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Effect on SARS-CoV-2 viral load using combination therapy with casirivimab/imdevimab and remdesivir

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ABSTRACT

Evidence suggests that SARS-CoV-2 viral load is an independent predictor of disease severity and mortality. A 61-year-old woman presented with severe COVID-19 and was treated with casirivimab/imdevimab and remdesivir. Quantitative nasopharyngeal (NP) viral loads were trended throughout the treatment course. Baseline NP viral load was 25,860,901 copies/mL (7.4 log10). Casirivimab/imdevimab was administered, with subsequent reduction in NP viral load to 26,049 copies/mL (4.4 log10) on hospital day 4. A repeat NP viral load on day 7 was 13,113 copies/mL (4.1 log10). Despite uncertainty regarding correlation with reduction in viral load and outcomes, NP viral load may be considered when selecting treatment options and evaluating treatment response in hospitalized patients with early infection.

KEYWORDS anti-infectives; COVID; infectious diseases

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in an ongoing pandemic, in which disease severity and spectrum vary significantly. Established risk factors for severe disease consist of vaccination status, underlying comorbidities, and age ≥65 years.[1–4] Moreover, recent evidence suggests that high SARS-CoV-2 viral load is an independent predictor of disease severity and mortality.[5] While management largely consists of supportive care, numerous therapeutics have been developed to augment viral replication and/or host immune response to mitigate disease progression and improve clinical outcomes. Current pharmacologic treatment strategies for patients with SARS-CoV-2 consist of monoclonal antibody therapy, antiviral medications, and anti-inflammatory agents. While anti-inflammatory agents and the antiviral remdesivir are almost exclusively utilized in severe disease, monoclonal antibodies are commonly utilized in patients with nonsevere disease who have a high risk for progression. Phase 3 clinical trials are limited to nonhospitalized patients with mild to moderate COVID-19; however, ongoing studies have investigated the role of monoclonal antibodies in hospitalized patients.[6–9]

We report a case of severe COVID-19 treated with casirivimab/imdevimab and remdesivir, in which quantitative nasopharyngeal (NP) viral loads were trended throughout the hospital/treatment course.

CASE DESCRIPTION

A 61-year-old black woman with known chronic obstructive pulmonary disease and interstitial lung disease on 4 L of oxygen per minute at baseline, heart failure with preserved ejection fraction, pulmonary hypertension, diabetes mellitus, and substance abuse disorder with crack/cocaine presented to the emergency department with a 2-day history of cough, dyspnea, fever, and chills. She had received a single dose of the Johnson & Johnson vaccine 8 months earlier. Admission chest x-ray was unchanged from prior admissions, and her SARS-CoV-2 polymerase chain reaction test was positive. No significant findings were identified on her laboratory tests *(Table 1)*; however, she developed profound hypoxemia requiring high-flow nasal cannula to sustain a peripheral oxygen saturation ≥92%. Her procalcitonin was below the limit of detection so antibiotics were withheld. Due to a sustained oxygen generation <94% on baseline

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Table 1. Laboratory data

Parameter	Value	Reference range
Serum creatinine (mg/dL)	0.53	0.51–0.95
Blood urea nitrogen (mg/dL)	10	8–23
Alanine transaminase (U/L)	19	0–33
Aspartate transaminase (U/L)	8	0–32
White blood cell count (K/μL)	9.1	4.5–11.0
Hemoglobin (g/dL)	7.8	12.0–16.0
Absolute neutrophil count (K/μL)	4.73	2.07–8.80
B-type natriuretic peptide (pg/mL)	<10	0–100
Troponin T, high sensitivity (ng/L)	11	<14
Venous blood gas		
pH	7.42	–
CO_2	41	–
HCO_3	26	–
C-reactive protein (mg/dL)	0.9	0.0–0.4
D-dimer (μg/mL)	0.28	0–0.49
Procalcitonin (ng/mL)	<0.05	–

oxygen support and tachypnea, she was classified as having severe COVID-19.

