ID CORNER

Remdesivir in the Treatment of Hospitalized Patients with COVID-19: Evolution of Use Over the Course of the Pandemic

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Since the beginning of the COVID-19 pandemic, significant effort has been directed towards optimizing pharmacologic treatment for patients hospitalized with SARS-CoV-2. Over the course of the past year, several drug classes have been used with limited success in an attempt to treat COVID-19. The World Health Organization (WHO) treatment guidelines have evolved based on ongoing clinical trials with various agents, including, but not limited to, remdesivir (Veklury®, Gilead). A continued debate about using remdesivir has been defining which group of hospitalized patients, as categorized by the WHO COVID-19 disease severity ordinals (Table 1), are likely to benefit the most given the varying results published from clinical evidence.[1] An ordinal, or ordinal number, defines an individual's position or category in a list, to make generalized interpretation easier in clinical studies.

Remdesivir inhibits SARS-CoV-2 ribonucleic acid (RNA)-dependent RNA polymerase, which is vital for viral replication. As an adenosine triphosphate analogue, it competes for integration into the RNA chains, resulting in delayed chain termination during viral RNA replication, thereby reducing the viral load. All medications do come with contraindications and a side effect profile. Currently, remdesivir is not recommended in patients who have a history of significant hypersensitivity reactions to remdesivir or any components within the product. Additional warnings associated with remdesivir include mild to moderate transaminase elevations, which have resolved upon discontinuation. Monitoring of hepatic laboratory testing should occur in each patient, and discontinuation of remdesivir should be considered if alanine transaminase levels increase to >10 times the upper limit of normal.[2] When looking at results from clinical trials with remdesivir, patients are often categorized into ordinals based on presenting symptoms.[3,4]

Clinical Data

The first published trial with remdesivir, released on April 29, 2020, was a randomized, double-blind, placebo-controlled, multicenter trial performed by Wang et al. in Hubei, China.[3] The investigators reviewed approximately 230 hospitalized COVID-19 adults with an onset of symptoms within the prior 12 days, SpO2 ≤94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300mmHg. Patients were given intravenous (IV) remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-10) or placebo once daily for 10 days; remdesivir was not significantly associated with shorter duration of mechanical ventilation or hospital stay. However, a non-significant numerical reduction in time to clinical improvement was observed with remdesivir compared to placebo, and the authors called for additional larger studies to evaluate this reduction.[3]

Remdesivir's expanded use in the treatment of COVID-19 manifested early in the pandemic when preliminary results from the first stage of the Adaptive COVID-19 Treatment Trial (ACTT-1) were released on April 29, 2020 and signaled that remdesivir was better than placebo in terms of shortening time to recovery (Figure 1).[4] Shortly after this data was released, the Food and Drug Administration (FDA) granted remdesivir Emergency Use Authorization (EUA) on May 1, 2020. The EUA was limited to patients with severe disease who

TABLE 1. WHO Ordinal COVID-19 Disease Severity Ordinals[1]

Patient State	Descriptor	Ordinal Score
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal cannula	4
Hospitalized, severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)	7
Dead	Death	8

FIGURE 1. Summary Timeline of Remdesivir for COVID-19

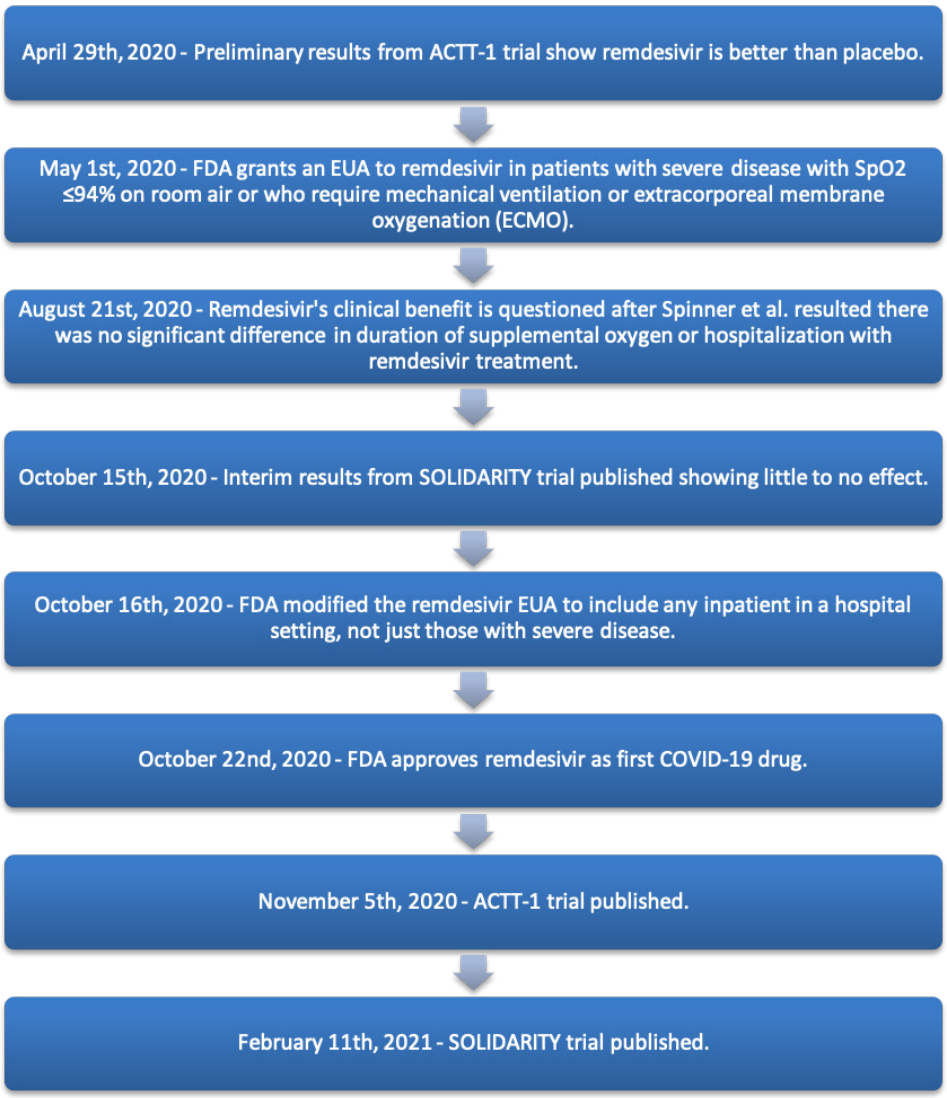


TABLE 2. ACTT-1 Disease Severity Ordinal[4]

Descriptor	*Ordinal Score*
Not hospitalized and no limitations of activities	1
Not hospitalized, with limitation of activities, home oxygen requirement, or both	2
Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons)	3
Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions)	4
Hospitalized, requiring any supplemental oxygen	5
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	6
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	7
Death	8

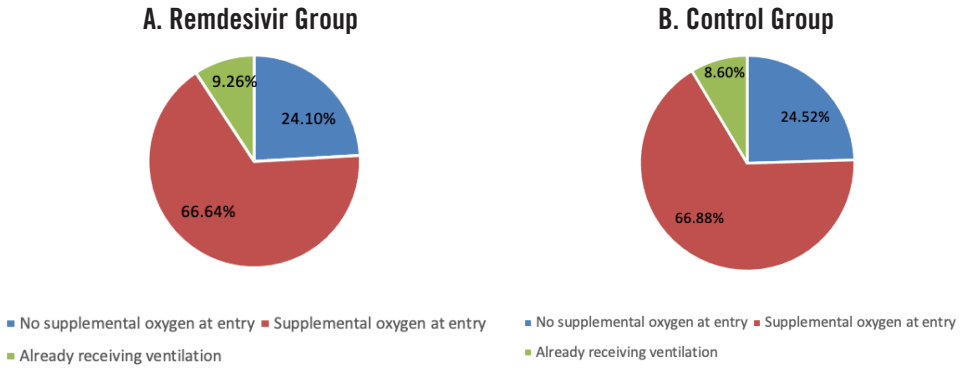
had an oxygen saturation (SpO2) ≤94% on room air, and required mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[5]

On August 21, 2020, results from a Gilead-sponsored trial comparing the effect of remdesivir versus the standard of care on clinical status at 11 days in patients with moderate COVID-19 were published; moderate infection was defined as any radiographic evidence of pulmonary infiltrates and SpO2 >94% on room air.[6] Patients were located in the United States, Europe, and Asia, and were randomized to receive a 10-day course of remdesivir (n=197), 5-day course of remdesivir (n=199), or standard of care (n=200). The trial evaluated clinical status assessed on a 7-point ordinal scale on study day 11. The authors concluded that patients who received a 5-day course of remdesivir had statistically significant odds of a better clinical status than those receiving standard of care (odds ratio, 1.65; 95% confidence interval, 1.09-2.48; P=.02), but had an effect size of uncertain importance. Patients who were randomized to receive a 10-day course of remdesivir had no statistical difference between the standard of care group (P=.18). Overall, the trial demonstrated little benefit for the use of remdesivir in hospitalized patients that required no supplemental oxygenation.

In mid-October 2020, the FDA modified the remdesivir EUA to include any inpatient in a hospital setting, not just those with severe disease as the previous EUA stated. A few weeks later at the end of October 2020, remdesivir was formally FDA approved for the treatment of COVID-19 in hospitalized adult and pediatric patients ≥12 years of age and weighing ≥40 kg.[7] Given the broad category of patients included under FDA approval and new circulating clinical trials, questions again circulated regarding whether the drug was truly beneficial across all WHO COVID-19 disease severity ordinals.

Completed results from ACTT-1 were published in November of 2020.[4] Beigel et al. performed a double-blind, randomized, placebo-controlled trial with 10 days of remdesivir in adult hospitalized patients with confirmed COVID-19 and evidence of lower respiratory tract infection. The trial results demonstrated that patients who received remdesivir had a median

FIGURE 2. WHO Solidarity Trial Entry Characteristics of Respiratory Support for Remdesivir versus Control Group



recovery time of 10 days, compared to 15 days among those who received placebo (recovery rate ratio 1.29; 95% confidence interval 1.12 to 1.49; P<.001). Therefore, the investigators concluded that remdesivir was overall superior to placebo in reducing the time to recovery in hospitalized patients with confirmed COVID-19. When interpreting the results of the ACTT-1 trial, however, it should be noted the median time to randomization for both treatment groups was nine days from symptom onset, which is later than the current recommendation and could explain the higher percentage of patients with severe disease upon randomization. In addition, a few months into the trial, the primary outcome was altered, from comparison of ordinal scale scores on day 15 to a comparison of time to recovery up to day 29. This change was secondary to evolving data on COVID-19 and its concern for a protracted course.

ACTT-1 included subgroup analyses based on presenting disease severity.[4] Of note, the ordinal scale used in the subgroup analysis was slightly different than the current WHO COVID-19 disease severity scale. The ACTT-1 trial used an ordinal scale ranging from 1-8 (Table 2), with ordinal score 7 indicating hospitalized patients with invasive mechanical ventilation or ECMO, and ordinal score 8 indicating death. Results indicated the largest rate ratio for recovery using remdesivir was seen in ordinal score 5 patients, or those hospitalized patients requiring supplement low-flow oxygen (recovery rate ratio 1.45; 95% confidence interval 1.18 to 1.79). Conversely, the subgroup analysis demonstrated the smallest rate ratio for recovery in patients with ordinal score 7.

A large international study published in early December 2020 challenged previous perspectives surrounding remdesivir's benefit in COVID-19 patients. The WHO Solidarity Trial was a randomized, open control trial that included patients receiving remdesivir, hydroxychloroquine, lopinavir, interferon, or no trial drug.[8] When looking specifically at remdesivir, the study found 10.95% (301/2,750) of remdesivir patients died compared to 11.19% (303/2,708) in the control group (rate ratio 0.95; 95% confidence interval 0.81 to 1.11; P=.50) resulting in no statistical significance between the two groups. Overall, it was concluded that no drug definitively reduced mortality, initiation of ventilation, or hospitalization duration for the COVID-19 patients studied. This study did not perform any subgroup analyses to determine a potential clinical benefit or difference with disease severity, but was able to obtain data surrounding respiratory support upon entry into the trial. Baseline respiratory support in the remdesivir group (n=2,743) and control group (n=2,708) (Figure 2) were similar. Approximately two-thirds of remdesivir patients were receiving supplemental oxygen at entry and 9.26% of those patients were already receiving mechanical ventilation at entry. In the control group, approximately two-thirds of patients were receiving supplemental oxygen at entry, but only 8.61% were receiving mechanical ventilation at entry. Limitations should be taken into account while assessing the results, including, as mentioned previously, that there were no subgroup analyses to determine clinical benefit with disease severity, the trial was open labeled, and wide confidence intervals were found.

Of note, the FDA labeling for remdesivir does not align with clinical evidence or national guidelines. The package insert states remdesivir is approved in adults and pediatric patients (≥12 years of age and weighing ≥40 kg) for the treatment of COVID-19 requiring hospitalization.[9] Currently, the Infectious Diseases Society of America's guideline recommends remdesivir use only in hospitalized patients with severe disease defined as SpO2 ≤94% on room air or those who require supplemental oxygen.[10] The National Institutes of Health Therapeutic Management of Adults with COVID-19 recommends remdesivir use in hospitalized patients requiring supplemental oxygen via noninvasive ventilation or high-flow device.[7] Lastly, the Society of Critical Care Medicine (SCCM) recommends remdesivir use in adults with severe COVID-19 who do not require mechanical ventilation, but it should be ideally started within 72 hours of positive SARS-CoV-2 polymerase chain reaction or antigen testing. Furthermore, SCCM recommends against starting remdesivir in adults undergoing mechanical ventilation for critical COVID-19.[11] Both of these recommendations are in line with the findings from both Spinner et al. and ACTT-1 trials, as seen in Table 3.[4,6]

The clinical benefit of remdesivir in hospitalized patients not requiring supplemental oxygen or hospitalized patients requiring any supplemental oxygen (WHO COVID-19 disease severity ordinal 4 and 5) is where opinions are most variable. Although the clinical trials for remdesivir are not directly comparable (e.g. different methods, durations, etc.), they lend evidence to initiate remdesivir treatment early, before patients progress to a severe state and are placed on mechanical ventilation. Based on the ACTT-1 trial results, ordinal 4 in the WHO COVID-19 disease severity ordinal demonstrate the most clinical benefit from remdesivir.[4] It can be concluded that the finding is based on this ordinal group having the largest recovery rate ratio favoring remdesivir, meaning a faster recovery time with the use of remdesivir. In addition, this ordinal group likely received remdesivir early in the viral course of COVID-19 due to their earlier presentation to the hospital, and therefore the virus did not have the

TABLE 3. Summary of Key Clinical Trials with Remdesivir Use in COVID-19

Source	Wang et al.[3]	Spinner et al.[6]	ACTT-1 Study[4]	SOLIDARITY Study[8]
Published	April 29, 2020	August 21, 2020	November 5, 2020	February 11, 2021
Study Design	Randomized, double-blind, placebo-controlled, multicenter trial	Randomized, open-label, Phase 3 trial	Double-blind, randomized, placebo-controlled trial	Multinational, pragmatic, adaptive, open-label trial
Interventions	Randomly assigned in a 2:1 ratio to remdesivir or placebo for 10 days	Randomly assigned in a 1:1:1 ratio to 10-day course of remdesivir versus 5-day course of remdesivir versus standard of care	Randomly assigned in a 1:1 ratio to remdesivir or placebo for up to 10 days or until discharge	Randomly assigned into equal proportions to no trial drug or one of the trial drug regimens that was locally available (remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a)
Primary Outcomes	Time to clinical improvement within 28 days after randomization	Clinical status on day 11 assessed on a 7-point ordinal scale	Time to recovery, defined as the first day on which a patient met criteria for category 1, 2, or 3 on the eight-category ordinal scale	Assess effects on in-hospital mortality
Secondary Outcomes	Proportions of patients in each category of the six-point scale at day 7, 14, and 28 days after randomization	Proportion of patients with adverse events throughout the duration of the study	Clinical status on day 15, time to improvement of one category, mean change in status on the ordinal scale, time to discharge, number of days with supplemental oxygen, incidence and duration of new oxygen use, number of days of hospitalization, and mortality	Initiation of mechanical ventilation and hospitalization duration
Results	Remdesivir was adequately tolerated, but clinically meaningful differences cannot be excluded due to size of trial	Statistical significance between 5-day course of remdesivir and standard of care, but with uncertain clinical importance	Remdesivir was superior to placebo in shortening the time to recovery in adults	Remdesivir had little to no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay

opportunity to progress into requiring ventilation or additional oxygen support prior to admission. As treatments evolve, patient and provider awareness and encouraging earlier patient presentation for treatment will be a paramount to successful outcomes.

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