

REMDESIVIR FOR 5 OR 10 DAYS IN PATIENTS WITH SEVERE COVID-19

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ABSTRACT

Remdesivir is an RNA polymerase inhibitor with potent antiviral activity in vitro and efficacy in animal models of coronavirus disease 2019 (Covid-19). We conducted a randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia. Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale. In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, however, the magnitude of benefit cannot be determined.

KEYWORDS: Coronavirus disease 2019 (Covid-19); Remdesivir; Patients monitoring.

INTRODUCTION

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide. As of June 23, 2020, there have been more than 8 9, 93,659 reported cases and 4, 69,587 deaths in more than 216 countries. In India 1, 83,022 active cases, 2, 58,684 cured / discharged and 14,476 deaths in coronavirus. This novel *Betacoronavirus* is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV); based on its genetic proximity, it likely originated from bat-derived corona viruses with spread via an unknown intermediate mammal host to humans.^[1] The viral genome of SARS-CoV-2 was rapidly sequenced to enable diagnostic Testing, epidemiologic tracking, and development of preventive and therapeutic strategies. Currently, there is no evidence from randomized clinical trials (RCTs) that any potential therapy improves outcomes in patients with either suspected or confirmed COVID-19. There are no clinical trial data supporting any prophylactic therapy. More than 300 active clinical treatment trials are underway. This narrative review summarizes current evidence regarding major proposed treatments, repurposed or

experimental, for COVID-19 and provides a summary of current clinical experience and treatment guidance for this novel epidemic coronavirus.

Remdesivir is an RNA polymerase inhibitor with potent antiviral activity in vitro and efficacy in animal models of coronavirus disease 2019 (Covid-19). Remdesivir is prodrugs of an adenosine analogue with demonstrated antiviral activity against a broad range of RNA virus families.^[2-5] Remdesivir has shown nanomolar in vitro activity against SARS-CoV-2 in human airway epithelial cells and clinical and virologic efficacy in a primate model of SARS-CoV-2.^[6-8] Clinical trials of remdesivir for the treatment of Covid-19 have used a 10-day course of treatment that was based on efficacy data in animal models of Middle East respiratory syndrome and supported by safety data in approximately 500 healthy volunteers and patients infected with Ebola virus.^[9,10] Identifying the shortest duration of effective treatment with remdesivir is an urgent medical need. A shorter course of treatment without a loss of efficacy could reduce hospital stays and potential adverse events and could extend the limited supply of remdesivir available during this pandemic. In this report, we describe the results of an open-label, randomized, multicenter trial evaluating the efficacy and safety of treatment with

remdesivir for 5 or 10 days in patients with severe Covid-19 disease.

Trial Design and Oversight

For this ongoing phase 3 trial, patients were enrolled at 55 hospitals in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan between March 6 and March 26, 2020. Patients were randomly assigned in a 1:1 ratio to receive intravenous treatment with remdesivir for 5 days or 10 days. The randomization was not stratified. All the patients were to receive 200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days. Both treatment groups continued supportive therapy at the discretion of the investigator throughout the duration of the trial. The protocol was amended on March 15, 2020, after the beginning of enrollment but before any results were available. The lower age limit for eligibility was reduced from 18 years to 12 years, and a requirement for an axillary temperature of at least 36.6°C at screening was eliminated. In addition, one of the primary efficacy assessments the proportions of patients with normalization of temperature at day 14 - was changed to assessment of clinical status on a 7-point ordinal scale on day 14 (described below). This change was made in response to an evolving understanding of the signs and symptoms of Covid-19 during hospitalization and in recognition of emerging standards for assessment of Covid-19.^[11,12] The protocol was also amended to add an extension phase involving an additional 5600 patients, including a cohort of patients receiving mechanical ventilation.

Efficacy

In all, 65% of patients who received a 5-day course of remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at day 14, as compared with 54% of patients who received a 10-day course (Table 2). After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course ($P = 0.14$ by stratified Wilcoxon rank-sum test). For other efficacy end points of interest, the two groups had similar outcomes after adjustment for baseline clinical status (Table 2). The median duration of hospitalization among patients discharged on or before day 14 was 7 days (interquartile range, 6 to 10) for the 5-day group and 8 days (interquartile range, 5 to 10) for the 10-day group. Numerically more patients were discharged from the hospital in the 5-day group than in the 10-day group (60%, vs. 52%), and mortality was numerically lower (8%, vs. 11%). Discharge rates were higher in the overall population among patients who had had symptoms for less than 10 days before receiving the first dose of remdesivir (62%) than among those who had had symptoms for 10 or more days before receiving the first dose (49%).

