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Acute Kidney Injury in Participants With Moderate COVID-19 Treated With RDV vs SOC

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Introduction

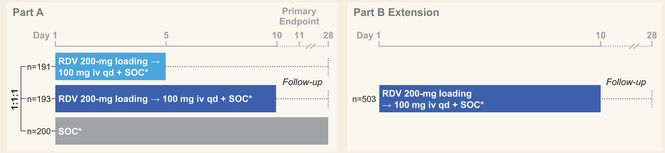
- Remdesivir (RDV) is approved for the treatment of COVID-19 in hospitalized patients aged ≥12 years
- Results from the Phase 3 SIMPLE-Moderate study (GS-US-540-5774; NCT04292730) showed that hospitalized COVID-19 participants not requiring O_2 support who were treated with 5 d of RDV had higher odds for improvement vs those treated with standard of care (SOC) at Day 11 (primary endpoint)[1]
- RDV and its excipient cyclodextrin are renally cleared,[2,3] prompting evaluation in patients with severely reduced renal function

Objective

- To determine whether RDV for 5 or 10 days was associated with acute kidney injury (AKI) in hospitalized participants with moderate COVID-19

Methods

SIMPLE-Moderate Study Design



*SOC continued throughout study duration; agents with actual or possible direct-acting antiviral activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were not allowed.

- Enrolled March 15–April 18, 2020; date of final follow-up: June 26, 2020
- 110 centers in 14 countries: Asia (Hong Kong, Japan, Republic of Korea, Singapore, and Taiwan), Europe (France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, and UK), and North America (USA)
- Key inclusion criteria: confirmed SARS-CoV-2 by reverse-transcriptase–polymerase chain reaction assay ≤4 d prior to randomization; peripheral O_2 saturation >94% on room air; radiographic evidence of pulmonary infiltrates; and estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2
- Key exclusion criteria: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal; creatinine clearance <50 mL/min; use of any experimental treatment for COVID-19 ≤24 h prior to dosing; and any requirement for invasive mechanical ventilation at screening
- AKI and eGFR were evaluated up to Day 14, and renal AEs were evaluated through Day 28 (post-hoc analyses in participants with available data)
- AKI was defined as increase in baseline (BL) serum creatinine and classified as: Stage 1: increase >0.3 mg/dL and ≤25% or >25–100%; Stage 2: increase >100–200%; or Stage 3: increase >200%

Results

Baseline Demographics*

	Overall		eGFR <60 mL/min		eGFR 60–89 mL/min		eGFR ≥90 mL/min	
	RDV n=870	SOC n=199	RDV n=78	SOC n=19	RDV n=221	SOC n=51	RDV n=571	SOC n=129
Median age, y (IQR)	57 (45, 66)	57 (45, 66)	72 (67, 80)	76 (71, 81)	66 (57, 74)	65 (59, 70)	50 (41, 59)	50 (37, 58)
Female sex at birth, n (%)	365 (42)	74 (37)	40 (51)	8 (42)	94 (43)	21 (41)	231 (40)	45 (35)
Race, n (%)								
White	469 (54)	111 (56)	48 (62)	11 (58)	116 (52)	33 (65)	305 (53)	67 (52)
Black or African descent	177 (20)	27 (14)	16 (21)	2 (11)	51 (23)	9 (18)	110 (19)	16 (12)
Other	224 (26)	61 (31)	14 (18)	6 (32)	54 (24)	9 (18)	156 (27)	46 (37)
Hispanic/Latinx ethnicity, n (%)	222 (26)†	33 (17)†	13 (17)	0	40 (18)	5 (10)	169 (30)	28 (22)
Median BMI, kg/m^2 (IQR)	27.4 (24.2, 32.4)	26.7 (23.6, 31.1)	23.8 (21.8, 27.4)	22.7 (20, 27.7)	25.2 (22.6, 28.5)	25.1 (23.2, 29.6)	28.9 (25.6, 34.1)	27.7 (25, 32.6)
Region, n (%)								
Asia	74 (9)†	26 (13)†	3 (4)	2 (11)	21 (10)	2 (4)	50 (9)†	22 (17)†
Europe	307 (35)†	88 (44)†	31 (40)	10 (53)	82 (37)	28 (55)	194 (34)†	50 (39)†
North America	489 (56)†	85 (43)†	44 (56)	7 (37)	118 (53)	21 (41)	327 (57)†	57 (44)†

*18 participants were excluded from present analysis due to missing eGFR data at BL; †Significant difference between RDV and SOC arms ($p<0.05$). BMI, body mass index; IQR, interquartile range.

