Feasibility of a Network Meta-Analysis Assessing Relative Effectiveness and Safety of Remdesivir Versus Other Treatments for COVID-19 Inpatients

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Executive Summary

- A feasibility assessment (FA) for a network meta-analysis (NMA) was conducted to assess the relative efficacy and safety of remdesivir versus other treatments for COVID-19 inpatients.
- Upon completion of a systematic literature review (SLR), an FA was conducted that assessed heterogeneity in study, patient and treatment characteristics, COVID-19 disease severity, as well as network connectivity with remdesivir.
- 11 potential networks, connected via standard of care (SoC), were identified across three COVID-19 disease severity groups: mild-moderate, mixed and severe.
- While potential networks were found, these networks included treatments indicated for patients of differing severity levels, limiting clinical relevance of available comparisons. Furthermore, due to substantial heterogeneity, it was concluded that NMAs would not be appropriate.

Introduction

- Remdesivir is an intravenous ribonucleic acid polymerase inhibitor that targets viral replication of SARS-CoV-2 and is used in the treatment of hospitalized COVID-19 patients.
- There is limited head-to-head evidence for remdesivir versus other treatments for COVID-19 inpatients.

Objective

To conduct an FA for NMA to assess the relative efficacy and safety of remdesivir versus other treatments for COVID-19 inpatients.

Methods

- An SLR was conducted to identify randomized controlled trials (RCTs) and observational studies involving searches of databases, conference literature and trial registries up to March 2023.
- As part of the FA, study, treatment and patient characteristics were assessed for heterogeneity.
- Outcomes of interest were all-cause mortality, length of hospital stay, proportion of patients recovered from COVID-19, proportion of patients discharged from hospital and number of patients experiencing at least one treatment-emergent adverse event at 2 and 4 weeks.
- Through assessment of reported disease severity, type of oxygen supplementation and inclusion criteria, study populations were categorized as having mild-moderate, mixed, or severe COVID-19.
  - Study populations categorized as having mild-moderate COVID-19 either explicitly stated that all patients included in the study had mild/moderate COVID-19 at baseline or detailed that all patients in the study were either provided with no oxygen or just low-flow oxygen at baseline.
  - Study populations categorized as having mixed COVID-19 either explicitly stated that patients in the study had a mixture of differing COVID-19 severities at baseline or detailed a mixture of oxygen supplementations given to patients at baseline (no oxygen/low-flow oxygen/high-flow oxygen/NIV/IMV/ECMO).
  - Study populations categorized as having severe COVID-19 either explicitly stated that all patients included in the study had severe or critical COVID-19 at baseline or detailed that all patients in the study were provided with high-flow oxygen/NIV/IMV/ECMO at baseline.
- Study populations that did not report baseline disease severity, type of oxygen supplementation and/or inclusion criteria related to baseline disease severity were excluded from the networks. Network connectivity was then assessed separately for mild-moderate, mixed or severe COVID-19 across all eligible studies. Additionally, network connectivity was then assessed for observational studies only.
- SoC and placebo treatment arms were assessed for heterogeneity (**Table 1**). Treatment in combination with SoC was considered to be equivalent to the relevant standalone treatment, with the effect of SoC ignored. Treatment arms reported as placebo were considered to be the same as SoC. Placebo/SoC arms where all patients received an antiviral treatment were considered to be arms of the administered treatment, while those where not all patients received an antiviral treatment were considered as SoC.

Results

SLR and Eligibility

- The SLR identified 135 publications reporting on 74 unique studies on patients hospitalized with COVID-19.
- Single-arm studies (n=14), studies not containing interventions of interest (n=5), studies not reporting the number of patients in each study arm (n=1), studies that did not connect with remdesivir (n=8), or studies without relevant outcomes or timepoints of interest (n=23) were excluded from networks.
- Heterogeneity and network connectivity were assessed for 23 comparative studies (12 RCTs, 11 observational) connecting to remdesivir for outcomes of interest, resulting in 11 potential networks (four in the mild-moderate population; four in the mixed population; three in the severe population). Treatments of interest included across the 11 networks were tofacitinib, molnupiravir, nirmatrelvir/ritonavir, tocilizumab, and baricitinib.

Heterogeneity Assessment

- While networks connected via SoC for some outcomes, due to differences in geographic region, study start date, and local treatment guidelines, substantial heterogeneity was observed in SoC received (**Table 1**). Additionally, there was substantial heterogeneity and an overall lack of data for reported disease severity (reported by 9/23 studies) and oxygen supplementation (reported by 15/23 studies).
- Where reported, substantial differences were also seen in sex (**Figure 1a**; reported by 18/23 studies and ranging from 26–50.2% female), race (**Figure 1b**; reported by 10/23 studies and ranging from 44.4–100% white), mean age (**Figure 1c**; reported by 16/23 studies and ranging from 46.5–67.5 years), body mass index, and smoker status.