The proportions of patients who recovered - those with a baseline score of 2 to 5 on the ordinal scale who improved to a score of 6 or 7 - showed the same trend: 64% of patients in the 5-day group, as compared with 54% of patients in the 10-day group (for a baseline-adjusted difference in proportions of -6.3% [95% confidence interval, -15.4 to 2.8]). The median time to recovery was 10 days (interquartile range, 6 to 18) among patients in the 5-day group and 11 days (interquartile range, 7 to not possible to estimate) among patients in the 10-day group. Evaluation of modified recovery showed similar trends, with nonsignificant differences between treatment groups after adjustment for baseline clinical status. We conducted a post hoc analysis to determine whether any subpopulation might have benefitted from receiving more than 5 days of therapy with remdesivir (Fig. 2). The oxygen-support status among all patients still hospitalized on day 5 was noted. Patients were then evaluated according to original treatment assignment for day 14 outcomes, to determine the effect of an additional 5 days of treatment with remdesivir. Among patients receiving mechanical ventilation or ECMO at day 5, 40% (10 of 25) in the 5-day group had died by day 14, as compared with 17% (7 of 41) in the 10-day group (Fig. 2). Treatment with remdesivir beyond 5 days among patients who were receiving noninvasive positive-pressure ventilation or high-flow oxygen, receiving low-flow oxygen, or breathing ambient air did not appear to improve outcomes.

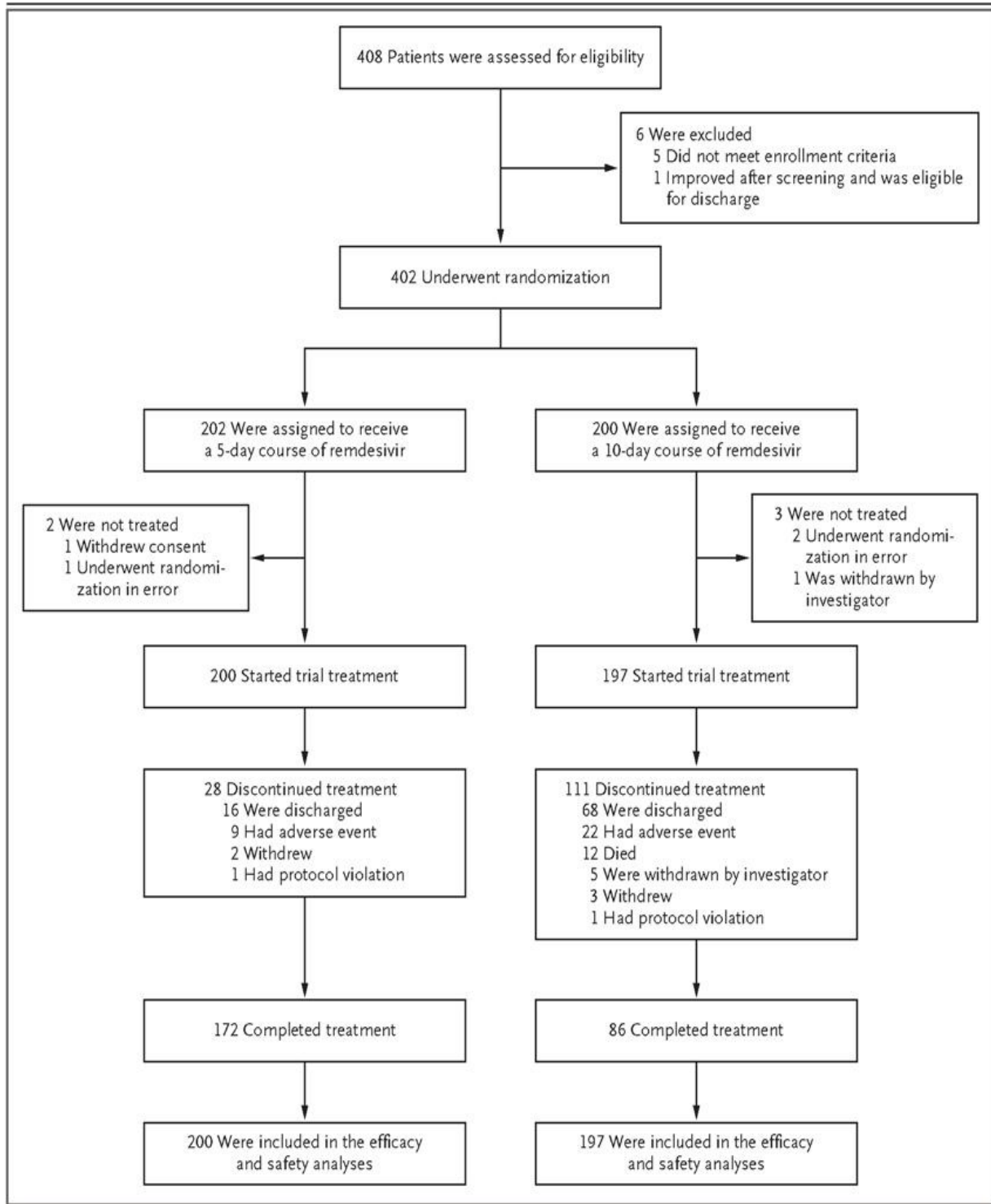


Figure 1: Enrollment and Randomization.

Table 1: Demographic and Clinical Characteristics of the Patients at Baseline According to Remdesivir Treatment Group.*

Characteristic	5-Day Group (N = 200)	10-Day Group (N = 197)
Median age (IQR) — yr	61 (50–69)	62 (50–71)
Male sex — no. (%)	120 (60)	133 (68)
Race — no./total no. (%) [†]		
White	142/200 (71)	134/192 (70)
Black	21/200 (10)	23/192 (12)
Asian	20/200 (10)	25/192 (13)
Other	17/200 (8)	10/192 (5)
Median body-mass index (IQR) [‡]	29 (25–34)	29 (25–33)
Coexisting conditions of interest — no. (%)		
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Hypertension	100 (50)	98 (50)
Asthma	27 (14)	22 (11)
Clinical status on the 7-point ordinal scale — no. (%) [§]		
2: Receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: Receiving noninvasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: Receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: Not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Median duration of hospitalization before first dose of remdesivir (IQR) — days	2 (1–3)	2 (1–3)
Median duration of symptoms before first dose of remdesivir (IQR) — days	8 (5–11)	9 (6–12)
Median AST level (IQR) — U/liter [¶]	41 (29–58)	46 (34–67)
Median ALT level (IQR) — U/liter	32 (22–50)	36 (23–58)
Median creatinine clearance by Cockcroft–Gault (IQR) — ml/min	106 (80–142)	103 (80–140)

* Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, AST aspartate aminotransferase and IQR interquartile range.

[†] Race was reported by the patients.

[‡] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[§] P = 0.02 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.

[¶] P = 0.008 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.

Safety

The percentages of patients experiencing adverse events were similar in the two groups: 70% in the 5-day group and 74% in the 10-day group (Table 3). In all, 21% of patients in the 5-day group and 35% in the 10-day group had serious adverse events. Similar results were seen in the percentages of patients experiencing any adverse event of grade 3 or higher: 30% in the 5-day group and 43% in the 10-day group. The most common adverse events overall were nausea (10% in the 5-day group vs. 9% in the 10-day group), acute respiratory failure (6% vs. 11%), increased ALT (6% vs. 8%), and constipation (7% in both groups). The percentage of patients who discontinued treatment owing to adverse events was 4% in the 5-day group, as compared with 10% in the 10-day group. In an exploratory analysis of the first 5 days of therapy, rates of adverse events differed between the two treatment groups despite their receiving the same

therapy. After adjustment for baseline clinical status, only serious adverse events were different between the two groups. The most common serious adverse events that were more common in the 10-day group were acute respiratory failure (9%, vs. 5%) and respiratory failure (5%, vs. 2%). Laboratory abnormalities of grade 3 or higher occurred among 27% of patients in the 5-day group and 34% of patients in the 10-day group (Table 3). Most abnormalities were transient, with no significant difference between the median changes in the two groups at day 14. Grade 4 creatinine clearance reductions were reported in 12% of patients in the 10-day group, as compared with 3% in the 5-day group. Most of these patients (71%) had been receiving either invasive mechanical ventilation or noninvasive positive pressure ventilation or high-flow nasal cannula at baseline, consistent with the observation that disease severity at baseline was associated with safety outcomes.

