Poster # P-2020

Combination Therapy with Remdesivir and Corticosteroids is Associated with Lower Mortality Risk vs. Corticosteroids Monotherapy in Patients Hospitalised for COVID-19.

Essy Mozaffari
Essy.Mozaffari@gilead.com
Gilead Sciences, Inc.
Foster City, CA, USA

Essy Mozaffari[1], Aastha Chandak[2], Robert L Gottlieb[3,4,5,6], Chidinma Chima-Melton[7], Mark Berry[1], Thomas Oppelt[1], Jason F Okulicz[1], Alpesh N Amin[8], Andre C Kalil[9], Paul E Sax[10]

[1]Gilead Sciences, Foster City, California, USA, [2]Certara, New York, New York, USA, [3]Baylor University Medical Center, Dallas, Texas, USA, [4]Baylor Scott & White Heart and Vascular Hospital, Dallas, Texas, USA, [5]Baylor Scott & White The Heart Hospital, Plano, Texas, USA, [6]Baylor Scott & White Research Institute, Dallas, Texas, USA, [7]University of California, Los Angeles, California, USA, [8]University of California, Irvine, California, USA, [9]University of Nebraska Medical Center, Omaha, Nebraska, USA, [10]Brigham and Women's Hospital, Boston, Massachusetts, USA

Conclusions

- In this study, about half of the patients not requiring supplemental oxygen at baseline, received CORT in the first 2 days of hospitalization despite guideline recommendation against the use of CORT for these patients[7-10]
- Of the 43,618 patients that received CORT monotherapy at hospital admission:
  - Majority of the patients did not require any supplemental oxygen at baseline (45%, n=19,592) also did not require supplemental oxygen therapy throughout the hospitalization but continued receiving CORT after the first two days of hospitalization
- The findings from this study demonstrated that the use of RDV in patients receiving corticosteroids was associated with a reduction in risk of mortality as compared to corticosteroid monotherapy for the treatment of patients hospitalized for COVID-19 across all levels of baseline supplemental oxygen requirements.
- The study highlights the important role of antiviral therapy with remdesivir in improving clinical outcomes in patients hospitalized for COVID-19, supporting guideline recommendations
- Our findings also confirm (per COVID-19 treatment guidelines) that corticosteroid monotherapy should not be used in COVID-19 patients who do not require supplemental oxygen, unless required for a distinct medical indication (e.g. background immunomodulation for a chronic condition).

Background

- Despite gradual declines in COVID-19 incidence and mortality, the World Health Organization (WHO) acknowledged that COVID-19 is a continuing threat to lives and health systems in 2024[1]
- The RECOVERY trial conducted in earlier stages of COVID-19 pandemic showed no difference in mortality rates for usual care vs. dexamethasone among patients not requiring supplemental oxygen with a potential paradoxical signal for harm in non-hypoxemic COVID-19 patients despite clear benefit for COVID-19 with hypoxemia[2]
- Studies conducted since the RECOVERY study have shown the potential for a detrimental effect of corticosteroid treatment in patients with mild-to-moderate (non-hypoxemic) COVID-19[3,4]
- COVID-19 treatment guidelines from National Institutes of Health (NIH) (last updated in February 2024 and retired in August 2024), WHO (last updated in November 2023), and Infectious Diseases Society of America (IDSA) (last updated in August 2024):
  - Recommended against the use of dexamethasone for COVID-19 patients who do not require supplemental oxygen[5-7]
  - Recommendations for treatment of patients hospitalized for hypoxemic COVID-19 with both remdesivir (RDV) and a corticosteroid such as dexamethasone (DEX). Other immunomodulators may also be considered in addition to, but not in substitution for, corticosteroids.
- Other corticosteroids (CORT) such as prednisone, prednisolone, methylprednisolone, and hydrocortisone can be used in place of dexamethasone or for other underlying conditions.
- The objective of this study was to examine all-cause mortality in hospitalised COVID-19 patients initiating RDV+CORT vs. CORT monotherapy in the more recent COVID-19 era.

