Immune-Viral Dynamics Modeling of the Basis for Individual Variation in COVID-19

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Background: Viral dynamics models provide mechanistic insights into viral disease and interventions. A mechanistic model of COVID-19 was developed and fit to data from molnupiravir (MOV) trials to characterise SARS-CoV-2 viral dynamics in MOV-treated and untreated participants, and individual variation.

Methods: An Immune-Viral Dynamics Model (IVDM) incorporating mechanisms of viral infection, viral replication, induced innate and adaptive immune response described the dynamics of viral load (VL) from pooled data from MOV clinical trials (N=1958). Population approaches were incorporated to estimate variation across individuals and conduct extensive covariate analysis. Nineteen parameters described SARS-CoV-2 viral dynamics in humans. Six population parameters were informed through fitting to observed trial data and remaining parameters were fixed based on literature values or calibrated via sensitivity analysis.

Results: Viral dynamics and immune response parameters were estimated with high certainty and reasonable inter-individual variabilities. viral load profiles across a wide range of subpopulations were captured and predicted lymphocyte dynamics without using this data to inform model parameters, suggesting inferred immune response curves from this model were accurate. This mechanistic representation of COVID-19 disease indicated processes of cellular infection, viral production, and immune response are in a time-varying, non-equilibrium state throughout the course of infection. MOV mechanism of action was described as an inhibitory process on infectivity in the model with estimated AUC50 of 10.5 μM*hr. Covariates included baseline viral load on infectivity and age, baseline disease severity, viral clade, baseline viral load, diabetes on immune response parameters. Greater variation was identified for immune parameters than viral kinetic parameters.

Conclusion: Variation in human immune response is more influential in COVID-19 disease than variations in virus kinetics. The model indicates immunocompromised patients (HIV, transplant, active cancer, immunosuppressed) develop an immune response to SARS-CoV-2, and MOV is effective in further reducing viral loads in the immunocompromised.

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