Given the absence of alternative etiologies of hypoxemia, therapy with remdesivir was initiated along with dexamethasone 6 mg daily. Results of SARS-CoV-2 nucleocapside antibodies were negative, indicating early infection. Her quantitative NP viral load was 25,860,901 copies/mL (7.4 log10 copies/mL). Moreover, genomic testing identified this patient's SARS-CoV-2 as the Delta variant (AY.3.121J Delta). Given early disease and lack of clinical improvement, on hospital day 2 casirivimab 600 mg/imdevimab 600 mg was administered. On hospital day 4, high-flow nasal cannula was successfully weaned to the patient's baseline oxygen requirement, but intermittent desaturations continued with exertion. A repeat quantitative SARS-CoV-2 NP viral load resulted as 26,049 copies/mL (4.4 log10). On hospital day 5, following the completion of remdesivir, no further desaturation episodes were reported. As a result, discharge planning was initiated on hospital day 6 with subsequent discharge on hospital day 7. Notably, the patient was not discharged with a prescription to complete the 10-day course of dexamethasone due to clinical improvement. Prior to discharge, a repeat NP quantitative SARS-CoV-2 viral load resulted as 13,113 copies/mL (4.1 log10).

DISCUSSION

In this case of severe COVID-19, combination antiviral and monoclonal antibody therapy resulted in a significant reduction in quantitative NP viral load and corresponding improvement in the clinical course. There have been no reports describing the impact of combination therapy with casirivimab/imdevimab and remdesivir on quantitative SARS-CoV-2 viral load, especially in the inpatient setting, where monoclonal antibody use is not the standard of care.

The utility of SARS-CoV-2 quantitative NP viral load and its impact on treatment outcomes is controversial. According to the US Food and Drug Administration, virologic measures are acceptable endpoints in phase 2 trials to support progression to phase 3 trials.[7] However, virologic measures are not appropriate as a primary endpoint in phase 3 trials due to a lack of an established predictive relationship between magnitude and timing of viral load reductions and the degree of clinical benefit observed.[7] Despite this, evidence from randomized and observational studies have provided insight on the utility of quantitative NP viral loads. A recent systematic review by Shenoy demonstrated a significant association between NP viral load at symptom onset and development of severe COVID-19.[5] Furthermore, in a study by Mollan and colleagues, seropositive patients had a significantly lower NP viral load compared to seronegative patients (4.4 vs 6.8 log10 copies/mL, $P < 0.0001$).[8] Due to humoral immunity and its role in limiting viral shedding, consideration of serostatus may serve as a reliable marker of disease onset. Moreover, serostatus and corresponding viral load may also assist with risk stratification when selecting antiviral therapy. Our patient presented in the early phase of disease, as indicated by high viral load (7.4 log10 copies/mL), symptom onset, and seronegative status.

In the REGEN-COV-2 trials, mean NP viral load on enrollment was ~5.0 log10 copies/mL.[9] Treatment resulted in a significant mean reduction in NP viral load compared to placebo at day 7 among seronegative patients (−1.9 vs −1.4 log10 copies/mL).[9] Treatment also resulted in a reduction in hospitalization or death.[10] The role of monoclonal antibodies was evaluated in hospitalized patients by both ACTIV-3/TICO and RECOVERY platforms.[11–13] Bamlanivimab/etesevimab, when coadministered with remdesivir among seronegative patients, reduced median time to recovery.[11,12] Similarly, casirivimab/imdevimab demonstrated a reduced 28-day mortality in seronegative patients.[13] Remdesivir, on the other hand, has had conflicting reports regarding the impact on viral load.[14,15] In the PINETREE trial, remdesivir halted progression to severe disease, hospitalization, or death, but had no impact on viral load reduction.[15] Our patient had severe disease with a high viral load that responded to combination therapy beyond the expected reported decrease.

New variants with unpredictable effects on transmissibility, virulence, and resistance may render currently available treatments ineffective. Continued mutations in the spike protein and receptor-binding domain of SARS-CoV-2 may enhance its ability to evade immunity.[16] With Omicron emergence, resistance developed to casirivimab/imdevimab and bamlanivimab/etesevimab. On the other hand, SARS-

CoV-2 genetic mutations have not affected the effectiveness of remdesivir, given it directly inhibits viral replication via its target of RNA polymerase.[17] As a result, development of novel and sustainable therapeutics will be vital in combating ongoing/emerging variants.

Although it may not be readily available in all institutions, quantitative NP viral load may be considered to further aid in the selection of treatment options and evaluation of treatment response in hospitalized patients with early infection due to SARS CoV-2.

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