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The Cost-Effectiveness of Remdesivir for Hospitalized Patients With COVID-19

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ABSTRACT

Objectives: This study aimed to estimate the cost-effectiveness of remdesivir, the first novel therapeutic to receive Emergency Use Authorization for the treatment of hospitalized patients with COVID-19, and identify key drivers of value to guide future pricing and reimbursement efforts.

Methods: A Markov model evaluated the cost-effectiveness of remdesivir in patients hospitalized with COVID-19 from a US healthcare sector perspective. A lifetime time horizon captured potential long-term costs and outcomes. Model outcomes included discounted total costs, life-years, and quality-adjusted life-years (QALYs). Remdesivir was modeled as an addition to standard of care and compared with standard of care alone, including dexamethasone for patients requiring respiratory support. COVID-19 hospitalizations were assumed to be reimbursed through a single payment based on the respiratory support received alongside a remdesivir carveout payment in the base case. Sensitivity and scenario analyses identified key drivers.

Results: At a unit price of $520 per vial and assuming no survival benefit with remdesivir, the incremental cost-effectiveness was $298,200/QALY for patients with moderate to severe COVID-19 and $1,847,000/QALY for patients with mild COVID-19. Although current data do not support a survival benefit, if one was assumed, the cost-effectiveness estimate was $50,100/QALY for the moderate to severe population and $103,400/QALY for the mild population. Another key driver included the hospitalization payment structure (per diem vs bundled payment).

Conclusions: With the current evidence available, remdesivir’s price is too high to align with its expected health gains for hospitalized patients with COVID-19. Results from this study provide a rationale for iterative health technology assessment.

Keywords: cost-effectiveness, COVID-19, remdesivir, value assessment.

INTRODUCTION

The COVID-19 pandemic rages on. As of August 2021, there were > 35 million COVID-19 cases and > 600,000 deaths in the United States. Despite the regulatory approval of vaccines in many countries, attention is also focused on potential therapeutics as cases continue to soar after the approval of vaccines, partially explained by vaccine hesitancy and the emergence of variants. Among the treatment options that have become available, remdesivir stands out for several reasons. It was the first therapeutic backed by randomized controlled trial evidence to receive Emergency Use Authorization for the treatment of COVID-19 in the United States. Remdesivir is also notable because at the time of its introduction it had not been approved for any other clinical use and therefore had no established price. Although clinical researchers, regulators, and others debated the strength of the evidence supporting the use of remdesivir, the drug’s manufacturer, Gilead, had the opportunity to set the price. The combination of these factors made remdesivir the center of a debate regarding how to assess the value of treatments for COVID-19 and how the price should reflect that value. This debate continues as further therapeutic agents progress through clinical trials toward regulatory approval.

Remdesivir has been extensively studied in randomized controlled trials, observational studies, and meta-analyses. The pivotal trial for remdesivir in the hospitalized population with severe COVID-19 showed that remdesivir was associated with a significant reduction in time to recovery (median 10 days vs 15 days). Among hospitalized patients with milder disease, patients receiving remdesivir had a higher likelihood of a better clinical status by day 11. Neither the pivotal trials nor the numerous meta-analyses now published suggested a significant impact of remdesivir on survival. This article presents the results of the earliest effort to perform a cost-effectiveness analysis of remdesivir within a policy framework intended to inform appropriate pricing in the US market. After the posting of initial cost-effectiveness results in May 2020, our model was revised after public comment and the publication...
of more detailed data in the peer-reviewed literature, including additional evidence on remdesivir’s reduction in respiratory support and hospitalization length of stay, an insignificant survival benefit, a standard of care that included dexamethasone, and a price for remdesivir. We present here the results of our updated cost-effectiveness analysis of remdesivir. To guide ongoing pricing and reimbursement efforts in this time of evolving evidence and clinical care, we also identify the key drivers of the cost-effectiveness of remdesivir.

