Designing impactful treatments against emerging SARS-CoV-2 variants

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Background

- Despite abundant drug repurposing efforts, no drug has proved effective; only corticosteroids have (limited) benefits.
- Emerging SARS-CoV-2 variants of concern (VOCs) [1-2] have a higher transmissibility [3] and could prove more susceptible to specific drug therapy.
- Molnupiravir (Merck) is an orally bioavailable prodrug, inhibiting SARS-CoV-2 replication through lethal mutagenesis, as it is a nucleoside analog.
- Through modeling and simulation we explored the effectiveness of antiviral therapy with molnupiravir in SARS-CoV-2 with different within-host reproduction numbers (Ro), as a proxy for altered within-host transmissibility.

Viral kinetics model

- Viral loads were simulated from a target-cell limited model (Fig.1A) with dynamics of an acquired immune response: 10 days post inoculation (dpi) [4]. Highly transmissible variants were set at 1.25-, 1.5-, 2-fold Ro, compared to wild type (Ro = 3.79), whereas a putative co-adaptation variant (less transmissible) was 0.75-fold Ro.
- Pharmacokinetic model and Pharmacodynamic effects
  - Dosing: molnupiravir 800 mg every 12h for 5 days with an impulsive antiviral framework (Fig.1B) [4,5,6]. Treatment initiated 3 days before to 5 days after virus inoculation.
  - NHCl (active drug) inhibits viral production in vitro in Calu-3 cells (human lung epithelial cell line) with IC50 = 0.4146 μM [7].

Methods

- Viral load dynamics of wild type SARS-CoV-2 (Fig.2): positivity reached at 5.4 dpi and maintained for 13.5 days, viral load peaks of 28.4 Ct (Fig.3)
  - An increased Ro results in earlier positivity (2.1–3.7 dpi), higher viral load peaks (25.2–27.4 Ct), and increased total viral load (152-402%), whereas decreased Ro has the opposite effect.
  - Treatment with molnupiravir leads to a reduced viral load (51-30%) in the highly transmissible variants, but only if treatment is started in the first 1–3 days post inoculation (Fig.3).
  - Duration was less sensitive to changes in Ro, with a tendency towards prolonged positivity with increasing Ro (Ro=1.25: 16.5 vs. 12.7 days untreated, Ro=2: 14.1 vs. 11.4 days untreated). In less transmissible variants, treatment effects are less pronounced.

Results

- Higher transmissibility of VOCs leads to a quicker infection of all target cells, which can be seen as steep ascent.
- Molnupiravir treatment was correlated with Ro, making highly transmissible VOCs more sensitive to antiviral therapy.
- Antiviral treatment for SARS-CoV-2 needs to be initiated early. This effect is accentuated in VOCs with higher within-host transmissibility.
- Results are in line with trial results reported by Merck, where earlier outpatient treatment (MOVe-OUT trial) was superior to late initiation in in-patients (MOVe-IN trial).
- Pre-emptive pre- or post-exposure prophylaxis appears to be the most effective intervention strategy.

Conclusions

References: