Remdesivir+Dexamethasone vs. Dexamethasone for the Treatment of COVID-19: Real-world Study in the US

Poster # 665

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], Tobias Welte[10], Paul E Sax[11]

[1]Gilead Sciences, Foster City, CA, USA; [2]Certara, New York, NY, USA; [3]Baylor University Medical Center, Dallas, TX, USA; [4]Baylor Scott & White Heart and Vascular Hospital, Dallas, TX, USA; [5]Baylor Scott & White The Heart Hospital, Plano, TX, USA; [6]Baylor Scott & White Research Institute, Dallas, TX, USA; [7]University of California, Los Angeles, CA, USA; [8]University of California, Irvine, CA, USA; [9]University of Nebraska Medical Center, Omaha, NE, USA; [10]Medizinische Hochschule Hannover, Hannover, Germany; [11]Brigham and Women's Hospital, Boston, MA, USA.

Conclusions

- Of the 151,215 patients eligible for this study, **35% of the hospitalized patients** with a primary diagnosis of COVID-19 **did not initiate RDV + DEX or DEX monotherapy** in the first 2 days of hospitalization. 97,725 patients receiving either RDV+DEX or DEX monotherapy were assessed:
  - 43% and 44% of the unmatched DEX + RDV and DEX cohort, respectively, all without supplemental oxygen charges at baseline, received DEX in the first 2 days of hospitalization **despite of NIH and WHO guidelines recommend against the use of dexamethasone** for these patients
  - Majority of the patients that received DEX monotherapy, not requiring supplemental oxygen at baseline, did not require supplemental oxygen therapy throughout the hospitalization **but continued receiving DEX** after the first two days in the hospital
  - Of the 36,489 patients receiving DEX monotherapy at hospital admission, **RDV was not administered to 90%** (n=32,840) of the patients during subsequent days in the hospital despite current guidelines which recommend use of RDV in hospitalized patients with NSOc, LFO, HFO and NIV
  - Based on current guidelines from NIH, WHO and IDSA for RDV use in hospitalized patients, **>50% of the patients that received DEX monotherapy should have also received RDV**
- The present study provides support for the benefit of following the guidelines with respect to the **use of RDV + DEX in reducing mortality compared to DEX monotherapy** for the treatment of hospitalized patients with COVID-19 across all levels of baseline supplemental oxygen requirements through PS matching and IPTW methods.
- Two well-established methods of addressing confounding by indication bias provide confidence that **RDV+DEX therapy was associated with a reduction in 14- and 28-day mortality as compared to DEX monotherapy** in patients hospitalized with COVID-19

References:

1. WHO. COVID-19: WHO Health Emergency Appeal 2024. Available at: https://www.who.int/publications/m/item/covid-19-who-health-emergency-appeal-2024. Accessed 16 January 2024.
2. Benfield T, Bodilsen J, Brieghel C, et al. *Clin Infect Dis* 2021; 73(11): 2031-6.
3. Marrone A, et al. *Clin Infect Dis* 2022; 75(1): e403-e9.
4. RECOVERY Collaborative Group, Horby P, Lim WS, et al. *N Engl J Med*. 2021;384(8):693-704.
5. Crothers K, DeFaccio R, Tate J, et al. *Eur Respir J* 2022; 60(1).
6. Pasin L, Navalesi P, Zangrillo A, et al. *J Cardiothorac Vasc Anesth* 2021; 35(2): 578-84.
7. WHO. Therapeutics and COVID-19: living guideline. Accessed 21 December 2023.
8. IDSA. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 21 December 2023.
9. NIH. COVID-19 Treatment Guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/table-of-contents/. Accessed 21 December 2023.

Disclosures: **EM, MB, TO, JFO**: employee and shareholder (Gilead Sciences, Inc.); **AC**: employee of Certara (contracted by Gilead Sciences, Inc. to conduct the study); **RLG**: advisor (AbbVie, Gilead Sciences, Inc., Eli Lilly, Roche, Johnson & Johnson), consultant (Eli Lilly, Gilead Sciences, Inc., Johnson & Johnson , Kinevant Sciences, Roche), de minimis investment (AbCellera), research contracts (Eli Lilly, Gilead Sciences, Inc., Johnson & Johnson, Pfizer), speaker's bureau (Pfizer); **CCM**: advisor (AstraZeneca, Gilead Sciences, Inc.), speaker's bureau (AstraZeneca, Boehringer Ingelheim), consultant (Gilead Sciences, Inc.); **ANA**: principal investigator or co-investigator (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 (Pfizer, Salix, Alexion, AstraZeneca, Bayer, Ferring, Seres, Spero, Eli Lilly, Nova Nordisk, Gilead, Renibus, GSK, Dexcom, Reprieve, HeartRite, Aseptiscope)- these relationships are unrelated to the current work; **ACK**: investigator (National Institutes of Health Adaptive COVID-19 Treatment Trial); **TW**: received grants (DFG, BMBF, EU, WHO), fees for lectures (AstraZeneca, Bayer, Biontech, Boehringer, Berlin Chemie GSK, MSD, Novartis, Pfizer, Roche, Sanofi Aventis), served on Advisory Boards (AstraZeneca, Bayer, Boehringer, GSK, Novartis, Pfizer, Roche, Sanofi Aventis); **PES:** study investigator (Gilead Sciences, ViiV), advisor or review panel member (Gilead Sciences, ViiV, Janssen, Merck)- all of these relationships are unrelated to COVID-19

Background

- Despite gradual decline in COVID-19 incidence and mortality, the WHO acknowledged that COVID-19 is a continuing threat to lives and health systems in 2024[1]
- Dual therapy with remdesivir (RDV) and dexamethasone (DEX) among patients with COVID-19 demonstrated improved clinical outcomes compared to DEX monotherapy early in the pandemic.[2-3] However, there is a lack of real-world evidence on the use of remdesivir+dexamethasone versus dexamethasone alone in the Omicron period.
- 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[4]
- Studies conducted since the RECOVERY study have shown the potential for a detrimental effect of corticosteroid treatment in patients with low-severity COVID-19[5-6]
- Current clinical guidelines for treatment of COVID-19 vary by supplemental oxygen requirements and include recommendations for use of RDV and/or DEX[5-7]
- National Institutes of Health (NIH) and World Health Organization (WHO) treatment guidelines recommend against the use of dexamethasone for COVID-19 patients who do not require supplemental oxygen[5,7]
- The objective of this study was to assess the effectiveness of RDV + DEX compared to DEX monotherapy in patients hospitalized for COVID-19 during the Omicron period using a large real-world database in the United States

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 Dec 1, 2021-Apr 30, 2023 ✓ Age ≥18 years old ✓ ***Primary* discharge diagnosis of COVID-19** (ICD-10-CM: U07.1) flagged for being "present-on-admission" ✓ **Initiated either RDV+DEX or DEX mono** 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	
	RDV + DEX	**DEX mono**
Treatment	RDV + DEX initiated in first 2 days of admission	DEX monotherapy initiated in first 2 days of admission

Primary End Points: 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 DEX monotherapy cohort, whichever was earlier
- Following a per-protocol treatment approach, patients were not followed further if RDV was added to the DEX monotherapy group after the first two days of hospitalization

Statistical analysis

- Propensity scores (PS) were estimated using separate logistic regression models for each baseline supplemental oxygenation requirement; covariates shown in **Table 2**
- The following effects were estimated:
  - **Average treatment effect on the treated (ATT):** 1:1 propensity score matching (PSM) without replacement, estimates the effectiveness of RDV+DEX by matching patients in the RDV + DEX and DEX monotherapy groups excluding unmatched patients
  - **Average treatment effect (ATE):** Inverse probability of treatment weighting (IPTW) balances the RDV + DEX and DEX monotherapy cohorts by weighting the two groups and allowing all patients to be retained. In this approach, PS scores <0.05 and >0.95 were trimmed
- A sensitivity analysis using 1:1 PS matching without replacement was conducted to examine the use of corticosteroids (prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone) instead of only examining dexamethasone
- Cox Proportional Hazards Model was used to assess time to 14- and 28-day mortality
- Models were adjusted for hospital-level cluster effects, and key covariates: age, admission month, hospital admission ward (ICU/ Step-down unit vs. general ward), and time-varying covariates for treatment initiated after baseline (baricitinib, tocilizumab, oral antivirals, or corticosteroids other than dexamethasone)

Results

Study population

- 280,114 patients hospitalized for COVID-19 during the study period
- After applying the inclusion and exclusion criteria, 151,215 patients hospitalized for COVID-19 were included in the analysis.
  - 61,236 (40%) initiated RDV+DEX in the first 2 days
  - 36,489 (24%) initiated DEX monotherapy in the first 2 days
- Of the 36,489 patients receiving DEX monotherapy, 90% (n = 32,840) did not receive RDV during the subsequent days in the hospital
- Before matching:
  - Most patients in the RDV + DEX and DEX monotherapy cohort, respectively, did not receive supplemental oxygen at baseline (43, 44%), the rest received LFO (37%, 36%), HFO/NIV (18%, 16%), and IMV/ECMO (2%, 4%)
  - Of the 15,792 patients that received DEX monotherapy and did not require any supplemental oxygen at baseline, 11,814 (74%) patients did not require supplemental oxygen therapy throughout the hospitalization and 9,641 (61%) continued receiving DEX after the first two days in the hospital
- After 1:1 matching with replacement, 33,037 RDV + DEX patients were matched to 33,037 DEX monotherapy patients
  - Most patients were ≥65 years (72%), white (78%), and non-Hispanic (84%).
  - Most patients did not receive supplemental oxygen at baseline (45%), the rest received LFO (37%), HFO/NIV (16%), and IMV/ECMO (2%) (**Table 2**)
- After IPTW, patients in each treatment group were weighted to reflect the full population of patients that initiated either RDV+DEX or DEX monotherapy:
  - Most patients were ≥65 years (68%), white (78%), and non-Hispanic (83%)
  - Most patients did not receive supplemental oxygen at baseline (44%), the rest received LFO (37%), HFO/NIV (17%), and IMV/ECMO (3%) (**Table 2**)
- Post-matching balance was achieved for all covariates with a standardized difference absolute value of <0.15 through both methods

Unadjusted analysis (PS-matched cohort)

- Unadjusted mortality rates were significantly lower for RDV+DEX vs. DEX monotherapy across all baseline supplemental oxygen requirements

	PS Matching				IPTW			
	14-day mortality		28-day mortality		14-day mortality		28-day mortality	
	Dex Mono	RDV+DEX	Dex Mono	RDV+DEX	Dex Mono	RDV+DEX	Dex Mono	RDV+DEX
NSOc	6.1%	5.6%	7.7%	7.2%	5.7%	5.1%	7.1%	6.5%
LFO	7.7%	6.1%	9.7%	8.1%	7.3%	5.7%	9.2%	7.6%
HFO/NIV	15.7%	12.7%	20.7%	17.6%	14.3%	12.3%	18.9%	16.7%
IMV/ECMO	27.1%	23.5%	35.4%	32.7%	25.1%	23.6%	32.4%	31.4%

DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc- no supplemental oxygen charges; RDV=remdesivir

Adjusted analysis (PS-matched cohort)

- **Using 1:1 propensity score matching without replacement analysis**
  - After adjusting for baseline and clinical covariates, RDV+DEX had a significantly lower mortality risk compared to DEX monotherapy across all supplemental oxygen requirements at 14-days and 28-days (**Figure 1**)
- **Using IPTW approach, consistent results were obtained**
  - After adjusting for baseline and clinical covariates, RDV + DEX had a significantly lower mortality risk versus DEX monotherapy across all baseline oxygen requirements at 14 days and 28-days (**Figure 1**)
- A **sensitivity analysis using 1:1 PS matching without replacement** conducted to examine the use of corticosteroids) showed consistent results (prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone
  - RDV+Corticosteroids had a significantly lower mortality risk compared to Corticosteroids monotherapy across all supplemental oxygen requirements at 14-days and 28-days

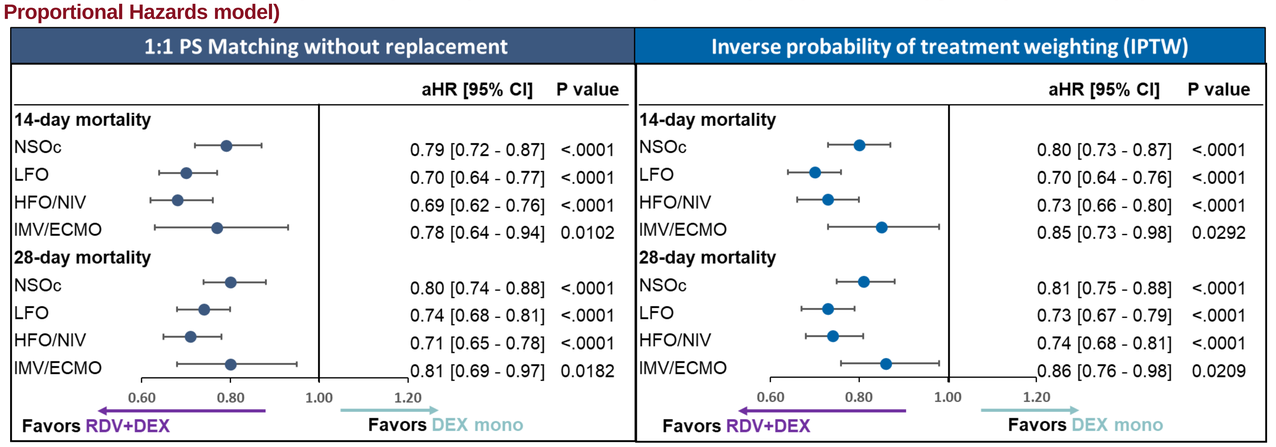
Table 2. Baseline characteristics

		Before Matching/IPTW		After PS Matching		After IPTW[1]	
		DEX mono n = 36,489	RDV + DEX n = 61,236	DEX mono n = 33,037	RDV + DEX n = 33,037	DEX mono n = 97,780	RDV + DEX n = 97,697
Age group, y	18-49	8%	10%	8%	8%	9%	9%
	50-64	22%	23%	21%	21%	22%	22%
	65+	70%	67%	72%	72%	68%	68%
Gender	Female	51%	51%	51%	51%	51%	51%
Race	White	77%	78%	78%	78%	78%	78%
	Black	14%	12%	13%	14%	13%	13%
	Asian	2%	2%	2%	2%	2%	2%
	Other	7%	8%	7%	7%	8%	8%
Ethnicity	Hispanic	9%	11%	9%	9%	10%	10%
	Non-Hispanic	84%	82%	84%	84%	83%	83%
	Unknown	7%	6%	7%	7%	7%	7%
Primary Payor	Commercial	14%	17%	14%	14%	16%	16%
	Medicare	72%	69%	73%	72%	70%	70%
	Medicaid	8%	9%	8%	8%	9%	9%
	Other	6%	5%	5%	5%	5%	5%
Hospital size, no. of beds	<100	9%	8%	9%	8%	8%	8%
	100-199	16%	17%	16%	17%	17%	17%
	200-299	21%	20%	21%	21%	20%	20%
	300-399	20%	18%	20%	20%	19%	19%
	400-499	12%	10%	11%	12%	10%	11%
	500+	23%	26%	23%	23%	25%	25%
Comorbidities	Obesity	30%	31%	29%	30%	30%	30%
	COPD	36%	38%	37%	37%	38%	38%
	Cardiovascular disease	88%	85%	88%	88%	86%	86%
	Diabetes	42%	38%	40%	40%	40%	40%
	Renal disease	36%	23%	32%	32%	28%	28%
	Cancer	7%	7%	7%	7%	7%	7%
Immunocompromised condition		16%	17%	16%	16%	17%	17%
Hospital ward on admission	General ward	83%	83%	84%	85%	83%	83%
	ICU/step-down unit	17%	17%	16%	15%	17%	17%
Other treatments at baseline	Anticoagulants	75%	81%	78%	77%	79%	79%
	Convalescent plasma	<1%	<1%	<1%	<1%	<1%	<1%
	Other corticosteroids	14%	15%	14%	14%	15%	15%
Baseline supplemental oxygen requirements	NSOc	44%	43%	45%	45%	44%	44%
	LFO	36%	37%	37%	37%	37%	37%
	HFO/NIV	16%	18%	16%	16%	17%	17%
	IMV/ECMO	4%	2%	2%	2%	3%	3%

COPD: Chronic Obstructive Pulmonary Disorder; DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; ICU: Intensive Care Unit; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc- no supplemental oxygen charges; RDV=remdesivir

[1]In IPTW method, patients in each group are weighted to be similar to the full study cohort of patients (n=97,725) that initiated either RDV+DEX or DEX monotherapy in the first two days of hospitalization. However, the sample sizes noted here are not exactly equal to 97,725 due to trimming of the extreme PS values before weighting and rounding to the nearest number

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 upon admission (ICU vs general ward), and time-varying treatment with other COVID-19 medications (baricitinib, tocilizumab, oral antivirals, or corticosteroids other than dexamethasone.
95% CI= 95% confidence interval; aHR= adjusted hazard ratio; DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc- no supplemental oxygen charges; RDV=remdesivir