Methods

Model Development

A Markov model was developed to evaluate the cost-effectiveness of remdesivir in adult patients hospitalized with COVID-19 from a US healthcare sector perspective. A lifetime time horizon was used to capture potential long-term costs and outcomes with all future costs and outcomes discounted at 3% per year. Model outcomes included total costs, life-years, and quality-adjusted life-years (QALYs). Remdesivir was modeled as an addition to standard of care and compared with standard of care alone. Standard of care consisted of dexamethasone for patients requiring respiratory support in alignment with the World Health Organization’s clinical care guidance for COVID-19.18

A Markov model was used over a system dynamics model because remdesivir does not reduce COVID-19 transmission and is administered to patients who are already hospitalized and thus does not prevent hospitalizations. The Markov model consisted of 2 health states, alive and dead, with a 1-month cycle length. The first cycle of the Markov model corresponded to the COVID-19 hospitalization assessment period and differentiated the cohort based on the highest level of respiratory support required (eg, no supplemental oxygen, supplemental oxygen, noninvasive mechanical ventilation, or mechanical ventilation). Costs and health outcomes were assigned based on the highest level of respiratory support required. Patients who survived the COVID-19 hospitalization entered the second cycle of the Markov model in the alive health state and were followed over the lifetime time horizon using general population estimates for mortality, utility, and cost. General population estimates for healthcare costs were capped within each cycle to not exceed the lower bound of the cost-effectiveness thresholds report (ie, $50,000/QALY) based on the general population utility estimates used within that cycle. The purpose of this was to ensure that life extension would not exceed a potential cost-effectiveness threshold of $50,000/QALY gained. A detailed model description can be found elsewhere,19 and the model can be accessed through ICER AnalyticsTM.20

Model Assumptions

A summary of key model choices and assumptions are detailed in Table 1. Briefly, the analysis was from the healthcare sector perspective. A vial price of $520 was used for remdesivir, aligning with the price the manufacturer stated would be charged to private payers. Given the consistent failure of remdesivir to show a significant survival benefit associated with remdesivir, we did not assume a survival benefit associated with remdesivir in the base case of this analysis. We assumed the reimbursement for the hospitalization varied based on the highest level of respiratory support received, which most closely aligns with a bundled payment approach where an episode of care is reimbursed as a single payment.21 Finally, no ongoing cost or disutility associated with COVID-19 was applied after hospital discharge given the lack of robust data available on the frequency and magnitude of symptoms post-COVID infection.

Model Inputs

Key model inputs included baseline and highest ever levels of respiratory support received, effectiveness of remdesivir and standard of care, utility values, acquisition cost of remdesivir, and hospitalization costs. All inputs used to inform the model and their respective sources are detailed in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1378.

Population

Population characteristics and remdesivir efficacy differ by the severity of the patient population treated. Without current evidence on the composition of COVID-19 hospitalizations based on severity before receipt of treatment, we present results separately for the moderate to severe population (ie, those requiring respiratory support before receiving remdesivir) and the mild population (ie, those not requiring respiratory support before receiving remdesivir) to reflect the differing effect of remdesivir between these populations. In the moderate to severe population, we assumed population characteristics consistent with the pivotal Adaptive COVID-19 Treatment Trial (ACTT-1) trial.2 Patients with moderate to severe COVID-19 were older and had a higher risk of death from COVID-19.3 Evidence from ACTT-1 suggested remdesivir reduced the time to recovery, hospital length of stay, and the progression to more severe levels of respiratory support in patients with moderate to severe COVID-19.4 Although the hazard ratio of death for remdesivir was trending favorable, statistical significance was not achieved in either ACTT-1 or in a recent meta-analysis conducted by the Solidarity trial consortium.5,7 In the mild population, we assumed population characteristics similar to the pivotal trial in this population, NCT04292730.6 In patients with mild COVID-19, remdesivir has been shown to reduce the time to recovery.6 Similar to the moderate to severe population, the hazard ratio of death for remdesivir was trending favorable; nevertheless, statistical significance was not achieved in neither NCT04292730 nor a recent meta-analysis conducted by the Solidarity trial consortium.5,7