Table 2: Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring on-going medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7. Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (-7.0 to 7.5)
Day 7	71 (36)	54 (27)	-5.0% (-14.0 to 4.0)
Day 11	116 (58)	97 (49)	-4.8% (-14.1 to 4.6)
Day 14	129 (64)	107 (54)	-6.5% (-15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (-7.0 to 7.1)
Day 7	71 (36)	51 (26)	-6.0% (-14.8 to 2.7)
Day 11	115 (58)	97 (49)	-3.7% (-12.8 to 5.5)
Day 14	129 (64)	106 (54)	-6.3% (-15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	-2.3% (-10.5 to 5.9)
Day 7	84 (42)	69 (35)	-3.4% (-12.6 to 5.8)
Day 11	128 (64)	106 (54)	-5.7% (-14.6 to 3.2)
Day 14	140 (70)	116 (59)	-6.7% (-15.3 to 1.9)

* Differences are expressed as rate differences, except in the case of time to clinical improvement, time to recovery, and time to modified recovery, for which differences are expressed as hazard ratios; for these time-to-event end points, the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model including treatment and baseline clinical status as covariates. For events at prespecified time points (e.g., days 5, 7, 11, and 14), the difference in the proportion of subjects with an event under evaluation between treatment groups and the 95% confidence interval were estimated from the Mantel–

Haenszel proportions adjusted according to baseline clinical status.

* The P value was calculated from a Wilcoxon rank-sum test stratified by baseline clinical status.

*Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale; recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7; and modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7. Cumulative incidence functions were

calculated for each Treatment group for days to the event under evaluation (i.e., clinical improvement, recovery, or modified recovery), with death as the competing risk. Data for patients not achieving the event under

evaluation at the last assessment were censored on the day of the last clinical assessment. Patients who died before achieving the event under evaluation were considered to have experienced a competing event.

