Remdesivir in an Outpatient Setting Improves Biomarkers for Progression of COVID-19

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Introduction

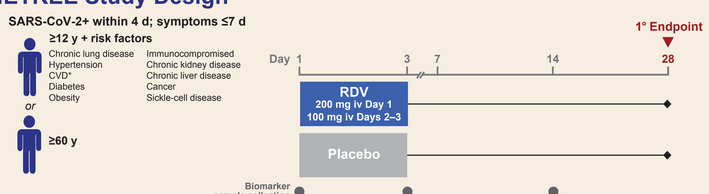
- Early intervention may curb progression to more severe COVID-19 requiring hospitalization
- The PINETREE Study (GS-US-540-9012; NCT04501952) evaluated the efficacy and safety of remdesivir (RDV) for nonhospitalized individuals with early-stage COVID-19 who were at higher risk of disease progression
  - Early RDV treatment improved COVID-19 outcomes in high-risk, nonhospitalized SARS-CoV-2–infected individuals, particularly in those aged ≥60 y, male participants, and those with diabetes, obesity, or hypertension[1]

Objectives

- To evaluate inflammatory, coagulopathic, and hematologic biomarkers of COVID-19 to better understand early RDV treatment response using longitudinal biomarker sampling from the Phase 3 PINETREE clinical trial

Methods

PINETREE Study Design



*Cerebrovascular or cardiovascular disease (CVD).

- Phase 3, double-blind, placebo-controlled, multicenter study (N=562)
  - Randomized 1:1 to RDV or placebo
- Serum and plasma were collected for biomarker analyses from 312 participants at Days 1, 3, and 14
- Serum and plasma biomarkers were adjusted for baseline age, and stratified by sex at birth
- Logistic regression was used to identify prognostic baseline comorbidities and biomarkers
- Linear mixed-effect models were used to:
  - Assess if a biomarker had a significant change from its baseline value
  - Determine if there was a significant difference between treatment groups or outcomes

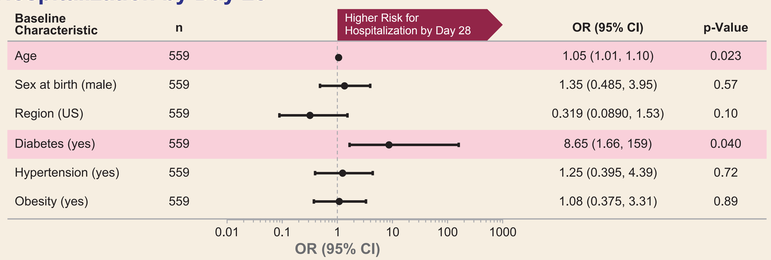
Results

Participant Demographics for Biomarker Assessments

	RDV: n=168	Placebo: n=144
Mean age, y (SD)	51 (14)	53 (14)
Aged ≥60 y, n (%)	55 (33)	44 (31)
US region, n (%)	156 (93)	134 (93)
Female sex at birth, n (%)	78 (46)	69 (48)
Race, n (%)		
White	147 (88)	130 (90)
Black	10 (6)	7 (5)
American Indian or Alaska Native	2 (1)	2 (1)
Hispanic or Latinx ethnicity, n (%)	72 (43)	55 (38)
Median exposure to study drug, doses received (IQR)	3 (3, 3)	3 (3, 3)

IQR, interquartile range; SD, standard deviation.

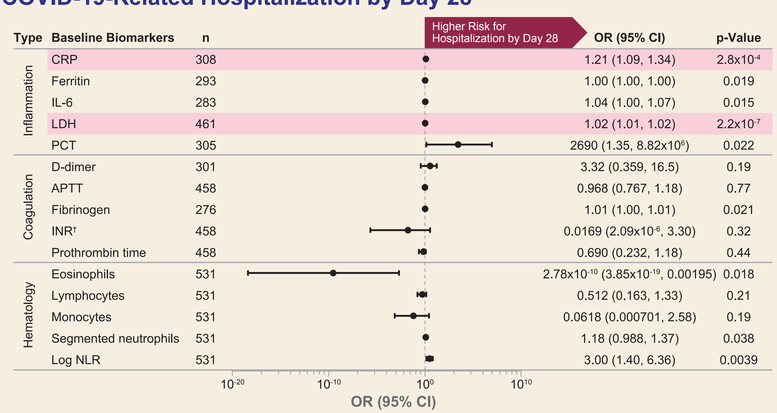
Age and Diabetes Status Were Prognostic for COVID-19-Related Hospitalization by Day 28*



*Since a single logistic regression model was used including all variables, as well as age and sex at birth as covariates, p<0.05 is considered significant (*highlighted in red*). CI, confidence interval; OR, odds ratio.