Analysis

We first estimated the deterministic cost-effectiveness of remdesivir plus standard of care versus standard of care alone using clinical effectiveness evidence identified from published literature. We conducted a one-way sensitivity analysis to identify the 3 most influential model inputs or assumptions and a probabilistic sensitivity analysis to access uncertainty in the cost-effectiveness findings. Given the evolving landscape of the COVID-19 pandemic and the frequent evidence updates, we conducted and present numerous scenario analyses to illustrate the variation in cost-effectiveness of remdesivir resulting from the top 3 inputs and assumptions. These scenario analyses included incorporating a survival benefit associated with remdesivir, varying the risk of death among standard of care to account for potential changes in the population infected and clinical care guidance, and assuming a per diem reimbursement structure in lieu of the bundled payment approach. For the scenario analysis that assumed a survival benefit associated with remdesivir, we used a hazard ratio of death of 0.91 in the moderate to severe population, which was the statistically nonsignificant hazard ratio of death reported in the largest meta-analysis of remdesivir’s effect on mortality at 30 days.17 In the mild population, we used a
Table 1. Rationale for model choices and assumptions.

| Model choice or assumption | Rationale |
|---------------------------|-----------|
| The perspective of our analysis focuses on costs to the healthcare payer. | The complexity of the societal impact of the COVID-19 pandemic challenges the ability to estimate the impact of a noncurative treatment on societal factors such as unemployment, taxes, and education. Further, it is unlikely that policy makers will find pricing that shifts societal economic benefits to a single life science company appropriate. |
| The price of remdesivir was $520 per vial and was in addition to the price of the COVID-19 hospitalization. | This price aligns with the price the manufacturer stated would be charged to private payers. The manufacturer announced a lower price for government-sponsored payers; nevertheless, because the government-sponsored price is only for those government payers who directly purchase remdesivir from the manufacturer, which represents a minority of government-sponsored payers in the United States, the private payer price was used in this analysis. Patients not receiving mechanical ventilation received 6 vials; patients receiving mechanical ventilation received 11 vials based on the FDA package insert. |
| Remdesivir is not associated with a survival benefit. | Neither individual trials nor a large meta-analysis suggested a significant improvement in survival associated with remdesivir. Extensive consideration of all the data and engagement with stakeholders informed this decision, and this assumption was tested in a scenario analysis. |
| The COVID-19 hospitalization would be reimbursed as a bundled payment that varied based on the level of respiratory support received. | This most closely aligns with a bundled payment approach where an episode of care is reimbursed as a single payment. In a scenario analysis, we modeled the reimbursement for the hospitalization based on a per diem payment structure. |
| No ongoing cost or disutility associated with COVID-19 was applied after hospital discharge. | We do not attempt to quantify long-term sequelae in the results for numerous reasons, including a lack of consensus on a standardized definition and duration of long COVID-19, mixed estimates of the percentage of patients who experience long COVID-19, no data on the influence of remdesivir on long COVID-19, no data to suggest long COVID-19 differs by time to recovery, and currently available data originating from small samples. Primarily, we do not quantify long COVID-19 in our analyses because it would not be a key driver of the findings for the cost-effectiveness of remdesivir. |

FDA indicates Food and Drug Administration.

hazard ratio of death of 0.804. This estimate was calculated from the recently conducted meta-analysis but only included those studies with patients with mild COVID-19.27,28 Because current clinical and epidemiological evidence for COVID-19 suggest the average age of those who die of COVID-19 is higher than the average age of those hospitalized with COVID-19,27 the model allowed for the average age of the treated population to differ from the average age of the population who died of COVID-19. When a survival benefit is observed, this results in a different average age for those who recovered between the intervention and comparator arms. The estimated age for those who recovered, by treatment arm, was used as the starting age for the second cycle of the Markov model.

Results

Deterministic Analysis

Using the deterministic model inputs and our base-case assumptions of no survival benefit and a bundled hospitalization payment, the incremental cost per QALY for remdesivir was $298,200/QALY for the moderate to severe population and $1,847,000/QALY for the mild population (Table 2). In the moderate to severe population, remdesivir was associated with fewer hospitalization costs (savings of approximately $2200) from reducing the progression of some patients to more severe levels of respiratory support and thus avoiding a more expensive bundled payment; nevertheless, the treatment cost of approximately $4000 outweighed these savings. There were very small improvements in quality of life (and thus small QALYs gained) associated with a quicker time to recovery in the mild and moderate to severe populations and differences in the respiratory support required in the moderate to severe population; nevertheless, without an increase in survival (ie, life-years), the gain in QALYs was small for both populations.

