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

Carolin Zitzmann[1], Ruy M. Ribeiro[1], Sergey Izmailyan[2], Shannan Lynch[2], Keith Pietropaolo[2], Arantxa Horga[2], Xiao-Jian Zhou[2], Janet Hammond[2], Alan S. Perelson[1]
[1]Theoretical Biology and Biophysics, Los Alamos National Laboratory, NM, United States [2]Atea Pharmaceuticals, Inc., Boston, MA, United States

For further info, contact: Xiao-Jian Zhou
Early-Stage Development
Atea Pharmaceuticals, Inc.
zhouxj@ateapharma.com

For further info, contact: Alan S Perelson
Theoretical Biology and Biophysics
Los Alamos National Laboratory
asp@lanl.gov

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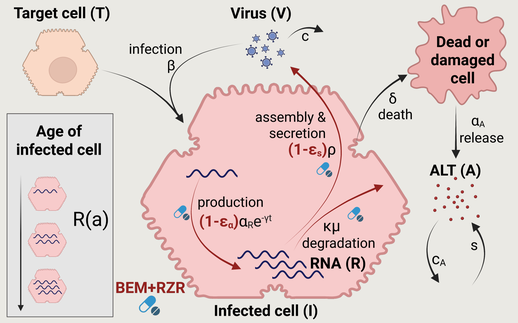
BACKGROUND

- Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic HCV polymerase and NS5A inhibitors, respectively. The novel combination BEM/RZR was assessed for safety and efficacy in a phase 2 open-label study of 275 HCV-infected individuals, including those with compensated cirrhosis (NCT05904470). Participants received 550 mg BEM once daily (QD) + 180 mg RZR (QD) for 8 wks.
- The primary analysis population included a subset of n=215 who were study drug adherent (corroborated by pill counts and plasma drug levels). A previously developed multiscale model was simultaneously fit to the plasma viral load (VL) measured using the Roche Cobas® HCV quantitative nucleic acid test, with an LLOQ of 15 IU/mL, and the ALT data from all subjects via population fitting.[1]

STUDY PARTICIPANTS

Per-Protocol Treatment-Adherent (N=215)	
Mean age, yr (range)	50.5 (20—85)
Male sex, n	100 (46.5)
Genotype n (%)	
1	151 (70.2)
2	4 (1.9)
3	58 (27.0)
4	2 (0.9)
Fibrosis n (%)	
F0	48 (22.3)
F1	61 (28.4)
F2	51 (23.7)
F3	21 (9.8)
F4	34 (15.8)
Race n (%)	
Asian	44 (20.5)
Caucasian	156 (72.6)
Black/African American	6 (2.8)
Other	9 (4.2)

MATHEMATICAL MODEL



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

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

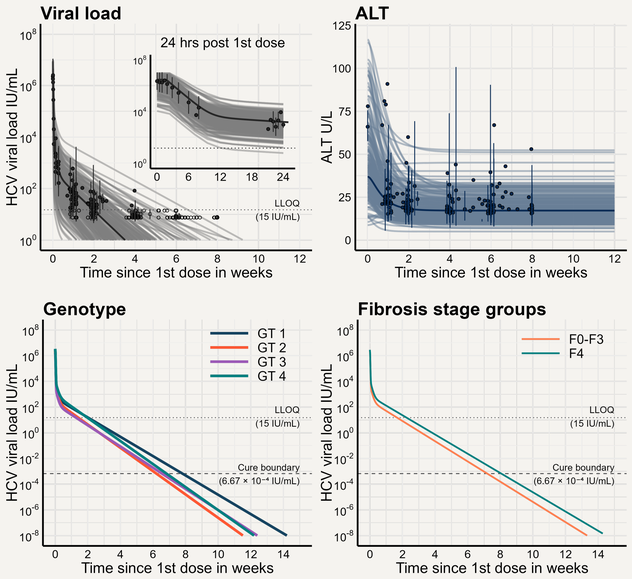
$$\frac{\partial R}{\partial a} + \frac{\partial R}{\partial t} = (1-\varepsilon_\alpha)\alpha_R e^{-\gamma t} - \kappa\mu R - (1-\varepsilon_s)\rho R$$

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

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

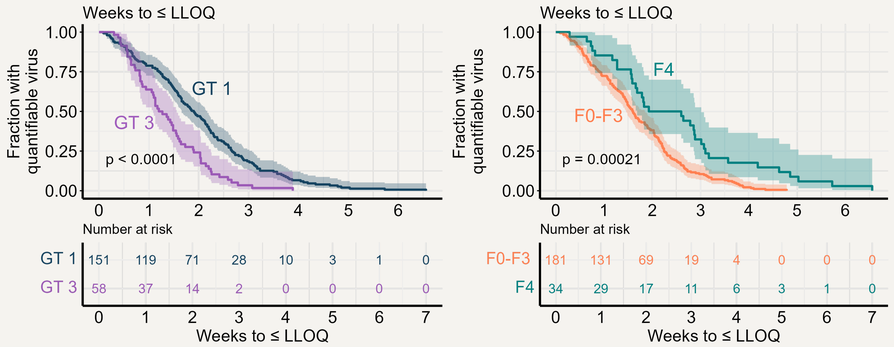
- We model the dynamics of intracellular positive-strand viral RNA (R) at time t in cells infected for a time a, as well as the extracellular components of uninfected cells (T), infected cells (I), virus (V), and ALT (A).[2]
- We tested different effects of treatment modeled as inhibition of the intracellular viral production (ε_α) and inhibition of virus assembly and release (ε_s) [Schematic created with BioRender.com]
- We used Monolix (Lixoft SA, Antony, France) to fit nonlinear mixed effects models to the log of VL and ALT data, assuming 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 was 12 days for individuals with F0-F3 and 16 days for those with F4, while the population estimate of the time to cure (VL ≤ 6.7 × 10^{-4} IU/mL) was 7.3 wks for F0-F3 and 8.2 wks for F4, with some variability between individuals.
- The population estimate of the effectiveness of the combination in blocking viral assembly/secretion was extremely high at 0.998 for F0-F3 [95% CI: 0.997–0.999] and 0.995 for F4 [95% CI: 0.991–0.997], while the population estimate of the effectiveness in blocking viral replication was 0.988 for F0-F4 [95% CI: 0.984–0.991].
- The estimated efficacy of therapy was similar across genotypes.

TIME TO UNDETECTABLE



- A rapid virologic response (RVR; undetectable by week 4) was achieved in 95.4% [95% CI: 91.7–97.5%] overall, including 93.4% [95% CI: 88.2–96.4%] of GT 1 and 100% of GT 3.
- RVR was achieved in 97.8% [95% CI: 94.5–99.1%] of non-cirrhotic patients (F0-F3) and 82.4% [95% CI: 66.5–91.7%] of cirrhotic (F4) patients.

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 and fibrosis score. The time to cure estimates support 8 wk treatment for non-cirrhotic patients and longer treatment duration (e.g., up to 12 wks) for those with compensated cirrhosis.

REFERENCES

[1]Jucov A., et al. (2024). Efficacy and safety of bemnifosbuvir and ruzasvir after 8 weeks of treatment in patients with chronic hepatitis C Virus (HCV) infection. Poster presented at The European Association for the Study of the Liver (EASL) Congress, May 7–10 2025, The Netherlands.

[2]Guedj, J., et al. (2013). Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. *Proc Natl Acad Sci USA*, 110, 3991-3996.