- When accounting for baseline status of comorbidities for severe COVID-19, participants with diabetes and advanced age had higher risk for requiring hospitalization by Day 28

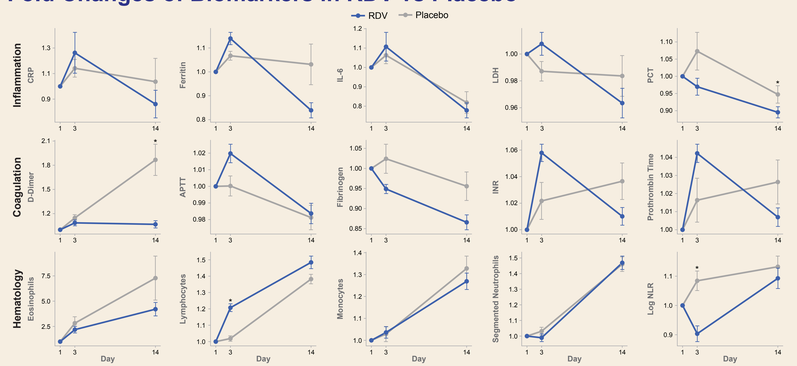
Baseline Inflammation Biomarkers CRP and LDH Were Prognostic for COVID-19-Related Hospitalization by Day 28*



*Significant biomarkers were determined after correction of p-values using Bonferonni correction for 15 biomarkers (p<0.05/15; *highlighted in red*); †International normalized ratio (INR) is ratio of measured and normal prothrombin time, which may lead it to be a more sensitive index compared with measured prothrombin time itself. APTT, activated partial thromboplastin time; CRP, C-reactive protein; IL, interleukin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin.

- Multiple baseline biomarkers required age correction due to significant correlation with age
- Baseline inflammation biomarkers were prognostic for worse outcomes in participants with COVID-19 ($p_{Bonferonni}$<0.05)
  - CRP and LDH were significantly elevated in participants requiring hospitalization by Day 28

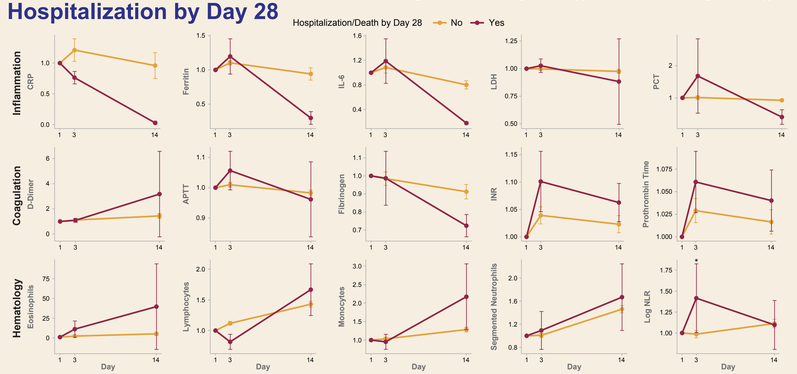
Fold Changes of Biomarkers in RDV vs Placebo



*Significant difference between baseline (Day 1) values and follow-up time point, as well as difference between participants on RDV and placebo, as determined by linear mixed model.

- RDV-treated participants showed greater decreases on Day 14 compared with baseline in PCT (inflammation, sepsis) and D-dimer (coagulation) vs placebo
- Lymphocyte (hematology) count increased while NLR (hematology) decreased significantly on Day 3 compared with baseline in participants on RDV vs placebo

Fold Changes of Biomarkers in Participants Requiring vs Not Requiring Hospitalization by Day 28



*Significant difference between baseline (Day 1) values and follow-up time point, as well as difference between participants on RDV and placebo, as determined by linear mixed model.

- While lymphocytes (hematology) and neutrophils (hematology) alone did not show significant changes, NLR (hematology) significantly increased on Day 3 for participants requiring hospitalization by Day 28

Conclusions

- RDV treatment improved COVID-19 outcomes in high-risk SARS-CoV-2–infected individuals, particularly those aged ≥60 y (hazard ratio: 0.11), male participants (HR: 0.11), and those with diabetes (HR: 0.14), obesity (HR: 0.11), or hypertension (HR: 0.17)[1]
- Inflammation biomarkers CRP and LDH were prognostic for poor outcomes and were identified in early infection[2]
- RDV treatment led to more rapid recovery of lymphopenia as seen in NLR, which is commonly associated with more severe COVID-19[3]

References: **1.** Gottlieb RL, et al. N Engl J Med 2022;386:305-15; **2.** Akdogan D, et al. J Infect Dev Ctries 2021;15:766-72; **3.** Tan L, et al. Sig Transduct Target Ther 2020;5:33. **Acknowledgments:** We extend our thanks to the participants, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead.