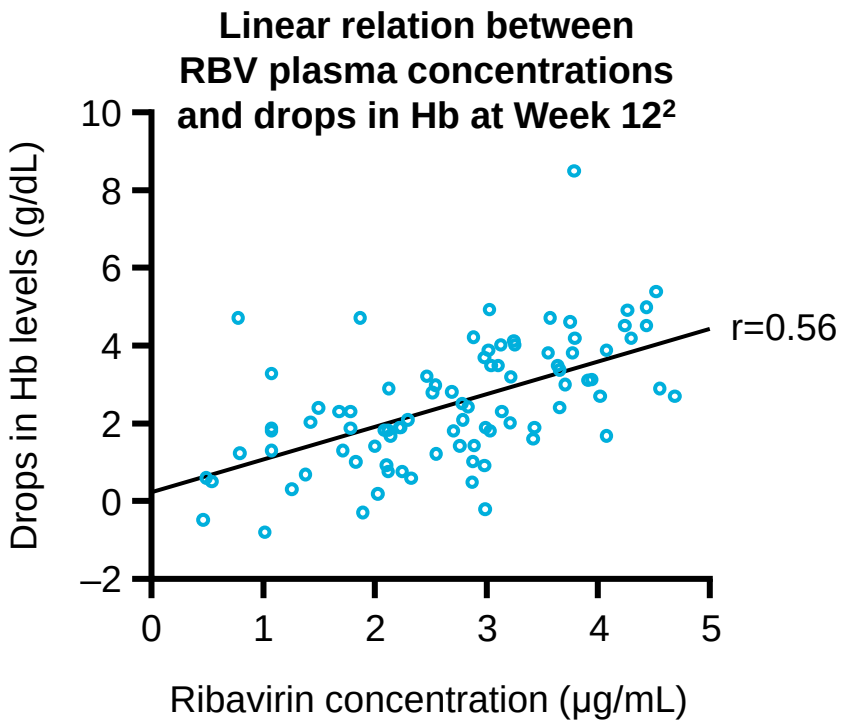
Therapeutic range of ribavirin in dual therapy





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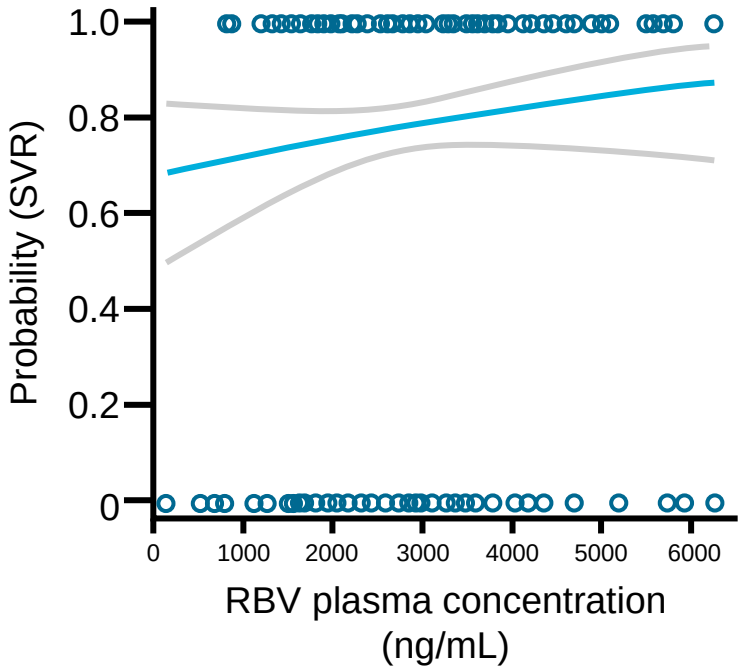
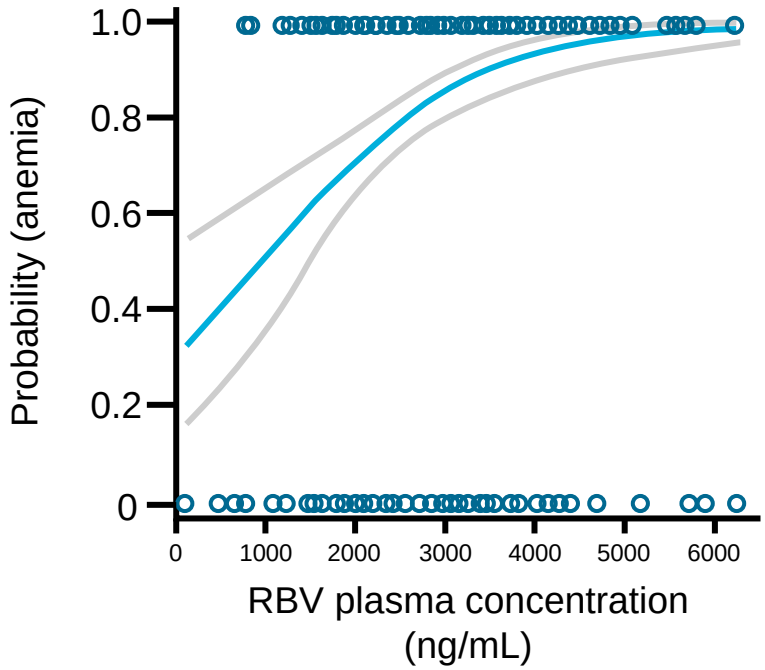
In telaprevir-based triple therapy?