Baseline Disease Characteristics*

	Overall		eGFR <60 mL/min		eGFR 60–89 mL/min		eGFR ≥90 mL/min	
	RDV n=870	SOC n=199	RDV n=78 (9%)	SOC n=19 (10%)	RDV n=221 (25%)	SOC n=51 (26%)	RDV n=571 (66%)	SOC n=129 (65%)
Clinical status, n (%)								
Noninvasive ventilation or high-flow O_2	4 (<1)	2 (1)	1 (1)	0	0	0	3 (1)	2 (2)
Low-flow O_2	102 (12)	36 (18)	9 (12)	3 (16)	26 (12)	12 (24)	67 (12)	21 (16)
Room air, requiring medical care	10 (1)	2 (1)	2 (3)	0	2 (1)	1 (2)	6 (1)	1 (1)
Room air	754 (87)	159 (80)	66 (85)	16 (84)	193 (87)	38 (75)	495 (87)	105 (81)
Median symptom duration before follow-up start, d (IQR)	8 (5, 11)	9 (6, 11)	8 (5, 12)	8 (7, 13.5)	7 (4, 11)	9 (6, 11)	8 (5, 11)	9 (6, 11)
Median eGFR, mL/min (IQR)	104.1 (80.5, 193.8)	102.7 (78.6, 128.9)	54.4 (51.8, 57.7)	53.1 (49.4, 56.1)	76.1 (68.1, 83.9)	74.8 (70.0, 83.8)	127.6 (105.4, 157.4)	121.7 (103.6, 144.7)
Comorbidities, n (%)								
Hypertension	410 (47)	81 (41)	53 (68)	13 (68)	142 (64)†	24 (47)†	215 (38)	44 (34)
Diabetes mellitus	411 (47)†	76 (38)†	43 (55)	10 (53)	122 (55)	22 (43)	246 (43)	44 (34)
Cardiovascular disease	535 (61)	107 (54)	66 (85)	15 (79)	169 (76)	32 (63)	300 (53)	60 (47)
Asthma	123 (14)	28 (14)	15 (19)	3 (16)	24 (11)	4 (8)	84 (15)	21 (16)
CKD‡	55 (6)	7 (4)	13 (17)	1 (5)	27 (12)	4 (8)	15 (3)	2 (2)
Mean AST, U/L (SD)	39.7 (27.2)	42 (30.9)	39.9 (29.8)	36.1 (10.7)	39.1 (26.5)	44.7 (33)	39.9 (27.1)	41.8 (32)
Mean ALT, U/L (SD)	37.9 (31.1)	41.4 (35.5)	33.6 (32.9)	28.8 (14.1)	32.3 (26)	35.8 (30.4)	40.7 (32.3)	45.5 (38.9)
Concomitant medication at/prior to treatment start, n (%)								
Azithromycin	190 (22)	56 (28)	14 (18)	3 (16)	37 (17)	14 (27)	139 (24)	39 (30)
Hydroxychloroquine group	173 (20)†	84 (42)†	12 (15)	4 (21)	45 (20)†	21 (41)†	116 (20)†	59 (46)†
HIV protease inhibitor	87 (10)†	44 (22)†	4 (5)	2 (11)	23 (10)†	12 (24)†	60 (11)†	30 (23)†
Biologics	4 (<1)†	5 (3)†	0	0	0†	2 (4)†	4 (1)	3 (2)
Ribavirin	2 (<1)†	8 (4)†	0	1 (5)	1 (<1)	1 (2)	1 (<1)†	6 (5)†
Corticosteroids	54 (6)	14 (7)	6 (8)	0	16 (7)	4 (8)	32 (6)	10 (8)

*18 participants were excluded from present analysis due to missing eGFR data at BL; †Significant difference between RDV and SOC arms ($p<0.05$); ‡Chronic kidney disease (CKD) determined by medical history. SD, standard deviation.

- BL demographics and eGFR were mostly similar between RDV and SOC arms

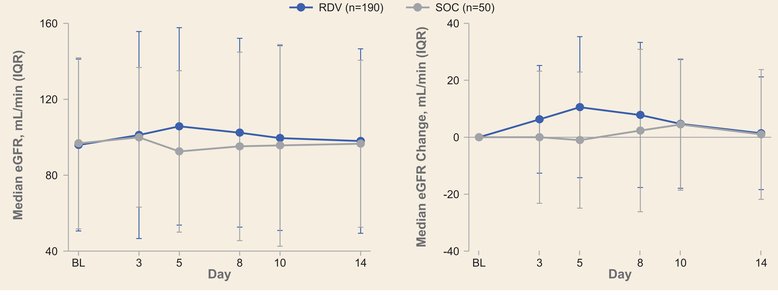
AKI by Treatment Arm and BL eGFR Category Through Day 14*

		Overall		eGFR <60 mL/min		eGFR 60–89 mL/min		eGFR ≥90 mL/min	
		RDV n=822	SOC n=183	RDV n=71	SOC n=17	RDV n=211	SOC n=48	RDV n=540	SOC n=118
No AKI, n (%)		765 (93)	164 (90)	69 (97)	16 (94)	194 (92)	44 (92)	502 (93)	104 (88)
AKI, n (%)	Stage 1	52 (6)	15 (8)	2 (3)	0	14 (7)	3 (6)	36 (7)	12 (10)
	Stage 2	3 (<1)	0	0	0	1 (<1)	0	2 (<1)	0
	Stage 3	2 (<1)	4 (2)	0	1 (6)	2 (1)	1 (2)	0	2 (2)
Fisher exact p-value (unadjusted)		**0.03**		0.22		0.71		**0.03**	
Age-adjusted RR (95% CI): AKI vs no AKI		0.67 (0.41, 1.10) p=0.079		NC		0.96 (0.34, 2.73) p=0.455		0.58 (0.32, 1.04) p=0.164	

*82 participants excluded due to missing creatinine data post-BL. CI, confidence interval; NC, not calculated due to low number of events; RR, risk ratio.