Methods

Study Design

- Comparative Effectiveness Retrospective cohort study (**Table 1**)
- Data source: PINC AI Healthcare Database (formerly Premier Healthcare Database)
  - US hospital-based, service-level, all-payer (Commercial, Medicare, Medicaid, others) database
  - Covers ~25% of all US hospitalizations from 48 states
  - Includes patient-level information on billed services for each day of hospitalization

Table 1. Study design

Inclusion criteria	✓ First admission to the hospital December 1, 2021-April 30, 2023 ✓ Age ≥18 years old ✓ ***Primary* discharge diagnosis of COVID-19** (ICD-10-CM: U07.1) and flagged as being "present-on-admission" ✓ **Initiated either RDV+ CORT or CORT monotherapy** in the first two days of hospitalization
Exclusion criteria	✗ Pregnant ✗ Had incomplete/erroneous data fields ✗ Transferred from another hospital or hospice ✗ Admitted for elective procedures ✗ Discharged or died during the baseline period (first two days of hospitalization) ✗ Initiation of other COVID-19 treatments (baricitinib or tocilizumab or oral antivirals) at baseline

Treatment	RDV + CORT	CORT mono
	RDV + CORT initiated in first 2 days of admission (baseline)	CORT monotherapy initiated in first 2 days of admission (Baseline)

- Baseline is defined as the first two days of hospitalization
- **Primary Endpoints:** 14-day and 28-day all-cause inpatient mortality (defined as a discharge status of "expired" or "hospice")
- Endpoints were examined according to baseline supplemental oxygen requirements: No supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV), and invasive mechanical ventilation (IMV)/ECMO
- Patients were followed from the day after treatment initiation until day 28 or discharge status of expired or hospice, transfer to another hospital, or addition of RDV after the first 2 days of hospitalization for the CORT monotherapy cohort, whichever was earlier.
  - If RDV was initiated in the CORT monotherapy group after the first two days of hospitalization, patients were only followed until the day RDV was added to the CORT monotherapy group following a per protocol treatment approach (censored upon cross-over).

Statistical analysis

- All analyses were conducted for the overall study cohort hospitalized during the Omicron period (December 2021 to April 2023) and stratified by baseline supplemental oxygen requirements (no supplemental oxygen charges [NSOc], low-flow oxygen [LFO], high-flow oxygen or non-invasive ventilation [HFO/NIV] and invasive mechanical ventilation and/or extracorporeal membranous oxygenation support [IMV/ECMO]).
- Propensity scores (PS) were estimated using separate logistic regression models for each baseline supplemental oxygenation requirement group separately
- Covariates used in PS calculation: demographics (age, gender, race, ethnicity), primary payor (commercial, Medicare, Medicaid, other), comorbidities (obesity, diabetes, cancer, chronic obstructive pulmonary disorder cardiovascular [including hypertension], or renal disease), hospital characteristics (bed size, urban or rural, teaching, US region), type of hospital ward on admission (general ward or intensive care unit [ICU]), COVID-19 treatments during baseline (anticoagulants, convalescent plasma, admission month, and admission from a skilled nursing facility (**Table 2**).
- Using the derived PS, distribution of underlying confounders in the two treatment groups was balanced using propensity score matching (PSM) as the primary analysis using a 1:1 preferential within-hospital matching approach without replacement with a caliper distance of 0.2 times standard deviation of the logit of the PS was implemented as follows:
  - Patients receiving RDV+CORT were matched to corticosteroids monotherapy patients in the same hospital within the specified caliper distance in the same age group (18-49, 50-64, 65+ years), and admission month groups (two-to-three-month blocks of admission month).
  - The unmatched patients in the RDV+CORT group were then matched to CORT monotherapy patients in another RDV-using hospital of similar bed-size (<200, 200-499, 500+ beds) within the specified caliper distance in same age group (18-49, 50-64, 65+ years), and admission month groups (two-to-three-month blocks of admission month).
- Cox Proportional Hazards Model was used to assess time to 14- and 28-day mortality adjusting for hospital-level cluster effects, and key covariates: age, admission month, hospital admission ward (documented location for ICU/ Step-down unit vs. general ward), and time-varying covariates for treatments initiated after baseline (baricitinib, tocilizumab, or oral antivirals).
- A sensitivity analysis was conducted to examine initiation of RDV+DEX vs. DEX monotherapy

Results

Study population

- 151,215 patients hospitalized for COVID-19:
  - 67,580 (45%) initiated RDV+CORT in the first 2 hospital days
  - 43,618 (29%) initiated CORT monotherapy (24% DEX monotherapy; 5% non-DEX corticosteroid monotherapy) in the first 2 hospital days
- Before matching (**Table 2**):
  - The plurality of patients in the RDV+CORT and CORT monotherapy cohort, respectively, did not receive supplemental oxygen at baseline (44%, 45%), the rest received LFO (36%, 35%), HFO/NIV (18%, 16%), and IMV/ECMO (2%, 4%).
- After 1:1 matching without replacement, 39,104 RDV + CORT patients were matched to 39,104 CORT monotherapy patients (in matching without replacement, matching % is dependent on available patients in the treatment group with smaller sample size) (**Table 2**):
  - Post-matching balance was achieved across groups of baseline supplemental oxygen with all covariates with a standardized difference absolute value of <0.15
  - Almost half of the patients did not receive supplemental oxygen at baseline (46%), the rest received LFO (36%), HFO/NIV (16%), and IMV/ECMO (2%)