- In Phase III trials (ADVANCE and ILLUMINATE) of telaprevir plus pegylated interferon and ribavirin in treatment-naïve patients, concentrations of ribavirin were weakly associated with SVR, while the association between ribavirin concentrations and the development of anemia was much stronger.

Gordon SC *et al*. EASL 2012. Poster 1116

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Objective of this analysis

- To explore how ribavirin concentrations change over time during triple therapy with telaprevir
- Verify if a therapeutic range for ribavirin concentrations can be defined and used in the management of patients on telaprevir treatment (reduce anemia, maintaining SVR)

Materials & methods (1)

- Post-hoc analysis
- HCV treatment-naïve mono-infected patients from Phase III studies ADVANCE, ILLUMINATE and OPTIMIZE using telaprevir-based triple therapy
- Patients included had a ribavirin concentration available at Week 4
- Ribavirin concentrations were measured throughout the study period including at Weeks 1, 2, 4 and 8

Materials & methods (2)

- Multivariable logistic regression analyses were performed to evaluate whether ribavirin plasma concentrations were an independent predictor of
  - SVR (undetectable viral load 24 weeks after treatment) or
  - clinically significant anemia (hemoglobin level <8.5 g/dL)
- Odds ratios adjusted for known predictors of SVR and anemia
- ROC analyses to determine the optimal cut-off values for ribavirin concentrations at each available time point
- The percentage of patients within these proposed therapeutic ranges were calculated with their associated chances for response

Results - SVR and anemia incidence in Phase III studies with telaprevir

	SVR24 (%)	Anemia (%)
ADVANCE[1] (N=1088)	69–75	37–39*
ILLUMINATE[2] (N=540)	72	39‡
OPTIMIZE[3] (N=740)	73–75	42‡

* Defined as a hemoglobin level < lower limit of normal
‡ Defined as a hemoglobin level < 10.9 g/dL