- AKI was observed less frequently in participants receiving RDV vs SOC (7% vs 10%; p=0.03)
- Age-adjusted relative risk estimates also showed no significant association of RDV with risk of AKI relative to SOC
- Most AKI events were observed in participants with BL eGFR ≥90 mL/min, with few events occurring in participants with BL eGFR <60 mL/min
- No difference in AKI between treatment arms was observed in participants with history of CKD (RDV vs SOC: n=6/51 [12%] vs n=2/5 [40%]; p=0.14)

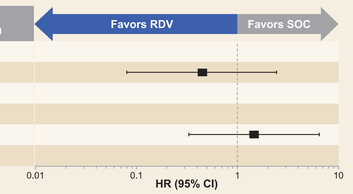
eGFR Over Time



- Linear mixed effects model showed no statistical difference in eGFR over time between treatment arms

Risk of Renal AEs Through Day 28

	RDV n=887	SOC n=200
Serious AEs, n (%)*	4 (<1)	2 (1)
Age-adjusted HR (95% CI)†	0.45 (0.08, 2.44)	
p-value	0.35	
Grade 3 AEs, n (%)*	13 (1)	2 (1)
Age-adjusted HR (95% CI)†	1.46 (0.33, 6.47)	
p-value	0.62	



*All adverse events (AEs) were based on Standardised Medical Dictionary for Regulatory Activities Query term Acute Renal Failure; †Cox models run with death as competing risk. HR, hazard ratio.

eGFR Categorical Shifts From BL at Day 10*

	RDV: eGFR at Day 10, mL/min				SOC: eGFR at Day 10, mL/min			
BL eGFR, mL/min (n %)	<30 n=0	30–<60 n=19	60–89 n=98	≥90 n=197	<30 n=2	30–<60 n=9	60–89 n=17	≥90 n=43
<60 n=24	0	11 (4)	11 (4)	2 (1)	1 (1)	5 (7)	3 (4)	0
60–89 n=104	0	8 (3)	72 (23)	24 (8)	0	2 (3)	10 (14)	5 (7)
≥90 n=186	0	0	15 (5)	171 (54)	1 (1)	0	4 (6)	38 (55)
Worsened at Day 10	23/314 (7)				8/69 (12)			

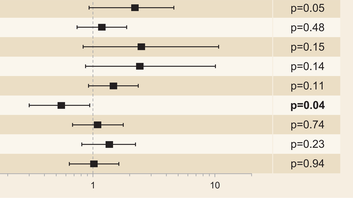
IRR 0.63 (95% CI 0.30, 1.35)
p=0.24

*Analysis limited to participants with eGFR data on Day 10. IRR, incidence rate ratio.

- Results were similar at Day 14 (IRR 0.72 [95% CI 0.32, 1.62]; p=0.43)

Univariate Analysis in Participants on RDV or SOC

	RR (95% CI)	p-value
Age ≥65 (vs <65) years	1.49 (0.9, 2.41)	p=0.11
RDV treated	0.63 (0.37, 1.12)	p=0.10
Cardiovascular disease	1.27 (0.79, 2.1)	p=0.33
CKD	2.21 (0.93, 4.61)	p=0.05
Diabetes	1.18 (0.74, 1.89)	p=0.48
BL eGFR 60–89 (vs <60) mL/min	2.49 (0.83, 10.73)	p=0.15
BL eGFR ≥90 (vs <60) mL/min	2.42 (0.87, 10.1)	p=0.14
Hypertension	1.47 (0.92, 2.35)	p=0.11
Obesity	**0.55 (0.3, 0.94)**	**p=0.04**
Male	1.09 (0.68, 1.77)	p=0.74
Symptom duration >10 d prior to treatment start	1.36 (0.81, 2.23)	p=0.23
White (vs other)	1.02 (0.64, 1.63)	p=0.94



- History of CKD and BL eGFR category were independently associated with AKI

Conclusions

- Considerations:
  - Relatively small numbers of AKI events
  - BL heterogeneity in RDV vs SOC arms due to inclusion of nonrandomized RDV extension cohort
- In patients with moderate COVID-19, RDV was not associated with worsening renal function
  - AKI events were observed less frequently with RDV vs SOC
  - There was no statistical difference in eGFR over time between treatment arms
  - There was no difference in risk of renal AEs with RDV vs SOC
- A trial of RDV in people with COVID-19 and severe renal impairment is planned (NCT04745351)

References: 1. Spinner CD, et al. JAMA 2020 Aug 21;e2016349; 2. Frank DW, et al. Am J Pathol 1976;83:367-82; 3. Yan VC, et al. Antimicrob Agents Chemother 2020;64:e01920-20.

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