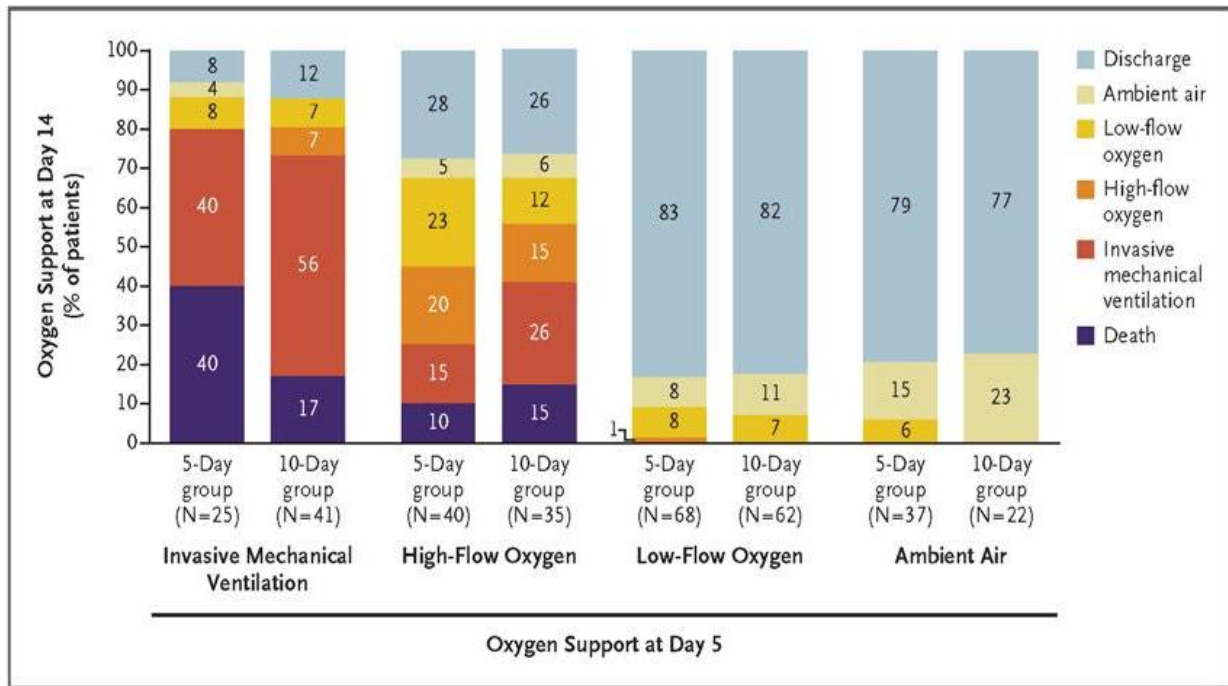


Figure 2: Oxygen Support on Day 14 According to Oxygen Support on Day 5.

Shown is the distribution of oxygen-support status on day 14 for the 5-day and 10-day treatment groups according to oxygen-support status at day 5 of therapy. Percentages are based on patients with both day 5 and day 14 oxygen support data available and exclude those with missing oxygen-support data for day 14. Oxygen-support status is derived from the clinical status according to the seven-point ordinal scale, as follows: 1, death; 2, receiving invasive mechanical ventilation; 3, receiving high-flow oxygen; 4, receiving low-flow oxygen; 5 or 6, breathing ambient air; and 7, discharge. Data on high-flow oxygen were missing for 1 patient in the 10-day group; data on low-flow oxygen were missing for 3 patients in the 5-day group and 6 patients in the 10-day group, and data on ambient air were missing for 3 patients in the 5-day group.

Other Selected Repurposed Drugs for COVID-19 Treatment

Agents previously used to treat SARS and MERS are potential candidates to treat COVID-19. Various agents with apparent in vitro activity against SARS-CoV and MERS-CoV were used during the SARS and MERS outbreaks, with inconsistent efficacy. Meta-analyses of SARS and MER Treatment studies found no clear benefit of any specific regimen. Below, the in vitro activity and published clinical experiences of some of the most promising repurposed drugs for COVID-19 are reviewed.

SARS-CoV-2: Virology and Drug Targets

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein.^[13] Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles.^[14-16] These viral lifecycle steps provide potential targets for drug therapy. Promising drug targets include nonstructural proteins (eg, 3-chymotrypsin-like protease, papainlike protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways.^[17,18] Table 1 summarizes the mechanism of action and major pharmacologic parameters of select proposed treatments or adjunctive therapies for COVID-19.

Table 3: Summary of Adverse Events According to Remdesivir Treatment Group.

Event or Abnormality	5-Day Group (N=200)	10-Day Group (N=197)
Any adverse event — no. of patients (%)	141 (70)	145 (74)
Nausea	20 (10)	17 (9)
Acute respiratory failure	12 (6)	21 (11)
Alanine aminotransferase increased	11 (6)	15 (8)
Constipation	13 (6)	13 (7)
Aspartate aminotransferase increased	10 (5)	13 (7)
Hypokalemia	10 (5)	12 (6)
Hypotension	9 (4)	12 (6)
Respiratory failure	7 (4)	14 (7)
Insomnia	10 (5)	11 (6)
Acute kidney injury	4 (2)	15 (8)
Adverse event leading to discontinuation of treatment — no. of patients (%)	9 (4)	20 (10)
Any serious adverse event	42 (21)	68 (35)
Acute respiratory failure	10 (5)	18 (9)
Respiratory failure	5 (2)	10 (5)
Septic shock	2 (1)	5 (3)
Acute respiratory distress syndrome	1 (<1)	5 (3)
Hypoxia	2 (1)	4 (2)
Respiratory distress	3 (2)	4 (2)
Dyspnea	4 (2)	1 (1)
Pneumothorax	2 (1)	3 (2)
Viral pneumonia	3 (2)	2 (1)
Aminotransferase levels increased	3 (2)	2 (1)
Any grade ≥ 3 laboratory abnormality — no. of patients/total no. (%)	53/195 (27)	64/191 (34)
Selected grade ≥ 3 laboratory abnormalities — no. of patients/total no. (%)		
Creatinine clearance decreased		
Grade 3	13/193 (7)	13/188 (7)
Grade 4	5/193 (3)	23/198 (12)
ALT elevation		
Grade 3	8/194 (4)	11/191 (6)
Grade 4	4/194 (2)	5/191 (3)
AST elevation		
Grade 3	11/194 (6)	7/190 (4)
Grade 4	3/194 (2)	4/190 (2)
Bilirubin increased		
Grade 3	1/193 (1)	3/190 (2)
Grade 4	0	1/190 (1)

* Adverse events listed are those that occurred in at least 5% of patients in either treatment group, and serious adverse events listed are those that occurred in 5 or more patients.

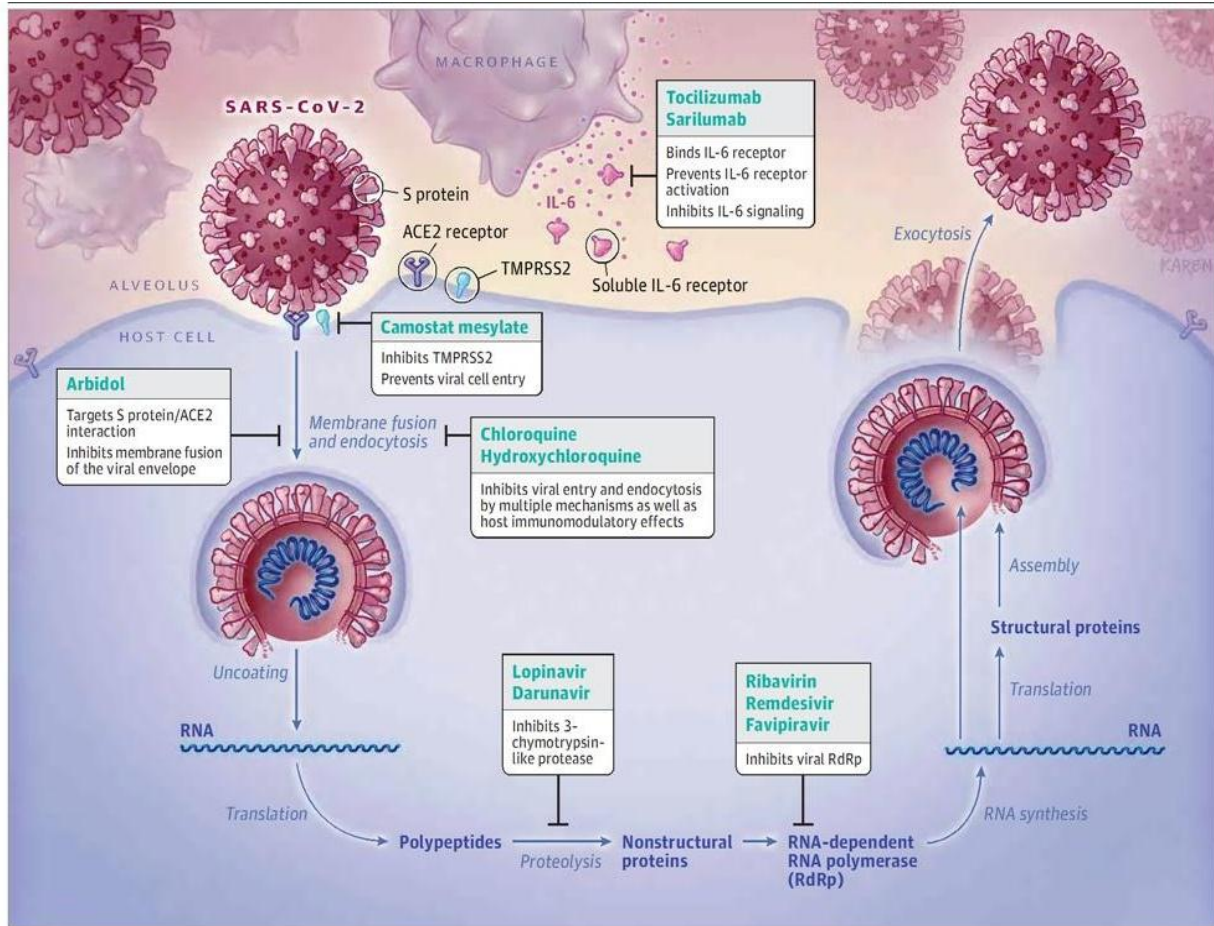


Figure 3: Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets.