Sensitivity and Scenario Analyses

A one-way sensitivity analysis suggested that the survival benefit associated with remdesivir, the probability of death among the standard of care, and the amount paid for the COVID-19 hospitalization were the 3 most influential model parameters on the results. The cost-effectiveness estimates for remdesivir assuming there was a survival benefit associated with remdesivir similar to the estimates reported in the meta-analysis conducted by the Solidarity trial consortium are presented in Table 3.7 This translates to cost-effectiveness estimates within commonly used value thresholds of $50,000/QALY to $150,000/QALY gained. Scatterplots from the probabilistic analyses are available for this scenario analysis in Appendix Figures 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1378.
The cost-effectiveness also varies as the risk of death among standard of care treated patients changes. Assuming remdesivir is associated with a survival benefit, the cost-effectiveness becomes more favorable as the risk of death for standard of care increases. The results of a two-way sensitivity analysis that varies the standard of care mortality across various hazard ratios of death are presented in Figure 1. Using a remdesivir hazard ratio of death of 0.91 equivalent to the nonsignificant point estimate from a meta-analysis conducted by the Solidarity trial consortium,7 the standard of care mortality in those eligible for treatment with remdesivir would need to be 3% to generate cost-effectiveness estimates, $100 000/QALY gained.

The influence of hospital payment on cost-effectiveness is dependent on how hospitalizations are reimbursed. Under an assumption that hospitalizations are paid as a bundled payment dependent on the level of respiratory support required, as in our base-case analysis, the cost-effectiveness of remdesivir becomes more favorable when more costly hospitalization bundled payments are prevented (eg, preventing the progression to a hospitalization that includes mechanical ventilation). Under a per diem hospitalization reimbursement structure, the value profile for remdesivir improves if there is a length of stay improvement associated with the treatment. The incremental cost-effectiveness ratio for remdesivir assuming a per diem reimbursement structure in the moderate to severe population is presented in Figure 2. Even without a survival benefit, reductions in length of stay can produce relatively favorable cost-effectiveness estimates when the per diem for a hospitalization is $600. A study published in 2020 estimated the costs per day of hospitalizations for a patient with influenza or viral pneumonia, as a proxy for a COVID-19 hospitalization.23 The authors reported a per diem cost of between $475 and $668 for the Medicare population (which would generate cost-effectiveness estimates $100 000/QALY) and a per diem cost of between $2158 and $3900 in the commercial population (which would generate cost saving estimates).23 Significant reductions in length of stay were not observed in the mild COVID-19 population, and therefore, changes in per diem cost would not be as influential in this population.

### Table 2. Cost-effectiveness of remdesivir compared with standard of care, base-case analysis.

| Population          | Remdesivir costs, $ | Hospitalization costs, $ | Other healthcare costs, $ | Total QALYs* | ICER ($/QALY), $ | Value-based price, $*† |
|---------------------|---------------------|--------------------------|--------------------------|--------------|------------------|------------------------|
| Moderate to severe  |                     |                          |                          |              |                  |                        |
| population          |                     |                          |                          |              |                  |                        |
| Remdesivir + SoC    | 3989                | 36 694                   | 272 764                  | 12.189       | $298 200         | 2470-3080              |
| SoC                 | 0                   | 38 853                   | 272 764                  | 12.182       |                  |                        |
| Incremental         | 3989                | –2159                    | 0                        | 0.006        |                  |                        |
| Mild population     |                     |                          |                          |              |                  |                        |
| Remdesivir + SoC    | 2746                | 12 913                   | 302 716                  | 13.702       | 1 847 000        | 70-220                 |
| SoC                 | 0                   | 12 913                   | 302 716                  | 13.701       |                  |                        |
| Incremental         | 2746                | 0                        | 0                        | 0.001        |                  |                        |

*Given no survival benefit, the life-years were the same for the intervention and SoC arm, equating to 15.164 life-years in the moderate to severe population and 16.995 life-years in the mild population.
†Value-based prices reported are for a range of thresholds from $50 000/QALY to $150 000/QALY.

