Context of Rising B.1.526 Prevalence in New York City

Methods. This retrospective analysis was conducted at an urban hospital in the Bronx, NY and evaluated adult monoclonal antibody recipients from any of its infusion sites. Patients initially received BAM but given the high prevalence of variants, treatment was transitioned to first B/E and then C/I exclusively. We compared BAM versus combination therapy as well as B/E versus C/I individually. The primary outcome was all-cause hospital admission within 30 days post infusion.

Results. From February 1 to March 7, 2021, 358 patients received BAM and from March 17 to May 9, 2021, 86 and 179 patients received B/E and C/I, respectively. Compared to any combination infusion, patients who received BAM were significantly more likely to be hospitalized, whereas patients with sore throat (OR=0.42, 95% CI=0.20-0.89) were less likely to be hospitalized than patients not having such symptoms. Every unit increase in patients’ age and temperature increased the likelihood of hospitalization by 7.6% and 62.7%, respectively. Every unit increase in patients’ diastolic pressure and SpO₂ decreased the likelihood of hospitalization by 6.1% and 3.6%, respectively.

Conclusion. From February 1 to March 7, 2021, 358 patients received BAM and from March 17 to May 9, 2021, 86 and 179 patients received B/E and C/I, respectively. Compared to any combination infusion, patients who received BAM were significantly more likely to be hospitalized, whereas patients with sore throat (OR=0.42, 95% CI=0.20-0.89) were less likely to be hospitalized than patients not having such symptoms. Every unit increase in patients’ age and temperature increased the likelihood of hospitalization by 7.6% and 62.7%, respectively. Every unit increase in patients’ diastolic pressure and SpO₂ decreased the likelihood of hospitalization by 6.1% and 3.6%, respectively.

522. Evaluation of Three COVID-19 Monoclonal Antibody Regimens in the Context of Rising B.1.526 Prevalence in New York City
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Session: P-24. COVID-19 Treatment

Background. Monoclonal antibodies were given emergency use authorization (EUA) by the Food and Drug Administration for the treatment of high-risk, outpatient COVID-19 infection. In New York City (NYC), the emergence and rapid growth of the B.1.526 variant of concern (VOC) possessing the E484K mutation was first noted in February 2021. In-vitro studies subsequently confirmed attenuated monoclonal antibody neutralization against VOCs. At our institution, bamlanivimab (BAM) alone or with etesevimab (B/E) and casirivimab/imitrivimab (C/I) were utilized at different phases of the pandemic. The objective of this study was to assess their comparative efficacies in a highly variant prevalent setting.

Methods. This retrospective analysis was conducted at an urban hospital in the Bronx, NY and evaluated adult monoclonal antibody recipients from any of our infusion sites. Patients initially received BAM but given the high prevalence of variants, treatment was transitioned to first B/E and then C/I exclusively. We compared BAM versus combination therapy as well as B/E versus C/I individually. The primary outcome was all-cause hospital admission within 30 days post infusion.

Results. From February 1 to March 7, 2021, 358 patients received BAM and from March 17 to May 9, 2021, 86 and 179 patients received B/E and C/I, respectively. Compared to any combination infusion, patients who received BAM were significantly more likely to be hospitalized, whereas patients with sore throat (OR=0.42, 95% CI=0.20-0.89) were less likely to be hospitalized than patients not having such symptoms. Every unit increase in patients’ age and temperature increased the likelihood of hospitalization by 7.6% and 62.7%, respectively. Every unit increase in patients’ diastolic pressure and SpO₂ decreased the likelihood of hospitalization by 6.1% and 3.6%, respectively.

Conclusion. Combination therapy may be associated with fewer hospital admissions following infusion, although there were no statistically significant differences between the individual combination infusions. We suggest similar studies be conducted by other sites to understand the clinical impact of local SARS-CoV-2 variants on antibody efficacy.

Disclosures. Yi Guo, PharmD, BCIDP; Kelsie Cowman, MPH; Merck (Research Grant or Support); Priya Nori, MD; Merck (Grant/Research Support); Priya Nori, MD. Nothing to disclose

523. Use of Immune-Viral Dynamics Modeling to Understand Molnupiravir Drug Effect for COVID-19
Youfang Cao, PhD1; Wei Gao, PhD2; Ruthie Birger, PhD3; Julie Stone, PhD3; Merck & Co. Inc, West Point, Pennsylvania; Merck & Co., Inc., Kenilworth, New Jersey

Session: P-24. COVID-19 Treatment

Background. Molnupiravir (MOV) is an orally administered ribonucleoside pro-drug of β-D-N4-hydroxycytidine (NHC) against SARS-CoV-2. Here we present viral dynamics analysis of Phase 2 clinical virology data to inform MOV Phase 3 study design and development strategy.

Methods. An Immune-Viral Dynamics Model (IVDM) was developed with mechanisms of SARS-CoV-2 infection, replication, and induced immunity, which together describe the dynamics of viral load (VL) during disease progression. Longitudinal virology data from ferret studies (Cox, et al. Nat. Microbiol 2021-6) were used to inform IVDM, which was further translated to human by adjusting parameter values to capture clinical data from MOV-In/MOv-OUT studies. Different placements of drug effects (on viral infectivity vs. productivity) and representations of immune response were explored to identify the best ones to describe data. A simplified 95% drug effect was implemented to represent a highly effective dose of MOV.

Results. IVDM showed data were best described when MOV acts on viral infectivity, consistent with the error catastrophe mechanism of action. A cascade of innate and adaptive immune response and a basal level activation enabled durable immunity and continued viral decay after treatment end. IVDM reasonably describes VL and viral titer data from animals and humans. Influence of MOV start time was explored using simulations. Consistent with the ferret studies, simulations showed when treatment is started within the first week post infection, MOV reduces viral growth, resulting in a lower and shortened duration of detectable VL. When started later (e.g. >7 days since symptom onset), the magnitude of drug effect is substantially diminished in a typical patient with an effective immune response which reduces VL prior to treatment start. Further work is needed to model response in patients with longer term infection, where MOV drug effects may have more persistent utility.

Table 1.

| Parameter | Value |
|-----------|-------|
| NHC (µM) | 9.52 |
| IC₅₀ (µM) | 2.34 |
| IC₉₀ (µM) | 4.78 |
| IC₉₅ (µM) | 9.52 |
| IC₉₉ (µM) | 19.04 |

Disclosures. Youfang Cao, PhD; Wei Gao, PhD; Ruthie Birger, PhD; Julie Stone, PhD; Merck & Co. Inc. Nothing to disclose.

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524. Assessing the Safety of an Outpatient Remdesivir Infusion Program for Patients with Severe COVID-19 in the Setting of a Pandemic Surge

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Session: P-24. COVID-19 Treatment

Background. (i) Remdesivir (RDV) shortens recovery time among COVID-19 patients in an inpatient setting. (ii) Treatments for outpatient patients diagnosed with COVID-19 are limited. (iii) In early 2021, there was a national surge in COVID-19 hospitalizations, which resulted in hospital bed and staff shortages. (iv) In the face of this pandemic surge, we piloted a program to expand our RDV treatment capacity by establishing an off-label, outpatient infusion tent (OIT) for patients with severe COVID-19. (v) This is a retrospective, descriptive report examining the safety and efficacy of this program, with outcomes of interest being 30-day mortality and hospital admission within the subsequent 30 days.

Methods. (i) The OIT, consisting of 11 chairs capable of treating 35 patients per day, was operational from January 1 to February 19, 2021. (ii) Patients were referred to the outpatient RDV program primarily from urgent care (UC) and the emergency department (ED), and from the inpatient setting to complete therapy. Patients received at least one dose prior to referral. (iii) Eligibility criteria included a confirmed COVID-19 diagnosis, (ED), and from the inpatient setting to complete therapy. Patients received at least one dose prior to referral. (iv) Exclusion criteria included pregnancy, sepsis, end-stage renal disease, radiographic evidence of viral pneumonia, and an oxygen saturation less than or equal to 94 on room air. (v) This is a retrospective, descriptive report examining the safety and efficacy of this program, with outcomes of interest being 30-day mortality and hospital admission within the subsequent 30 days.

Results. (i) A total of 88 patients received 258 infusions. The average number of outpatient infusions per participant was 2.9. (ii) Four out of 88 patients died (4.5%). (iii) Eligibility criteria included a confirmed COVID-19 diagnosis, (ED), and from the inpatient setting to complete therapy. Patients received at least one dose prior to referral. (iv) Exclusion criteria included pregnancy, sepsis, end-stage renal disease, radiographic evidence of viral pneumonia, and an oxygen saturation less than or equal to 94 on room air. (v) Exclusion criteria included pregnancy, sepsis, end-stage renal disease, radiographic evidence of viral pneumonia, and an oxygen saturation less than or equal to 94 on room air. (vi) This is a retrospective, descriptive report examining the safety and efficacy of this program, with outcomes of interest being 30-day mortality and hospital admission within the subsequent 30 days.

Table 1. Patient Characteristics

| Characteristic          | N (%)          |
|------------------------|----------------|
| Sex – Male             | 57 (64.8%)     |
| Sex – Female           | 31 (35.2%)     |
| Race/Ethnicity – Black | 11 (12.5%)     |
| Race/Ethnicity – Latino| 45 (51%)       |
| Race/Ethnicity – White | 15 (17.1%)     |
| Age – Median           | 57.5           |
| BMI – Median           | 32             |
| BMI > 30               | 59 (67.2%)     |
| Hypertension           | 54 (61.4%)     |
| Diabetes I / II        | 39 (44.3%)     |
| Coronary Artery Disease| 6 (6.8%)       |
| Congestive Heart Failure| 3 (3.4%)      |
| COPD                   | 5 (5.7%)       |
| Asthma                 | 9 (10.2%)      |
| Chronic Kidney Disease | 9 (10.2%)      |
| Chronic Liver Disease  | 1 (1.1%)       |

Table 2. Admissions Within Subsequent 30 Days

| Reason for subsequent admission          | N (%)          |
|------------------------------------------|----------------|
| Worsening COVID-19 Pneumonia            | 11 (78.6%)     |
| Pulmonary embolus                       | 1 (7.14%)      |
| Bacteremia                              | 1 (7.14%)      |
| Progression of metastatic cancer        | 1 (7.14%)      |

Conclusion. A COVID-19 IVDM developed using multiscale MOV virology data supports drug action on viral infectivity and importance of interplay of treatment and immune response and can describe infection time course and drug effect. IVDM provided mechanistic interpretations for IV drug effect in clinical studies.

Disclosures. Youfang Cao, PhD, Merck & Co. (Employee); Wei Gao, PhD, Merck & Co., Inc. (Employee, Shareholder); Ruthie Birger, PhD, Merck (Employee); Julie Stone, PhD, Merck & Co., Inc. (Employee, Shareholder)

525. Atovaquone for Treatment of COVID-19 (Ataq COVID-19) Trial

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Session: P-24. COVID-19 Treatment

Background. Our group performed an in-silico screen to identify FDA approved drugs that inhibit SARS-C0V-2 main protease (Mpro), followed by in vitro viral replication assays, and in vivo pharmacokinetic studies in mice. These studies identified atovaquone as a promising candidate for inhibiting viral replication.

Methods. Enrolled patients were randomized in a 2:1 fashion to atovaquone 1500 mg twice daily versus matched placebo. Patients received standard of care treatment including remdesivir, dexamethasone, or convalescent plasma as deemed necessary by the treating team. Patients agreed to allow collection of saliva at baseline and twice a day while hospitalized or up to 10 days. Saliva was collected and RNA extracted for viral load (VL) measurement by Real-time PCR. Our primary outcome was to examine the between group differences in log transformed VL(copies/mL) using generalized linear mixed-effect models of repeated measures from all samples. Additional analysis of Atovaquone plasma concentrations were examined and correlated with viral load and body mass index (BMI).

Results. Of the 61 patients enrolled; 41 were received atovaquone and 19 placebo. Patients received standard of care treatment including remdesivir, dexamethasone, or convalescent plasma as deemed necessary by the treating team. Patients agreed to allow collection of saliva at baseline and twice a day while hospitalized or up to 10 days. Saliva was collected and RNA extracted for viral load (VL) measurement by Real-time PCR. Our primary outcome was to examine the between group differences in log transformed VL(copies/mL) using generalized linear mixed-effect models of repeated measures from all samples. Additional analysis of Atovaquone plasma concentrations were examined and correlated with viral load and body mass index (BMI).

Conclusion. Mortality rate in outpatients with severe COVID-19 treated with RDV was similar to that reported in inpatients. In this cohort of patients with severe COVID, a majority (84.1%) avoided hospitalization while still receiving appropriate treatment. Results suggest RDV can be safely delivered to outpatients with severe COVID-19.

Disclosures. All Authors: No reported disclosures