HCV viral kinetic analysis predicts shorter treatment duration with AT-527, a purine nucleotide prodrug with potent pan-genotypic antiviral activity in HCV-infected subjects regardless of cirrhosis status

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Background

AT-527 is a novel modified guanosine nucleotide prodrug inhibitor of the hepatitis C virus (HCV) NS5B polymerase, with a favorable/highly differentiated profile compared to sofosbuvir (1,2). A clinical trial evaluating AT-527 administered as a single agent for 7 days was successfully completed, allowing for the HCV viral kinetic analysis presented herein (3).

Methods

Subjects and Data: HCV RNA data obtained from 30 subjects in the 7-day study who received active AT-527 doses were used for viral kinetic analysis (3).

- Part C: Treatment-naive (TN) non-cirrhotic (NC) subjects with genotype (GT) 1b HCV (n=6) received AT-527 escalating doses of 183, 275, 550 mg QD for 7 days (expresses as approximate free base equivalent).
- Part D: TN GT3 subjects (n=6) received the 550 mg QD dose for 7 days.
- Part E: TN chronic GT1 (n=3), GT2 (n=6) or GT3 (n=5) subjects received the 550 mg QD dose for 7 days.

HCV RNA Samples:

- Serial samples were collected prior to (0 on study day 1) and post treatment initiation at 2, 4, 8, 12, 16, 24, 48, 72, 96, 120 and 144 h (7 days) during dosing and daily after completion of dosing on days 8 to 12, as well as on day 35.

HCV RNA levels were quantified using COBAS® AmpliPrep TaqMan® v2.0, with a lower limit of quantitation (LLQ) of 15 IU/mL. or 1.10 logIU/mL.

Viral Kinetic Modeling and Simulation:

- HCV viral load decline with AT-527 treatment and rebound after treatment completion was assumed to follow the standard model as described by the differential equations below (4,5):

\[
\frac{dS}{dt} = -\epsilon S
\]

\[
\frac{dE}{dt} = \epsilon S - \beta E
\]

\[
\frac{dI}{dt} = \delta E - \tau C
\]

\[
\frac{dC}{dt} = \tau C - \delta C
\]

Where \( S \) is the number of target hepatocytes susceptible to infection, \( E \) is the number of productively infected hepatocytes and \( C \) is the viral load. Susceptible hepatocytes are produced at rate \( \delta \) and die at rate \( \epsilon \). A novo infection of cells occurs at rate \( \epsilon \) and the infected cells are lost at rate \( \beta \). HCV virions are produced at rate \( \tau \) per hepatocyte and cleared at rate \( \tau \) per virion.

- Effectiveness of AT-527 in blocking viral replication is defined by \( \beta S \). Upon dosing completion, where \( \beta = 0 \), viral load starts to rebound.

- Parameter estimates and associated interindividual variability were obtained using a maximum-likelihood method by the stochastic approximation expectation-maximization (SAEM) algorithm implemented in MonolixSuite 2019R1 (Lixoft, Orsay, France).

- Simulation was performed using Simul for the 550 mg daily dose to estimate times to reach LLQ and cure. The latter is defined as HCV RNA < 1 IU in the entire extracellular rod-like body (35.5 kDa) 7.5±10^6 for 4.13 logIU/mL.

Results

Viral Kinetic Modeling

- A model incorporating pharmacological delay (\( d \)) as well as AT-527 dose as a covariate (\( g \)) was found to best describe the observed data.

- Goodness-of-fit:
  - Representative individual fitted vs. observed viral kinetics
  - Predicted vs. observed HCV RNA
  - Predicted vs. observed HCV RNA

Population Kinetic Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Log10 V0</th>
<th>( \delta ) (h-1)</th>
<th>( \tau ) (h)</th>
<th>HCV RNA LLQ (IU/mL)</th>
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<tbody>
<tr>
<td>Cohort</td>
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<td>550 mg</td>
<td>-4.32</td>
<td>48.0</td>
<td>0.35</td>
<td>1.10 logIU/mL</td>
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Simulation

- Simulation was performed with AT-527, using a 550 mg QD dosing regimen of AT-527 as a single agent to assess treatment duration required to achieve a cure, defined as plasma HCV RNA < 1.5 logIU/mL, 4.13 logIU/mL. Time to reach plasma HCV RNA LLQ was also evaluated.

- Simulation results showed that with AT-527 as a single agent at 550 mg/day:
  - About 80% and 95% of subjects would have plasma HCV RNA LLQ by wk 2 and 4 respectively.
  - Approximately 80% and 90% of subjects would achieve a cure by wk 4 and 8 of treatment, regardless of HCV genotype or cirrhosis status.

On-Treatment Response from an On-Going Phase II Study of AT-527 plus Daclatasvir

- AT-527 plus daclatasvir is well-tolerated for 5-12 weeks in HCV GT1 treatment-naive subjects (N=10).

- High proportions of subjects achieved HCV RNA target not detected (TND) at week 2 (60%) and week 4 (80%), with all subjects achieving TND at end of treatment. These on-treatment response rates are much higher than those observed with sofosbuvir plus velpatasvir (6).

- The very rapid early viral kinetics with AT-527 plus daclatasvir allowed for an 8 week treatment duration in all but one subject. SVR results are pending.

Conclusions

- Viral kinetic analysis based on data generated from 7-day dosing of AT-527 as a single agent suggests that 100% of all patients should be cured with 8 weeks of treatment.

- Interim data from on-going pilot study with AT-527 plus daclatasvir: the only commercially available simultaneous NS5A inhibitor, suggest that high cure rates and rapid virologic durability can be achieved with AT-527 containing regimens as compared to sofosbuvir-containing regimens.

- A highly effective single-tablet once daily pan-genotypic short treatment regimen with less drug-drug-interaction potential will greatly simplify the care for chronic hepatitis C especially in patients with cirrhosis.

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References


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