Poster #1149

Resistance Analyses of Patient Viral Samples From the Remdesivir Phase 3 Adaptive COVID-19 Treatment Trial-1 (ACTT-1)

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Introduction

- Remdesivir (RDV) is a broad-spectrum nucleotide analog prodrug approved for the treatment of COVID-19 in nonhospitalized and hospitalized adult and pediatric patients[1]
- The clinical benefit of RDV for patients with COVID-19 has been demonstrated in multiple clinical trials, including the randomized, double-blind, placebo-controlled, phase 3 Adaptive COVID-19 Treatment Trial-1 (ACTT-1),[2] PINETREE,[3] and SIMPLE studies[4,5]

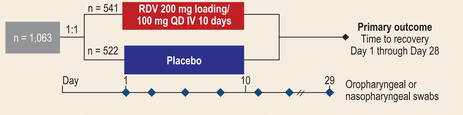
Objectives

- To determine amino acid substitutions in SARS-CoV-2 nsp12, the RNA-dependent RNA polymerase (RdRp), and nsp8, nsp10, nsp13, and nsp14 of the polymerase complex arising in patients treated with RDV compared with placebo
- To determine whether SARS-CoV-2 amino acid substitutions identified in RDV-treated participants alter antiviral susceptibility to RDV

Methods

- In ACTT-1, oropharyngeal or nasopharyngeal swab samples were collected on Days 1, 3, 5, 8, 11, 15, and 29 (**Figure 1**)

Figure 1. Study design.



Arm	Median time to recovery (days)	Mortality by Day 14 (%)	Serious adverse events (%)
RDV	11	7.1	21.1
Placebo	15	11.9	27.0

P <0.001

Virology
Exploratory endpoints
- Antiviral efficacy by SARS-CoV-2 RNA levels
- Resistance analysis

RDV, remdesivir; QD, once daily; IV, intravenous.

- All participants with >80th percentile and 50% of participants with <20th percentile of cumulative viral shedding underwent resistance analysis in both the RDV and placebo arms
- The SARS-CoV-2 genome was sequenced using next-generation sequencing
- Phenotyping was conducted using virus isolation from clinical samples or generation of select site-directed mutants (SDMs) in a SARS-CoV-2 subgenomic replicon system

Results

Participants Included in the Study

- Of 1,048 patients treated in total, 94 participants in the RDV arm and 79 participants in the placebo arm met resistance analysis criteria
  - Of those, 31 of 94 (33.0%) participants in the RDV arm and 30 of 79 (38.0%) participants in the placebo arm had both baseline and postbaseline sequencing data available (**Table 1**)

Table 1. Participants

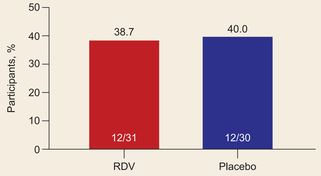
	Number of participants	
	RDV	Placebo
Treated population	532	516
Met resistance analysis criteria and sequencing attempted	94	79
Sequencing data available		
Baseline	47	44
Postbaseline	36	34
Baseline + postbaseline	**31**	**30**

RDV, remdesivir.

Frequency of Emergent Substitutions in nsp12

- Among participants with both baseline and postbaseline data, emergent substitutions in nsp12 were observed in 12 of 31 (38.7%) participants treated with RDV and 12 of 30 (40.0%) participants in the placebo arm (**Figure 2**)
- Overall, emergent substitutions in nsp12 were observed in 2.3% of participants in both the RDV arm and the placebo arm

Figure 2. Participants with emergent nsp12 substitutions.



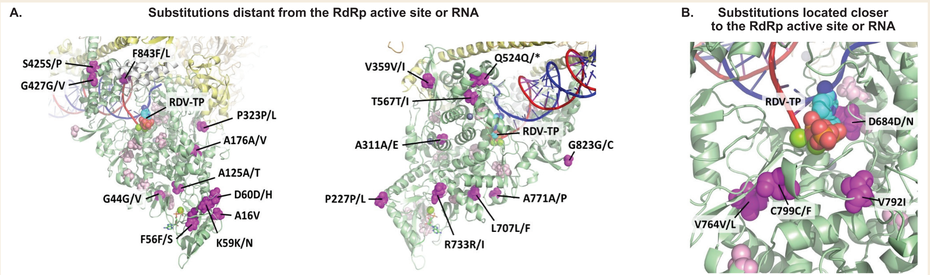
RDV, remdesivir.