Note. SoC includes dexamethasone for patients requiring respiratory support. ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care.

### Table 3. Cost-effectiveness of remdesivir, assuming a survival benefit.

| Population          | Remdesivir costs, $ | Hospitalization costs, $ | Other healthcare costs, $ | Total LYs | Total QALYs | ICER ($/QALY), $ | Value-based price, $* |
|---------------------|---------------------|--------------------------|--------------------------|-----------|-------------|------------------|------------------------|
| Moderate to severe  |                     |                          |                          |           |             |                  |                        |
| population          |                     |                          |                          |           |             |                  |                        |
| Emerging therapy + SoC | 3989                | 36 694                   | 275 717                  | 15.281    | 12.278      | 50 100           | 4000-13 500            |
| SoC                 | 0                   | 8 853                    | 272 764                  | 15.164    | 12.182      |                  |                        |
| Incremental         | 3989                | –2159                    | 2953                     | 0.117     | 0.095       |                  |                        |
| Mild population     |                     |                          |                          |           |             |                  |                        |
| Emerging therapy + SoC | 2746                | 12 913                   | 303 942                  | 17.043    | 13.739      | 103 400          | 700-4600               |
| SoC                 | 0                   | 12 913                   | 302 716                  | 16.995    | 13.701      |                  |                        |
| Incremental         | 2746                | 0                        | 1226                     | 0.049     | 0.039       |                  |                        |

*Value-based prices reported are for a range of thresholds from $50 000/QALY to $150 000/QALY.

Note. SoC includes dexamethasone for patients requiring respiratory support. ICER indicates incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SoC, standard of care.

*Value-based prices reported are for a range of thresholds from $50 000/QALY to $150 000/QALY.
likely not cost-effective at current prices. Large discounts are needed off the remdesivir list price to align the price with expected clinical value and commonly cited value thresholds. Nevertheless, we acknowledge that the landscape of this pandemic is constantly evolving (eg, different patient population infected, clinical care guidance improving standard of care) and new evidence and innovation are flowing at rapid paces. Conceivable updates to the model inputs and model assumptions, such as a small survival benefit associated with remdesivir, can generate cost-effectiveness estimates within commonly cited value thresholds. For this reason, we discuss key drivers of value to guide current and future reimbursement for remdesivir.

This analysis illustrated how the value of remdesivir is greatly influenced by and directionally increases under the following circumstances: (1) when the therapeutic is associated with a significant survival benefit, (2) when the therapeutic is used in a more severely ill population that is at a greater risk of poor clinical outcomes and high healthcare costs, and (3) when the therapeutic significantly improves time to recovery and this time is valued within the analysis beyond a patient’s utility gains. In this discussion, after featuring each of the abovementioned lessons learned, we will expand upon the findings from this study by examining 2 COVID-19 therapeutic value assessment framing options. We will then characterize the debate around the measurement and use of a societal perspective analysis for COVID-19 therapeutics and the debate around an appropriate threshold for COVID-19 therapeutics.

When we assumed a survival benefit for remdesivir, the incremental cost-effectiveness ratio was reduced by 83% to 95%, which was largely driven by larger QALY gains in this scenario. Furthermore, the severity of the population is important for COVID-19 therapeutics for at least 2 reasons. As supported by Figure 1, a treatment’s absolute difference in patient health is influenced by not only its mortality hazard ratio but also its background rate of mortality (as measured through the comparator). Furthermore, the severity of the treatment population had an impact on remdesivir’s cost-effectiveness findings. If remdesivir is used in a population with less severe illness, the potential mortality benefit will be attenuated, making the treatment less cost-effective. If remdesivir use expands to broader populations outside of those hospitalized, cost-effectiveness questions will depend upon the eligible treated population’s background risk of hospitalization, long-term complications, and mortality. Finally, our analyses suggested that valuing hospitalization time through a per day rate rather than a bundled payment by level of hospital care resulted in large cost-effectiveness changes for a COVID-19 treatment that reduces the duration of hospitalization stays (Fig. 2). COVID-19 hospitalization paid amounts were not observable at the time of our analysis. We recommend COVID-19 hospitalization cost studies that analyze economic impacts of hospitalization severity and duration to reduce the uncertainty in cost-effectiveness findings.

