Original Research

# Remdesivir versus usual care in the treatment of patients with COVID-19

Ivette M. Solís-Nolasco, PharmD[1], Ian Murphy, PharmD, BCIDP[2], Michael McAlister, PharmD, BCIDP[3], Cara Slaton, PharmD, BCIDP[2]

[1] Pharmacy Services, Orlando Health, Orlando Regional Medical Center, [2] Infectious Diseases & Antimicrobial Stewardship, Orlando Health, Orlando Regional Medical Center, [3] Infectious Diseases & Antimicrobial Stewardship, Orlando Health, Dr. P. Phillips Hospital

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## Background

Remdesivir was approved by the Food and Drug Administration in 2020 for treating hospitalized COVID-19 patients and those at high risk of severe disease. Although studies have shown a reduced risk of severe outcomes during the Omicron era compared to earlier variants, data on the effectiveness of remdesivir during this period remains limited.

## Objective

To evaluate the clinical benefit of remdesivir in comparison to no antiviral therapy for the treatment of more recent COVID-19 infections.

## Methods

This retrospective cohort study included patients admitted to seven hospitals in central Florida between January 2023 and December 2024. Patients included had a primary diagnosis of COVID-19 and required ⩾ 2 liters of nasal cannula oxygen for a minimum of 24 hours. Patients requiring higher levels of oxygen support were excluded. The primary outcome was the progression of oxygen supplementation requirements. Data were analyzed using REDCap® and SPSS®.

## Results

A total of 120 patients received remdesivir, and 52 patients received usual care (nasal cannula support ± steroids). The median age was 77 years (IQR: 67-85) with hypertension, chronic pulmonary disease, and diabetes as common comorbidities. No difference in progression of oxygen supplementation was observed between remdesivir (19 [15.8%] versus 7 [13.5%] usual care, p=0.16). Post-hoc analysis demonstrated Charlson Comorbidity Index was significantly associated with oxygen support progression (OR 1.98 [1.07-3.68] p=0.03).

## Conclusion

Remdesivir did not result in a reduction in oxygen supplementation progression in hospitalized COVID-19 patients during the Omicron era. Further large-scale prospective studies are needed to validate these findings.

## INTRODUCTION

Remdesivir is a SARS-CoV-2 nucleotide analog ribonucleic acid (RNA) polymerase inhibitor that impairs viral RNA synthesis.[1] The Infectious Diseases Society of America (IDSA) recommends remdesivir for hospitalized patients with coronavirus disease 19 (COVID-19) requiring supplemental oxygen but not mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[2] IDSA suggest against routine initiation of remdesivir in patients receiving invasive mechanical ventilation or ECMO (very low certainty of evidence). The most recent guideline update was published in February 2022.

Early randomized, placebo-controlled trials conducted during more virulent SARS-CoV-2 variants demonstrated that remdesivir shortened time to clinical recovery in hospitalized patients with results of 21 days versus 23 days in 158 patients receiving remdesivir compared to 79 patients receiving placebo for 10 days.[3,4] Another double-blind randomized, placebo-controlled trial involving 1,062

COVID-19 hospitalized patients demonstrated a reduced time to recovery of 10 days with remdesivir compared to 15 days with placebo.[5] During this period Wuhan-Hu-1 and Alpha were the predominant viral genomic sequencies.[4] In ACTT-1, the greatest benefit was observed among patients requiring supplemental oxygen, but no invasive mechanical ventilation.[5] These findings led the CDC to recommend the use of remdesivir in patients diagnosed with COVID-19.

In contrast the World Health Organization (WHO) SOLIDARITY trial and other contemporary studies did not demonstrate a mortality or clinical progression benefit with remdesivir.[6] During the same period, a Phase 3 open-label study with 857 patients showed no clinical advantage of remdesivir over standard care.[7] Despite mixed evidence, remdesivir is associated with substantial acquisition costs. The current cost per 100 mg dose in the United States is around $650 with an average cost of $3,900 per 5 days of therapy.[8] A remdesivir cost effectiveness analysis from 2022 estimated up to $1,847,000/quality-adjusted life-years (QALY) in patients with mild cases of COVID-19 and $298,000/QALY in moderate to severe cases. These results are significantly higher than the common cost-effective threshold of $50,000 QALY even after assuming survival benefit.[9]

The global epidemiology of SARS-CoV-2 has been characterized by the sequential emergence and predominance of distinct viral variants; each associated with varying clinical outcomes and degrees of severity.[10] Following the original strain in 2019, the Alpha, Beta, and Gamma variants emerged in late 2020. These were succeeded by the Delta variant, which became globally predominant in mid-2021.[11] The Delta variant was characterized by increased transmissibility and a higher disease severity compared to its predecessors.[12] At the end of 2021, the WHO classified the newly emerging Omicron variant as a variant of concern due to its increased transmissibility.[13] Since late 2021, the subsequent variants have been associated with a substantially lower risk of hospitalization, intensive care unit (ICU) admission, need for oxygenation or ventilation, and death compared to Delta and earlier variants even after accounting for prior infection and vaccination.[14-17] Reduced severity has been attributed to both intrinsic viral properties and increasing population immunity.[13]

Remdesivir demonstrated activity against SARS-CoV-2 in cell culture, maintaining potency across multiple variants including Alpha, Beta, Delta, and Omicron.[1] Nevertheless, despite the emergence of six new COVID-19 variants between 2021 and 2024, contemporary data evaluating its effectiveness in lower severity post Omicron populations remains limited. Considering the change in clinical impact and the high cost of treatment, the need to re-evaluate the role of remdesivir in the management of subsequent strains with reduced disease severity is relevant. This retrospective study aims to assess the clinical benefit of remdesivir in comparison to no antiviral therapy for the treatment of more recent COVID-19 infections.

## METHODS

This retrospective cohort study reviewed and approved by the Orlando Health Institutional Review Board utilized electronic health record Epic from seven hospitals within a large community health system in central Florida between January 1, 2023, and December 31, 2024. Adult patients with a primary diagnosis of COVID-19 (ICD-10 code U07.1) confirmed by antigen or polymerase chain reaction test (PCR), who required ⩾2 liters of nasal cannula support for at least 24 hours were included. Patients requiring high-flow nasal cannula, bi-level positive pressure, noninvasive or invasive positive mechanical ventilation, or ECMO within 24 hours of admission, as well as pregnant patients and those with mortality within 48 hours of admission were excluded.

Baseline characteristics included age, race, sex, weight, height, comorbidities, and Charlson Comorbidity Index (CCI). Collected clinical data included highest level of oxygen support within 24 hours of admission, timing and duration of remdesivir and corticosteroid therapy, COVID-19 vaccination status, prior SARS-CoV-2 infection within the last 12 months, duration of symptoms prior to diagnosis, concomitant use of tocilizumab or baricitinib and SARS-CoV-2 IgG nucleocapside (N) protein result. During the study period, SARS-CoV-2 IgG N testing was incorporated into the remdesivir order set and was therefore primarily obtained in patients receiving antiviral therapy. Demographic and clinical data were collected and analyzed using REDCap® and SPSS®.

The primary endpoint evaluated progression of oxygen supplementation, defined as escalation to high-flow nasal cannula, invasive mechanical ventilation, or ECMO during hospitalization. Secondary endpoints included all-cause inpatient mortality, 30-day all-cause mortality, and hospital length of stay. Hepatoxicity was defined as an increase of at least 5 times the upper limit of normal alanine aminotransferase or aspartate aminotransferase.

Statistical analysis was performed using SPSS®. Continuous, non-parametric variables are presented as median (interquartile range IQR) and analyzed using the Mann-Whitney U Test. Categorical data are described as frequencies and percentages and analyzed using chi-Square or Fisher's exact tests. A post-hoc logistic regression model was performed to assess the association between selective clinical variables and progression of oxygen support. Due to the limited sample size, neither sensitivity nor propensity score adjustments were performed. Two patients received adjunctive immunomodulatory therapy (tocilizumab or baricitinib). Corticosteroid use was comparable between groups. No subgroup or adjusted analysis was conducted for these variables.

## RESULTS

A total of 610 patients were screened and 172 were included (Appendix A). Among excluded patients, 416 did not require ⩾2 liters of nasal cannula oxygen for ⩾ 24 hours, and 22 required advanced oxygen support within 24 hours of admission. Of the 172 patients included, 120 received

**Table 1. Baseline Characteristics**

| Characteristic | Remdesivir (n=120)* | Usual Care (n=52)* | *p* value |
|---|---|---|---|
| 1. Female, No. (%) | 59 (49) | 29 (56) | 0.43 |
| 2. Race, No. (%)<br>Caucasian<br>African American<br>Hispanic or Latino<br>Asian<br>Other | <br>77 (64.2)<br>11 (9.2)<br>24 (20)<br>3 (2.5)<br>5 (4.2) | <br>27 (51.9)<br>12 (23.1)<br>11 (21.2)<br>1 (1.8)<br>1 (1.8) | <br>0.13<br>0.01<br>0.86<br>0.82<br>0.46 |
| 3. BMI (kg/m$^2$), median (IQR) | 29 (24-34) | 27 (23-36) | 0.98 |
| 4. Charlson Comorbidity Index (CCI), median (IQR) | 5 (4-6) | 5 (4-7) | 0.98 |
| 5. Hypertension, No. (%) | 89 (74.2) | 38 (73.1) | 0.88 |
| 6. Chronic lung disease, No.(%) | 55 (45.8) | 19 (36.5) | 0.26 |
| 7. Diabetes, No. (%) | 47 (39.2) | 19 (36.5) | 0.75 |
| 8. Coronary Artery Disease, No. (%) | 29 (24.2) | 13 (25) | 0.91 |
| 9. Chronic kidney disease, No.(%) | 28 (23.3) | 12 (23.1) | 0.97 |
| 10. Cerebrovascular accident or transient ischemic attack, No. (%) | 11 (9.2) | 6 (11.5) | 0.63 |
| 11. Immunosuppression, No. (%) | 6 (5) | 5 (9.6) | 0.31 |
| 12. COVID-19 vaccine within 12 months of admission, No. (%) | 31/112 (27.7) | 8/44 (18.2) | 0.22 |
| 13. History of COVID-19 within 12 months of admission, No. (%) | 6/118 (5.1) | 1/48 (2.1) | 0.35 |
| 14. Duration of symptoms prior to COVID-19 diagnosis (days), median (IQR) | 3/97 (2-7) | 3/30 (2-4) | 0.78 |
| 15. Positive SARS-CoV-2 IgG N protein, No. (%) | 11/97 (11.3) | 19/34 (55.9) | < 0.01 |

*Rows 1-11

**Table 2. Treatment of COVID-19 during admission**

| | n | Remdesivir | n | Usual Care | *p* value |
|---|---|---|---|---|---|
| Time to remdesivir, hours, median (IQR) | 120 | 13.9 (7.9-25.8) | --- | --- | --- |
| Time to dexamethasone, hours, median (IQR) | 93 | 17.1 (6-35) | 18 | 15.6 (8.3-28.1) | 0.62 |
| Duration of remdesivir, days, median (IQR) | 120 | 3.4 (1-5) | --- | --- | --- |
| Duration of dexamethasone, days, mean ±SD | 93 | 4 ±1.7 | 18 | 4±2.8 | 0.66 |
| Tocilizumab or baricitinib for COVID-19 treatment, No. (%) | 120 | 2 (1.7) | 52 | 0 | 0.35 |

remdesivir and 52 received usual care defined as nasal cannula support with or without corticosteroids. Baseline characteristics were well balanced between groups (Table 1), although the remdesivir group had a higher proportion of Caucasian patients and fewer African American patients (p=0.01). Rates of vaccination within 12 months and recent prior COVID-19 were not significantly different between groups. However, a higher incidence of positive SARS-CoV-2 IgG N protein was observed in the usual care group 19/34 (55.9%) versus 11/97 (11.3%) (p < 0.01) in the remdesivir group.

Treatment characteristics are summarized in Table 2. Remdesivir was initiated by a median of 13.9 hours (IQR 7.9 to 25.8) after hospital admission and continued for a median of 3.4 days (IQR 1 to 5). Corticosteroid administration and duration were similar between groups. Two patients (1.7%) in the remdesivir group received adjunctive therapy with tocilizumab or baricitinib.

Progression of oxygen support occurred in 19/120 (15.8%) patients of the remdesivir group and 7/52 (13.5%) patients of the usual care group (p=0.66) (Table 3). Progression to high-flow nasal cannula occurred in 13 (10.8%) vs. 2 (3.8%) patients (p=0.03) and CPAP-BiPAP in 6 (5%) vs. 5 (9.6%) (p=0.07). No patients require invasive mechanical ventilation or ECMO. There was no inpatient mortality and thirty-day all-cause mortality occurred in two patients from the remdesivir group. The median hospital length of stay was similar in both groups; 4.5 days (3.6 to 6.1) in the remdesivir group compared to 4 (2.6 to 6.1) in the usual care group (p=0.21). Hepatotoxicity occurred in 5 (9.6%) patients in the usual care group and none in the remdesivir group (p< 0.01). All elevated transaminase values were present on admission prior to antiviral initiation. In a post-hoc logistic regression (Appendix B), higher CCI was independently associated with progression of oxygen support (OR 1.98, 95% CI 1.07 to 3.68; p=0.03). No significant associations were observed with vaccination status, negative IgG N