Outcome Feasibility Assessment

- Within each COVID-19 severity population, all-cause mortality at Week 4 was the most commonly reported outcome and timepoint (**Figure 2**).
- While comparisons of remdesivir against other COVID-19 treatments would be possible, these comparisons would not be clinically meaningful considering many of these treatments are not used to treat patients with the same level of disease severity (e.g., while comparisons with tofacitinib would be possible in the mild/moderate COVID-19 population, remdesivir and tofacitinib are usually not comparators in this population in the real-world clinical practice).
- Findings were similar in the network containing only observational studies (**Figure 2d**). Based on observational evidence alone, the only network that could be connected with remdesivir was all-cause mortality at Week 4 amongst mixed severity patients.

Table 1. Placebo and Standard of Care Definitions for Study Populations Included in the Networks

Study	Control	Placebo/SoC Details
ACTT-1	• Placebo or Placebo & SoC	• Placebo: matching placebo administered intravenously
STOP-COVID		• SoC: per local standard of care, including glucocorticoids, antibiotic agents, anticoagulants, and oseltamivir; concomitant use of other JAK inhibitors, biologics, immunosuppressants, IL-1 or IL-6 inhibitors, or CYP450 inhibitors was not permitted
Wang 2020		• Placebo: matching placebo administered intravenously
Tin 2022	• Tocilizumab	• Tocilizumab: no further details
Cao 2023	• VV116	• 600 mg every 12 hours on Day 1 and 300 mg every 12 hours on Days 2 through 5
Bari-SolidAct	• SoC	• SoC: per local SoC; no further details
Chokkalingam 2022		• SoC: risk-set sample matched to the remdesivir cohort; no further details
COV-BARRIER		• SoC: in keeping with local clinical practice, including corticosteroids, antivirals, or both
DisCoVeRy		• SoC: per investigator's discretion, including corticosteroids and anticoagulants, 6 mg of dexamethasone was recommended
Aksak-Was 2022		• SoC: not receiving the treatment of interest (remdesivir or baricitinib); no further details
Finn 2022		
COVID-AGE/ AlbaScore		
Garibaldi 2022		
Mozaffari 2021b		
SIMPLE-Moderate		• SoC: per local standard of care, including other treatments with presumptive activity against SARS-CoV-2
Solidarity		• SoC: per local standard of care; no further details
Wai 2023		• SoC: not receiving antivirals; no further details
Lakatos 2022	• SoC	• SoC: including remdesivir (80.6% of patients), on-demand oxygen, intravenous fluids, antipyretics, antitussives, bronchodilators, dexamethasone
MOVe-IN		• SoC: patients could receive standard care with remdesivir and/or glucocorticoids, but other immunomodulator treatments were not permitted; • 23.0% and 25.6% of patients in the treated and SoC arms received remdesivir prior to or at randomization
TOFACOV		• SoC: per investigator's discretion, including remdesivir (89% of patients), corticosteroids, heparin, or antibiotics

Control arms in pink are those where all patients were treated with a COVID-19-specific treatment; Control arms in green were considered as equivalent, as patients receiving placebo treatments also received SoC; Control arms in grey are those where some but not all patients were treated with remdesivir or other antivirals; Studies bolded in **blue** are observational studies and those bolded in **red** are RCTs; COVID-19, coronavirus disease 2019; IL, interleukin; JAK, Janus kinase; RCT, randomized controlled trial; SoC, standard of care.

Figure 1a. Baseline Sex (Percentage Female)