- nsp12 substitutions that emerged in participants treated with RDV were observed in 1 participant each, and the majority were present as mixtures with wild-type sequence

Phenotype of Emergent nsp12 Substitutions

- The majority of substitutions identified were distant from the RdRp active site or RNA (**Figure 3A**); of the substitutions located closer to the RdRp active site or RNA (**Figure 3B**):
  - V792I and C799F have been previously identified through in vitro resistance selection experiments[6]
  - None of the other nsp12 substitutions observed in the RDV-treated participants have been previously associated with resistance to RDV

Figure 3. Emergent substitutions in nsp12 relatively A) distant and B) closer to the RdRp active site or RNA.



RdRp, RNA-dependent RNA polymerase.

- nsp12 mutations successfully phenotyped as clinical isolates or SDMs had low to no fold-change in RDV susceptibility (**Table 2**)

Table 2. Phenotyped nsp12 Mutations in Participants Treated With RDV

nsp12 substitution	RDV EC_{50} (nM)	EC_{50} fold-change from wild-type reference
Clinical isolates		
Wild type	235	1.00
A16V	175	0.75
V792I	503	2.17
C799C/F	584	2.51
Replicon SDMs		
Wild type	14.6	1.00
K59N	14.4	0.98
K59N+V792I	49.7	3.41
V792I	45.9	3.15
D684N	No replication	NA
V764L	No replication	NA

RDV, remdesivir; EC_{50}, 50% inhibition of virus replication; SDM, site-directed mutant; NA, not applicable.

- For substitutions D684N and V764L, recovery of neither clinical isolates nor SDMs for phenotypic analysis were successful
- A similar rate of emerging substitutions was observed in other proteins of the replication complex in participants treated with RDV compared with placebo (**Table 3**)

Table 3. Participants With Emergent Substitutions in Other Proteins of the Replication Complex

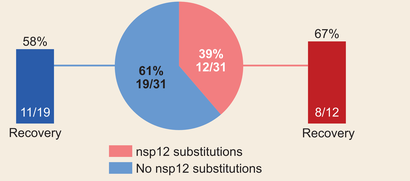
Substitution, n (%)	RDV (n = 31)	Placebo (n = 30)
nsp8	3 (9.7)	1 (3.3)
nsp10	2 (6.5)	0
nsp13	11 (35.5)	10 (33.3)
nsp14	7 (22.6)	6 (20.0)

RDV, remdesivir.

Clinical Outcomes in Participants With Emergent nsp12 Substitutions

- Clinical recovery was comparable between participants in the RDV arm with and without emergent nsp12 substitutions (**Figure 4**)

Figure 4. Clinical recovery[a] in participants treated with RDV with or without nsp12 substitutions.



RDV, remdesivir.
[a]Recovery was defined as either discharged from the hospital or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care at Day 28.

Conclusions

- Rates of emerging nsp12 substitutions were similar in participants treated with RDV compared with those who received placebo in the ACTT-1 study
- There was low to no fold-change in RDV susceptibility among the treatment-emergent nsp12 substitutions tested
- The resistance analysis results from the ACTT-1 study support a high barrier to RDV resistance development with lack of any considerable resistance emergence among COVID-19 patients
- Similar rates of clinical recovery were observed among participants in the RDV arm regardless of emergent nsp12 substitutions

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References: 1. VEKLURY (remdesivir) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; June 2022. 2. Beigel JH, et al. *N Engl J Med.* 2020;383(19):1813-1826. 3. Gottlieb RL, et al. *N Engl J Med.* 2022;386(4):305-315. 4. Spinner CD, et al. *JAMA.* 2020;324(11):1048-1057. 5. Goldman JD, et al. *N Engl J Med.* 2020;383(19):1827-1837. 6. Stevens LJ, et al. *Sci Transl Med.* 2022;14(656):eabo0718.

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