Severe COVID-19 Therapies: SIMIT's Position

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Abstract

Scope: The SARS-CoV-2 virus has caused a global pandemic, leading to nearly one million deaths. We don't yet have a clear standard treatment for COVID-19 because research results have been mixed and treatment guidelines keep changing. This paper aims to summarize the current research on how to manage COVID-19 and share insights from experts who are treating patients directly.

Methods: We have conducted a thorough review of the most recent studies and news from clinical trials concerning various treatments for COVID-19. Utilizing PubMed as our primary resource, we meticulously gathered and analyzed all relevant research to ensure a comprehensive understanding of the current treatment landscape. To systematically present our findings, we developed a detailed flowchart that illustrates recommended treatment options for COVID-19 patients. This flowchart is designed to provide clear and actionable guidance based on the latest evidence, facilitating informed decision-making for healthcare providers and stakeholders involved in the management of COVID-19. By consolidating and visualizing the data, we aim to support effective treatment strategies and enhance patient care during this critical period.

Implications: With the ongoing pandemic and the looming risk of a potential second wave in Europe, it has become increasingly important to identify and prioritize treatments that have proven to be effective. As the situation evolves, many clinical trial results are still pending, which adds to the uncertainty surrounding the best course of action. Therefore, it is crucial to meticulously evaluate the current evidence available. By thoroughly analyzing the data from existing studies and trials, we can make more informed and strategic decisions regarding treatment options. This approach not only helps in understanding the efficacy of various therapies but also in optimizing patient care and resource allocation amidst the ongoing health crisis. Ensuring that decisions are based on the most accurate and up-to-date information is essential for combating the pandemic effectively and mitigating its impact on public health.

Keywords: • Severe acute respiratory syndrome Coronavirus • SARS-CoV1 • Treatment recommendations • Influenza

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus responsible for the illness known as Coronavirus Disease 2019 (COVID-19). In the initial stages of the pandemic, treatment strategies for early COVID-19 cases primarily utilized medications that had been previously employed for other viral outbreaks, including those for influenza, SARS-CoV1, and Ebola. These initial approaches were based on the best available information at the time, but as the pandemic has progressed, treatment recommendations have undergone significant changes and refinements in response to new research findings. Presently, only a limited number of treatments for COVID-19 have received approval from regulatory agencies, and these approvals are largely based on evidence from Randomized Controlled Trials (RCTs). Clinicians managing patients during the ongoing first wave or preparing for a potential second wave are guided by the most recent studies as well as updates from press releases regarding RCT outcomes. This dynamic situation requires healthcare providers to stay informed about the latest evidence and recommendations to ensure that they can offer the most effective and up-to-date care for COVID-19 patients. Based on available evidence; the Italian Society of Infectious and Tropical Diseases (SIMIT) set out to identify which treatments should be considered the standard of care for severe COVID-19 cases. To do this, they conducted a thorough review of the literature on therapeutic options for severe COVID-19, with input from 24 infectious disease specialists from SIMIT.

A thorough search of PubMed was conducted to find relevant publications on the topic. The review included not only Randomized Controlled Trials (RCTs) but also observational studies with large sample sizes. Additionally, since some important RCTs have not yet been published, we incorporated data from press releases and preprint studies. The panel was divided into four groups, each responsible for evaluating evidence on different therapeutic strategies and drafting their sections of the document. A comprehensive review was then performed, and the entire panel reached a consensus to finalize the report and create a consensus flowchart for treating severe COVID-19 cases.

Treatment strategies

Antivirals: At the start of the SARS-CoV-2 pandemic, local guidelines suggested using HIV protease inhibitors as treatments for COVID-19, with lopinavir/ritonavir being the preferred option and Darunavir (DRV)/cobicistat as a secondary choice. Subsequent Randomized Controlled Trials (RCTs) assessed the effectiveness of these antiviral treatments. An early trial in China involving 199 patients with confirmed SARS-CoV-2 infection showed, though limited by sample size, that lopinavir/ritonavir did not provide any additional benefit beyond standard care for hospitalized adults. This finding was later supported by the RECOVERY and SOLIDARITY trials, which also found no significant benefit from lopinavir/ritonavir for COVID-19 patients in hospitals. For DRV/cobicistat, there is no strong clinical evidence supporting its use in treating viral infections other than HIV, and it has shown no antiviral activity against SARS-CoV-2 at effective concentrations.

Remdesivir (GS-5734) is a nucleoside analogue prodrug with in vitro activity against Several Coronaviruses, including SARS-CoV-2. Initial data

indicated that remdesivir was more effective than a placebo in reducing recovery time but did not significantly impact mortality rates [8]. In a later retrospective cohort study, which compared 312 patients with severe COVID-19 who received remdesivir to 818 matched patients, remdesivir was associated with significantly improved recovery rates and a 62% reduction in death odds compared to standard care.

However, a Randomized Controlled Trial (RCT) involving hospitalized patients with confirmed SARS-CoV-2 did not reveal a significant difference between a 5-day and a 10-day course of remdesivir. Clinical improvement was noted in 64% of patients in the 5-day group and 54% in the 10-day group. More recent data from the ACTT-1 double-blind RCT, which included 1,062 patients, showed that a 10-day course of remdesivir led to a shorter recovery time compared to placebo (10 days *vs.* 15 days, $p<0.001$) and a higher likelihood of clinical improvement at day 15. However, no significant difference in mortality was observed by day 29. The benefits were notably greater for patients receiving oxygen via a mask compared to those who were not on oxygen or required noninvasive or invasive mechanical ventilation.

Conclusion

Remdesivir (GS-5734) is a nucleoside analogue prodrug with in vitro activity against several coronaviruses, including SARS-CoV-2. Initial data indicated that remdesivir was more effective than a placebo in reducing recovery time but did not significantly impact mortality rates. In a later retrospective cohort study, which compared 312 patients with severe COVID-19 who received remdesivir to 818 matched patients, remdesivir was associated with significantly improved recovery rates and a 62% reduction in death odds compared to standard care.

However, a Randomized Controlled Trial (RCT) involving hospitalized patients with confirmed SARS-CoV-2 infection did not demonstrate a significant difference between administering a 5-day versus a 10-day course of remdesivir. In this study, clinical improvement was observed in 64% of patients receiving the 5-day regimen and in 54% of those receiving the 10-day regimen. This suggests that extending the duration of remdesivir treatment may not offer a substantial additional benefit in terms of overall clinical improvement.

More recent findings from the ACTT-1 trial, a large-scale double-blind RCT that enrolled 1,062 patients, provide additional insights. This study reported that a 10-day course of remdesivir was associated with a statistically significant reduction in recovery time compared to a placebo, with patients recovering in 10 days versus 15 days ($p<0.001$). Additionally, a higher likelihood of clinical improvement was noted at day 15 for those receiving remdesivir. Despite these positive outcomes regarding recovery time and clinical improvement, the trial did not reveal a significant difference in mortality rates by day 29 between the remdesivir and placebo groups. The benefits of remdesivir were particularly pronounced among patients who were receiving supplemental oxygen via a mask, as opposed to that not on oxygen or those requiring noninvasive or invasive mechanical ventilation. This underscores the need for careful patient selection and highlights the variable impact of treatment based on the severity of respiratory support required.

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