✚ Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

CONCLUSION

In this open-label, randomized, multicenter, phase 3 trial among patients with severe Covid-19 pneumonia due to infection with SARS-CoV-2, we did not find a significant difference in efficacy between 5-day and 10-day courses of remdesivir. After adjustment for baseline imbalances in disease severity, outcomes were similar as measured by a number of end points: clinical status at day 14, time to clinical improvement, recovery, and death from any cause. However, these results cannot be extrapolated to critically ill patients receiving mechanical ventilation, given that few of the patients in our trial were receiving mechanical ventilation before beginning treatment with remdesivir. The apparent trend toward better outcomes in patients treated with remdesivir for 5 days than in those treated for 10 days may have several causes. The 10-day group included a significantly higher percentage of patients in the most severe disease categories those requiring invasive mechanical

ventilation and high-flow oxygen and a higher proportion of men (68%, vs. 60%), who are known to have worse outcomes with Covid-19.^[19] Although eligibility criteria excluded patients receiving invasive mechanical ventilation, 13 patients who were enrolled in the trial were intubated before the start of treatment with remdesivir or were categorized as having protocol deviations at enrollment. Of these 13 patients, 9 were assigned to the 10-day group, whereas only 4 were assigned to the 5-day group. Although the results could suggest that longer treatment with remdesivir may be detrimental, we note that the trend toward improved outcomes in the 5-day group was already evident at day 5 of the trial when both groups had received the same amount of treatment which suggests that differences between the groups were not due to treatment duration but to observed imbalances in baseline characteristics between the two groups. Because our trial lacked a placebo control, it is not a test of the efficacy of remdesivir.

Results from two clinical trials of remdesivir in patients with severe Covid-19 have been reported. Wang and colleagues conducted a randomized, double-blind, placebo-controlled trial at 10 hospitals in Hubei, China.^[20] However, owing to a decline in the incidence of Covid-19 in China, enrollment was only about half of

the planned number of patients, with the result that the trial was not powered to show a statistical difference between the remdesivir and placebo groups. 22 Preliminary results from an ongoing randomized clinical trial conducted by the National Institute of Allergy and Infectious Diseases showed that 10 days of treatment with remdesivir was statistically superior to placebo for the primary end point, time to recovery.^[21] Our trial suggests that if remdesivir truly is an active agent, supplies that are likely to be limited can be conserved with shorter durations of therapy. Transient elevations in liver enzymes have been observed after treatment with remdesivir in phase 1 studies among healthy volunteers, and preclinical studies revealed renal toxicity at exposures higher than those in humans. In our trial, 2.5% and 3.6% of patients in the 5-day and 10-day groups, respectively, discontinued treatment owing to aminotransferase elevations. Covid-19 itself has been found to be associated with liver injury.^[22]

Patients in the 10-day group had more elevations in creatinine of grade 3 or higher and more declines in creatinine clearance than those in the 5-day group. The higher frequency of grade 4 decreases in creatinine clearance observed in the 10-day group may have been driven by the more severe disease status in that group, given that Covid-19 is associated with renal injury. Further studies will be needed to delineate the contribution of drug toxicity or the effects of the virus to these findings. Close monitoring of hepatic and renal tests is appropriate among patients who are severely ill. The interpretation of these results is limited by the lack of a randomized placebo control group and the open-label design. We designed this as an open-label trial for two reasons: the available supply of matched placebo vials had been allocated to other ongoing randomized, controlled clinical trials, 21, 23 and, more important, given the stretched health care resources during the pandemic, it seemed appropriate to allow for patients to be discharged from the hospital as soon as medically indicated, regardless of whether they had completed the full assigned course of treatment with remdesivir. As a result, only 44% of patients in the 10-day treatment group completed the full course of therapy. Patients who were not discharged were presumably those with more severe illness, which may account for the different rates of adverse events seen in the two groups. Another important limitation is that we do not have SARS-CoV-2 viral-load results during and after treatment, owing to the variability in local access to testing and practices across the global sites. Our trial did not show a significant difference in efficacy between a 5-day course and a 10-day course of intravenous remdesivir treatment in patients with severe Covid-19 due to SARS-CoV-2 who did not require mechanical ventilation at baseline. Patients who progress to mechanical ventilation may benefit from 10 days of remdesivir treatment; further evaluation of this subgroup and of other high-risk groups, such as immunocompromised persons, is needed to determine the shortest effective duration of therapy.

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