For COVID-19 and non–COVID-19 therapeutics, and consistent with best practices in the field,26 we advocate for value assessment analyses from the healthcare sector perspective and, depending on the availability of evidence, from the societal perspective.26 This article focuses on the healthcare sector perspective. At the time of our remdesivir analyses, we did not have evidence on changes in productivity or other societal costs because of remdesivir. Nevertheless, it was clear that remdesivir was not a cure for COVID-19, nor was it effective enough to have an impact on societal decisions on school openings, social distancing guidelines, etc. Future therapeutics may be able to have these types of broader effects. For COVID-19 therapeutics, a societal perspective may include their impact on hospitalization capacity,
medical staff resilience, and the ability for an economy to avoid lockdowns. The attribution of a particular COVID-19 therapeutic’s impact on reducing hospitalization beds may be measurable through randomized controlled trials, whereas changes to the economy will be more challenging to attribute to a particular therapeutic. Just as background mortality changes through the course of a pandemic, so might these broader societal attributes change. We call on the value assessment research community to develop further best practices around background characteristic dynamics to aid in decision making around conventionally static drug pricing. In this analysis, we supported pricing for remdesivir based on the healthcare sector perspective given the magnitude of its clinical benefits known at the time of the analysis and no evidence regarding productivity effects on individual patients after hospital discharge. Others feel differently.

Finally, research on appropriate cost-effectiveness thresholds is beginning to converge around $100 000/QALY in the United States from recent willingness-to-pay and opportunity cost approaches. Unique COVID-19 therapeutic factors could suggest that an appropriate threshold for US payers may be above, below, or in line with $100 000/QALY. Given the huge potential budget impact policy makers would face with treatment during a pandemic, the government investment in prioritizing COVID-19 interventions, and the uncertainty in the mortality benefits of remdesivir at the time of our analysis—an uncertainty that continues—we suggested an interpretation of cost-effectiveness findings at the lower end of conventional threshold ranges.

Limitations

Remdesivir may reduce utilization within the hospitalization stay (e.g., fewer days, fewer ventilators). This Markov model accounts for the reduction in utilization at the patient level by way of quality of life and costs; nevertheless, it does not include how this reduction in utilization could influence hospital capacity. The model described patients undergoing a COVID-19 therapeutic while hospitalized. Although interventions administered to outpatients are now available, they were not presented as cases in this article. Further, the use of remdesivir in the outpatient population was not examined in this analysis. Finally, our analysis did not account for any long-term sequelae of COVID-19 and instead assumed that patients returned to age-adjusted utility values characteristic of the general population. Our analysis did not incorporate consequences of long COVID-19 for numerous reasons. First, no evidence has suggested that treatment with remdesivir influences long COVID-19 or that long COVID-19 is improved with a quicker time to recovery among hospitalized patients. In addition, there is a lack of consensus on a standardized definition and duration of long COVID-19, there are widely varying estimates of the percentage of patients who experience long COVID-19, and currently available data originate from very small sample sizes. Even if an estimate of the occurrence of long COVID-19 was included in our base-case analysis, the incremental findings would not have been substantially different given the probability of recovery was the same with and without remdesivir. If we were to include long COVID-19 in our scenario analysis assuming a survival benefit, the incremental QALY gains would likely be modestly smaller given that additional patients surviving to hospital discharge in the remdesivir treated pathway would not have returned to general population utilities. Nonetheless, decision makers should consider long COVID-19 as an important contextual consideration when evaluating the value of remdesivir and other emerging COVID-19 therapeutics.

Conclusions

The coronavirus pandemic has put a magnifying glass on drug pricing as the world sits back from a social distance to observe evidence emerge on innovative therapeutics and vaccines and then waits to see what the asking price will be. Although the COVID–19 pandemic has changed the way we do nearly everything, the use of cost-effectiveness to inform a ceiling price for a therapeutic remains relevant even during a pandemic. This study uses cost-effectiveness analyses to suggest a range of value-based prices for remdesivir. Results from this study can focus future evidence generation activities for dynamic COVID–19 therapeutic value assessment.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.11.1378.

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