Multiscale modeling of lead-in results from a phase 2 study of an 8-week combination regimen of Bemnifosbuvir and Ruzasvir in patients with chronic hepatitis C virus infection

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INTRODUCTION

Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the HCV NS5B polymerase and the NS5A protein, respectively. The novel combination of BEM/RZR is being assessed for safety and efficacy in a phase 2 open-label study of 275 HCV-infected individuals including those with compensated cirrhosis after the lead-in phase (NCT05904470).

Previously we developed a multiscale model of HCV infection and treatment to estimate the in vivo effectiveness of daclatasvir in blocking HCV replication and viral assembly/secretion as well as various 3-drug combinations of direct-acting antivirals against HCV[1,2]. Here we use the same approach to evaluate the BEM/RZR combination in a lead-in cohort from the phase 2 trial.

In this single-arm study, a lead-in cohort (n=60) of treatment-naïve, non-cirrhotic individuals with chronic HCV (any genotype) received 550 mg BEM once daily (QD) + 180 mg RZR QD for 8 weeks. Plasma HCV RNA was evaluated frequently using the Roche Cobas® HCV quantitative nucleic acid test, with a lower limit of quantitation (LLOQ) of 15 IU/mL. The previously developed multiscale model was fit to the plasma viral load (VL) and the ALT data from all 60 subjects simultaneously via mixed-effects population fitting.

PATIENT CHARACTERISTICS

	Female	Male	Overall
n (%)	26 (43.3)	34 (56.7)	60 (100)
Genotype n (%)			
1	24 (92.3)	21 (61.8)	45 (75.0)
2	0 (0.0)	2 (5.9)	2 (3.3)
3	2 (7.7)	11 (32.4)	13 (21.7)
Fibrosis n (%)			
F0	4 (15.4)	5 (14.7)	9 (15.0)
F1	11 (42.3)	15 (44.1)	26 (43.3)
F2	6 (23.1)	9 (26.5)	15 (25.0)
F3	5 (19.2)	5 (14.7)	10 (16.7)
Median age (yr)	53.0	43.5	47.0
Race n (%)			
Caucasian	26 (100.0)	31 (91.2)	57 (95.0)
African American	0 (0.0)	1 (2.0)	1 (1.7)
Other	0 (0.0)	2 (5.9)	2 (3.3)

The 60 lead-in participants were infected with GT1 (n=45), GT2 (n=2), or GT3 (n=13), and 17% had F3 fibrosis. 57% were male, 95% were Caucasian, and the median age was 47 (range 25-79) years. All completed the 8 weeks of treatment.

MATHEMATICAL MODEL

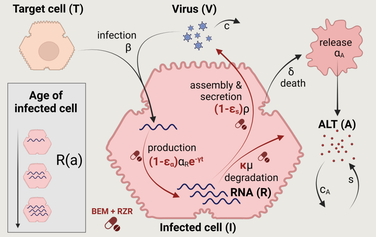
$$\frac{dT}{dt} = s_T - dT - \beta VT$$

$$\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = -\delta I(a,t)$$

$$\frac{\partial R}{\partial a} + \frac{\partial R}{\partial t} = (1-\varepsilon_\alpha)\alpha_R e^{-\gamma t} - \kappa\mu R - (1-\varepsilon_s)\rho R$$

$$\frac{dV}{dt} = (1-\varepsilon_s)\rho \int_0^\infty R(a,t)I(a,t)da - cV$$

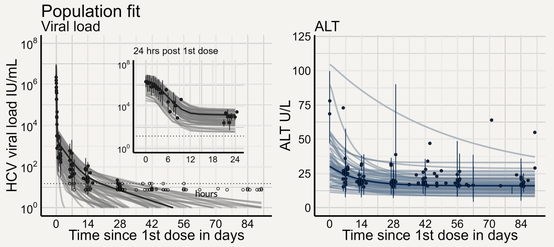
$$\frac{dA(t)}{dt} = s + \alpha_A \delta \int_0^\infty I(a,t)\,da - c_A A(t)$$



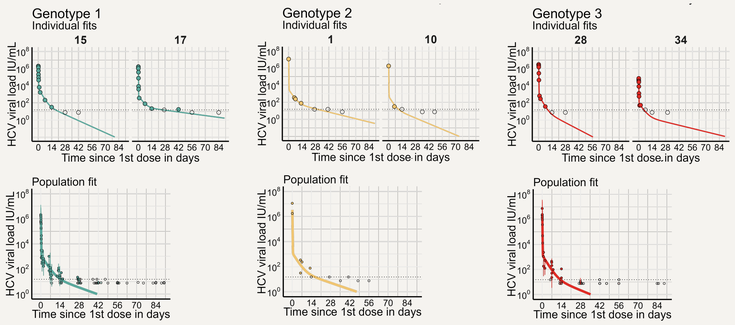
- We model the dynamics of intracellular positive-strand viral RNA (R) at time t in cells infected for a time a, as well as the extracellular components of uninfected cells (T), infected cells (I), virus (V) and ALT (A).
- We tested different effects of treatment modeled as inhibition of the intracellular viral production (ε_α and γ), inhibition of virus assembly and release (ε_s), and increased degradation of positive-strand viral RNA (κ). [Schematic created with BioRender.com]

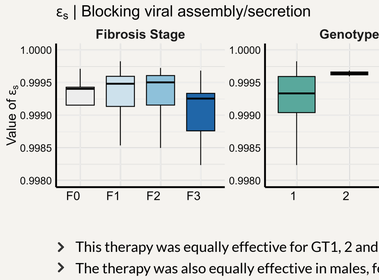
We used Monolix (Lixoft SA, Antony, France) to fit nonlinear mixed effects models to the log of viral load and ALT data, assuming that individual parameters differ from the population median by a random effect, which is normally distributed with mean zero and variance ω^2. This allows for individual variation while estimating population-level parameters.

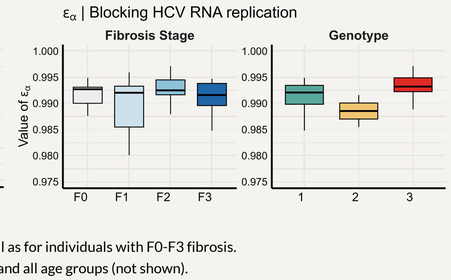
RESULTS



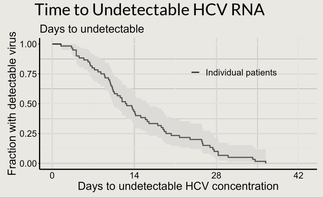
- Post-treatment, VL decreased in a triphasic manner, with a very rapid first phase lasting < 12 h, followed by a slower second and an even slower third phase.
- The model fits both the VL and ALT data well.
- The population estimate of the time to reach the LLOQ (15 IU/ml) was 19.7 days.
- The estimates of the effectiveness were very high at ε_s= 0.9993 [95% CI: 0.9990, 0.9995], and ε_α=0.992 [95% CI: 0.981, 0.997].







- This therapy was equally effective for GT1, 2 and 3 as well as for individuals with F0-F3 fibrosis.
- The therapy was also equally effective in males, females, and all age groups (not shown).



The model fits predicted that the median time to viral load below the LLOQ was 12.5 days and that the viral load in all individuals in the study reached the LLOQ.

CONCLUSION

BEM/RZR for 8 weeks was highly effective in blocking both viral replication and viral assembly/secretion in HCV-infected patients, independent of genotype, age, sex, or fibrosis score. A high SVR12 rate (97%) was observed in this lead-in cohort.[3] This analysis supports the shortened 8-week treatment with BEM/RZR for chronic HCV.

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