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2. Sherman KE *et al*. N Engl J Med. 2011 Sep 15;365(11):1014–24
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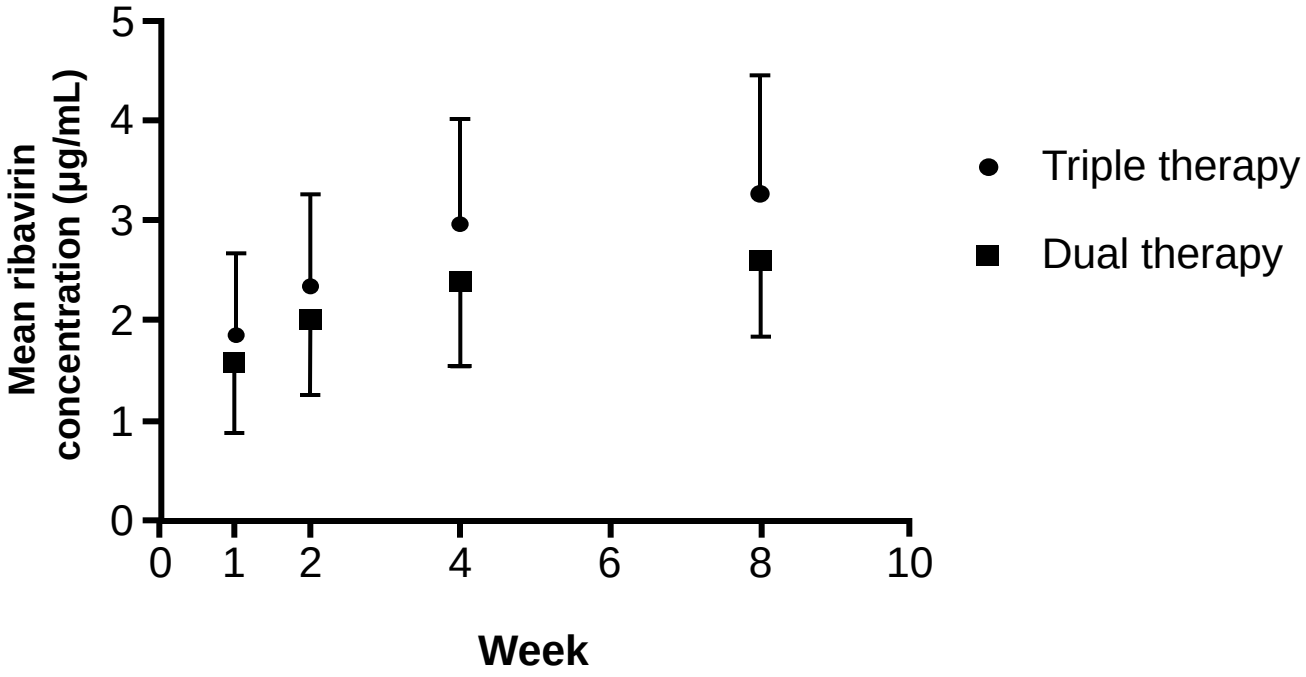
Results - Patients baseline characteristics and demographics

	Total patients N=904
Male, n (%)	547 (61)
Caucasian, n (%)	819 (91)
Age, years, mean (range)	48 (18–70)
BMI, kg/m^2, mean (range)	27 (17–53)
HCV genotype 1a, n (%)	532 (59)
Baseline HCV RNA ≥800,000 IU/mL, n (%)	740 (82)
F4 fibrosis, n (%)	101 (11)
Hemoglobin, g/dL, mean (SD)	14.9 (1.2)

Results - Ribavirin concentrations during triple therapy with telaprevir



- Mean (SD) ribavirin concentrations increase over time
- Mean ribavirin concentrations are higher during triple therapy including telaprevir

Results - Exploring the possibility of utilizing ribavirin concentrations as a predictor of anemia and SVR*

	SVR	Severe anemia (Hb <8.5 g/dL)
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Week 1	not significant	2.61 (1.80–3.79)
Week 2	not significant	1.99 (1.44–2.75)
Week 4‡	not significant	2.39 (1.95–2.93)
Week 8	1.43 (1.21–1.69)	1.78 (1.49–2.13)

- At all time points high ribavirin concentrations were significantly associated with severe anemia
- Only the ribavirin concentration at week 8 was associated with SVR

*Odds ratios are adjusted for known predictors of SVR and anemia, including AFP level, age, baseline hemoglobin, BMI, baseline viral load, fibrosis stage, platelet count and sex

‡Week 4 data includes rapid virologic response

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Results - Cut-off values for SVR and anemia

	Cut -off value for RBV concentration (µg/mL) for SVR	Cut -off value for RBV concentration (µg/mL) for severe anemia*
Week 1	not applicable	2.3
Week 2	not applicable	2.5
Week 4	not applicable	3.1
Week 8	2.2	3.5

- Therapeutic range for ribavirin concentrations at week 8: **2.2 - 3.5 µg/mL**

*defined as Hb <8.5 g/dL

Results - Therapeutic range for ribavirin

- Therapeutic range for ribavirin concentrations at week 8: **2.2 - 3.5 µg/mL**
- 48 % of patients had a ribavirin concentration at Week 8 within this range
- 81 % of these patients had an SVR
- Only 5.1 % of these patients developed severe anemia (Hb <8.5 g/dL)

Conclusions

- During triple therapy with telaprevir, a therapeutic range for ribavirin concentrations can be defined
- Higher ribavirin concentrations at week 8 lead to better SVR rates but also to more anemia
- A ribavirin concentration between 2.2 - 3.5 µg/mL at week 8 was found to be optimal
- There is data showing that ribavirin dose reduction for management of anemia does not impact SVR rate. Possibly because ribavirin concentration are above therapeutic range.

- Analyses will also be performed for other ribavirin containing HCV treatments with DAA's.