Table 2. Baseline characteristics before and after PS matching

Baseline characteristics		Before matching: CORT Mono n=43,618	Before matching: RDV+ CORT n=67,580	After matching: CORT Mono n=39,104	After matching: RDV+ CORT n=39,104
Age group, years	18-49	8.5%	10.0%	7.8%	7.8%
	50-64	21.6%	22.8%	21.0%	21.0%
	65+	69.8%	67.2%	71.2%	71.2%
Gender	Female	51.4%	51.4%	51.4%	51.8%
Race	White	76.3%	77.1%	77.4%	77.5%
	Black	15.0%	13.1%	13.9%	13.9%
	Asian	1.6%	2.0%	1.6%	1.6%
	Other	7.0%	7.8%	7.1%	7.0%
Ethnicity	Hispanic	8.7%	11.0%	8.9%	8.5%
Primary payor	Commercial	14.0%	16.6%	14.2%	14.0%
	Medicare	72.2%	68.8%	72.6%	72.5%
	Medicaid	8.5%	9.4%	8.0%	8.1%
	Other	5.3%	5.2%	5.2%	5.3%
Hospital size, no. of beds	<100	8.5%	8.2%	8.6%	8.4%
	100-199	15.8%	17.0%	16.1%	16.4%
	200-299	20.9%	20.3%	21.1%	20.8%
	300-399	20.3%	17.5%	19.6%	19.7%
	400-499	11.1%	9.9%	10.9%	11.2%
	500+	23.3%	27.2%	23.6%	23.6%
Hospital location	Urban	85.6%	87.2%	85.9%	86.2%
	Rural	14.4%	12.8%	14.1%	13.8%
Teaching Hospital		39.9%	42.0%	39.9%	39.5%
Key comorbidities	Obesity	29.3%	30.4%	29.1%	29.0%
	COPD	39.9%	40.0%	40.0%	40.1%
	Cardiovascular disease	88.4%	85.3%	87.9%	87.8%
	Diabetes mellitus	41.1%	38.3%	40.1%	40.0%
	Renal disease	35.3%	23.7%	31.4%	31.2%
	Cancer	7.2%	7.2%	7.3%	7.2%
	Immunocompromising condition[1]	18.3%	17.5%	18.0%	18.1%
Hospital ward upon admission	General ward	82.9%	82.6%	83.9%	84.5%
	ICU/Step-down unit	17.1%	17.4%	16.1%	15.5%
Other treatments at baseline	Anticoagulants	74.2%	80.5%	77.1%	77.1%
	Convalescent plasma	<1%	<1%	<1%	<1%
Baseline oxygen requirements	NSOc	44.9%	43.6%	45.6%	45.6%
	LFO	34.9%	36.3%	35.7%	35.7%
	HFO/NIV	16.3%	18.0%	16.4%	16.4%
	IMV/ECMO	3.9%	2.2%	2.4%	2.4%

Unadjusted analysis (PS-matched cohort)

Unadjusted mortality rates at 14- and 28-days were lower for patients receiving RDV+CORT vs. CORT monotherapy across all baseline supplemental oxygen requirements

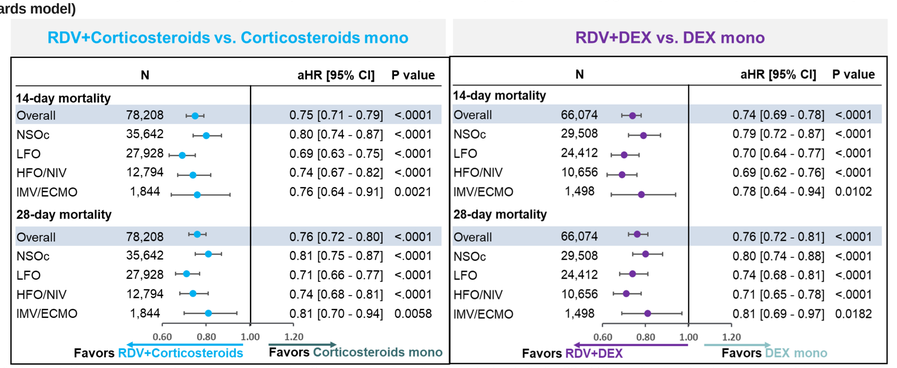
	14-day mortality		28-day mortality	
	CORT Mono	RDV+CORT	CORT Mono	RDV+CORT
Overall	**8.4%**	**7.2%**	**10.7%**	**9.5%**
NSOc	5.7%	5.3%	7.1%	6.7%
LFO	7.6%	5.9%	9.6%	7.8%
HFO/NIV	15.2%	13.2%	19.9%	17.5%
IMV/ECMO	28.1%	24.0%	35.0%	32.4%