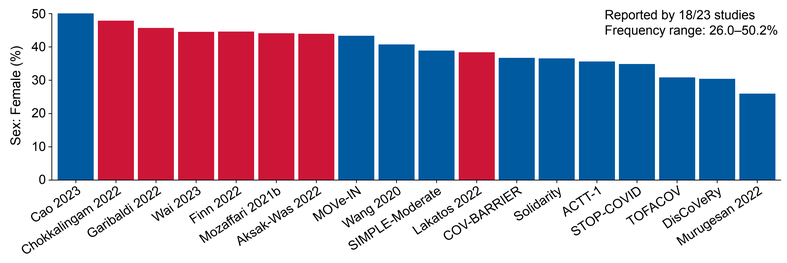
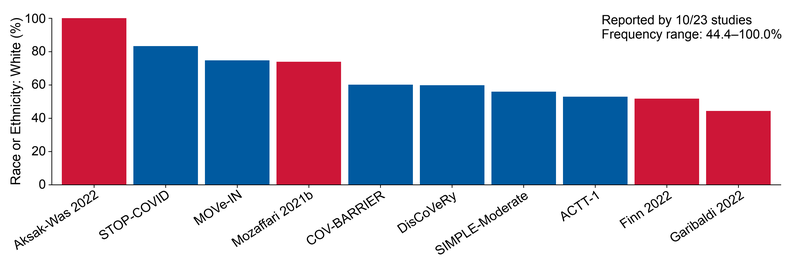
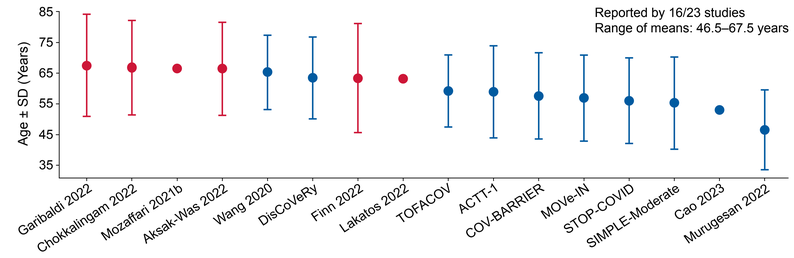


Figure 1b: Baseline Race (Percentage White)



Bars in **blue** indicate observational studies and bars in **red** indicate RCTs; RCT, randomized controlled trial.

Figure 1c. Baseline Age



Dots and error bars in **blue** indicate observational studies and dots and error bars in **red** indicate RCTs; RCT, randomized controlled trial; SD, standard deviation.

Figure 2. Network for All-Cause Mortality at Week 4 Among COVID-19 Inpatients

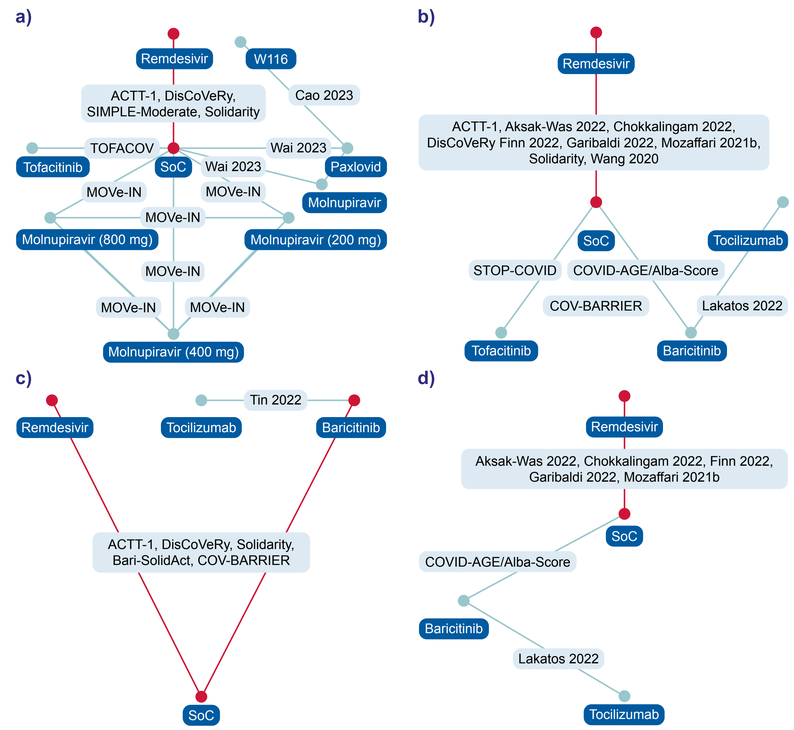


Figure 2a is among patients with mild/moderate disease; Figure 2b is among patients with mixed disease; Figure 2c is among patients with severe disease; Figure 2d is among patients with mixed disease from observational studies; Teal lines indicate one study and **red** lines indicate multiple studies; COVID-19, coronavirus disease 2019; SoC, standard of care.

Disclosure: James Jarrett and Arman Papadakis-Sali are employees of, and own stock in, Gilead Sciences, Ltd. Ryan Thaliffdeen is an employee of, and owns stock in, Gilead Sciences, Inc. Tristan Curteis, Hannah Luedke and Christopher J. Michaels are employees of Costello Medical, Ltd., which received payment from Gilead Sciences for analytical services for this study. Zarena Jafry is an employee of Costello Medical, Inc., which received payment from Gilead Sciences for analytical services for this study.

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Conclusions

Networks connected via SoC consisted of treatments indicated for patients of differing severity levels, limiting clinical relevance of available comparisons. Furthermore, due to substantial heterogeneity in patient characteristics and in the definition of the common comparator, SoC, it was concluded that NMAs would not be appropriate.