**Table 3. Outcome Results**

| Outcome | Remdesivir (n=120) | Usual Care (n=52) | *p* value |
|---|---|---|---|
| Oxygen supplementation progression, No. (%)<br>Continuous positive airway pressure- bilevel positive airway pressure<br>High-flow nasal cannula | 19 (15.8)<br>6 (5)<br>13 (10.8) | 7 (13.5)<br>5 (9.6)<br>2 (3.8) | 0.16<br>0.07<br>0.03 |
| All-cause inpatient mortality, No. | 0 | 0 | --- |
| 30-day all-cause mortality, No. (%) | 2 (1.7) | 0 | 0.35 |
| Length of stay, days, median (IQR) | 4.5 (3.3-6.1) | 4 (2.4-6.1) | 0.21 |
| Increase of liver enzymes ≥ 5 times the upper limit of normal No. (%) | 0 | 5 (9.6) | < 0.01 |

protein, immunosuppression, or comorbidities such as diabetes or heart failure.

## DISCUSSION

In this retrospective cohort trial conducted during a post-Omicron predominant era, remdesivir was not associated with reduced progression of oxygen support among hospitalized patients initially requiring low-flow oxygen. No differences were observed in hospital length of stay, inpatient all-cause mortality, or 30-day all-cause mortality in comparison to usual care. These results align with the decrease in clinical severity and lower rates of progression to severe disease associated with the Omicron variant era, the predominant variant since late 2021.[16]

These findings contrast with earlier randomized trials such as ACTT-1,[5] which demonstrated shortened recovery time, particularly among patients requiring supplemental oxygen but not invasive ventilation. However, pivotal remdesivir trials were conducted during periods of higher baseline severity and greater event rates. In contrast, progression to advanced respiratory support was uncommon in our cohort, and no patients required invasive mechanical ventilation or ECMO. The lower baseline risk observed in this period may attenuate the measurable absolute benefit of antiviral therapy compared with earlier waves.

Positive SARS-CoV-2 IgG N protein levels were significantly higher in the usual care group. At the institution, IgG N testing and IgG N signal-to-cutoff (S/C) ratio were incorporated into the remdesivir order set, and in some cases a positive result and a declining signal-to-cutoff (S/C) ratio was interpreted as suggestive of prior infection instead of an acute process which informed decisions to discontinue remdesivir. This practice, based on clinical expert opinion, may have influenced treatment allocation. Although seropositivity could reflect prior infection, the timing and clinical significance in this cohort remains uncertain. The post-hoc logistic regression aimed to identify clinical factors associated with progression to higher levels of oxygen support. The Charlson Comorbidity Index demonstrated a statistically significant association with increased progression of oxygen support highlighting the impact of overall comorbidity burden rather than individual risk factors on clinical deterioration.

The use of remdesivir was not associated with hepatotoxicity in this cohort. Nonetheless, most liver function tests were conducted on admission, which could have limited the identification of treatment-related effects. The observed difference in hepatoxicity reflects baseline hepatic comorbidity and potential selection bias rather than treatment-related effect. Remdesivir entails a high cost of treatment. The 2024 annual expenditure on remdesivir at an 808-bed hospital from our health system was $490,183. Although remdesivir entails a substantial acquisition cost, no measurable reduction in clinical progression was observed in this population, raising questions regarding its cost effectiveness.

This study has several limitations. The relatively small sample size limits statistical power and the ability to detect modest treatment effects. Although 610 patients were screened, most did not require supplemental oxygen and were excluded, consistent with the reduced clinical severity observed within the contemporary variants period. In addition, the absence of inpatient mortality or progression of oxygen support likely reduced the measurable benefit of antiviral therapy in this cohort.

The retrospective design limits the control of unmeasured confounding factors. Data regarding immunization status, history of recent COVID-19 infection, and duration of symptoms prior to diagnosis were incomplete. Data on secondary infections were not collected; their potential contribution to clinical outcomes cannot be excluded. Genomic sequencing data were not available to confirm specific SARS-CoV-2 variants. The variant predominance was inferred based on the study period and the epidemiological trend.

## CONCLUSION

Prior clinical trials have demonstrated a significant reduction in time to recovery with remdesivir during earlier, more virulent waves, but did not consistently show benefit on mortality or progression of oxygen supplementation requirements.[5,7] In this post-Omicron cohort characterized by lower severity and event rates, remdesivir was not associated with reduced progression of oxygen support. These findings suggest that the clinical benefit of antiviral therapy may be diminished in contemporary, lower severity populations. Larger prospectives studies are needed to val-

idate the role of remdesivir in the current epidemiologic landscape.

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CONFLICTS OF INTEREST

The authors have declared no potential conflicts of interest.

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