[1]Immunocompromised conditions: cancer, transplant, hematologic malignancies, immunosuppressive medications, toxic effects of antineoplastics, primary immunodeficiencies, severe combined immunodeficiencies, asplenia, bone marrow failure/aplastic anemia, or HIV;
ICU, Intensive Care Unit; COPD, Chronic Obstructive Pulmonary Disorder; NSOc, No supplementary oxygen charges; LFO, Low-Flow Oxygen; HFO/NIV, High-Flow Oxygen/Non-invasive ventilation; IMV/ECMO, Invasive Mechanical Ventilation/ Extracorporeal Membrane Oxygenation; RDV, remdesivir; CORT, corticosteroids

Adjusted analysis (PS-matched cohort)

- Using 1:1 propensity score matching without replacement:
  - After adjusting for baseline and clinical covariates, RDV+CORT was associated with a significantly lower mortality risk at 14-days and 28-days compared to CORT monotherapy overall and across all supplemental oxygen requirements (**Figure 1**).
- Sensitivity analysis of RDV+DEX vs. DEX monotherapy showed consistent results:
  - After adjusting for baseline and clinical covariates, RDV+CORT was associated with a significantly lower mortality risk at 14-days and 28-days compared to CORT monotherapy overall and across all supplemental oxygen requirements (**Figure 1**).

Figure 1. Time to 14- and 28-day mortality in hospitalized COVID-19 patients by supplemental oxygen requirements (adjusted Cox Proportional Hazards model)



Note: Estimates adjusted for age, admission month, hospital ward on admission (ICU vs general ward), and time-varying treatment with other COVID-19 medications (baricitinib, tocilizumab, oral antivirals)
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CORT, Corticosteroids, DEX, dexamethasone ; mono, monotherapy; HFO/NIV, high flow oxygen/non-invasive ventilation; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation; mono, monotherapy; LFO, low flow oxygen; mono, monotherapy; NSOc, no supplemental oxygen charges; RDV, remdesivir.

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Acknowledgments: This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by Certara, and funded by Gilead Sciences, Inc.

Disclosures: **EM, MB, TO** and **JFO** are employees and stockholders of Gilead Sciences, Inc. **AC** received funding and medical writing support from Gilead Sciences, Inc. for conduct of this study. **RLG** reports serving on scientific advisory boards for AbbVie, AstraZeneca, Eli Lilly, Gilead Sciences, Inc., GSK, Roche, Johnson & Johnson (coronavirus disease 2019 [COVID-19]–related randomized clinical trial, coordinating principal investigator), and Kinevant Sciences (academic steering committee, study investigator; fees to Baylor Scott & White Research Institute) serving as a consultant for Gilead Sciences, Inc. (honoraria for lectures), Johnson & Johnson, and Kinevant Sciences (through his institution); serving on a speaker bureau for Pfizer unrelated to COVID-19; his institution receiving a gift-in-kind from Gilead Sciences, Inc. to facilitate a multicenter clinical trial outside the scope of COVID-19; a de minimis investment in AbCellera; grants or contracts as a study investigator (fees to Baylor Scott & White Research Institute) from Regeneron, Eli Lilly, Gilead, Pfizer, JNJ, AstraZeneca, and Roivant Sciences (Kinevant Sciences); and receipt of travel support for original scientific presentations from Gilead Sciences, Inc. **CCM** reports payment or honoraria for lectures/speaker from AstraZeneca, Boehringer Ingelheim, aTyr Pharma; consulting fees from AstraZeneca; and participation on advisory board for Gilead Sciences, Inc. **ANA** reports being a principal investigator or co-investigator of clinical trials sponsored by NIH/NIAID, NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, Alexion; Speaker and/or consultant for Pfizer, Salix, Alexion, AstraZeneca, Bayer, Ferring, Seres, Spero, Eli Lilly, Novo Nordisk, Gilead, Renibus, GSK, Dexcom, Reprieve, HeartRite, and Aseptiscope, unrelated to this study. **PES** reports research grants from Gilead and ViiV for HIV clinical trials and consulting fees from Gilead Sciences, Inc., Merck, and ViiV. **ACK** reports grants from the National Institutes of Health Adaptive COVID-19 Treatment Trial.