Advances in Infectious Diseases & Therapy

Research Article

Evolving Pattern of Remdesivir Prescribing During the COVID-19 Pandemic: Outcome and Cost Implications

Anthony Sophonsri[1,2], Pamela Ny[2], Paul Nieberg[3], Annie Wong-Beringer[1,2,*]

[1]*Department of Clinical Pharmacy, University of Southern California (USC) School of Pharmacy, Los Angeles, USA.*
[2]*Department of Pharmacy, Huntington Hospital, Pasadena, USA.*
[3]*Department of Medicine – Infectious Diseases, Huntington Hospital, Pasadena, USA.*

ABSTRACT

Purpose: Remdesivir has become a part of the treatment standard for patients hospitalized with COVID-19 since its initial availability under the Expanded Access Program in March 2020. Here, we describe our evolving experience with remdesivir utilization during the pandemic.

Methods: Medical records of patients prescribed remdesivir during March to December 2020 at a community teaching hospital were reviewed for baseline characteristics, clinical presentation and management, outcomes, and cost of remdesivir treatment. The pattern of remdesivir prescribing was compared pre- and post-formulary addition of the drug for use in hospitalized COVID-19 patients.

Results: Criteria for remdesivir use evolved from requiring mechanical ventilation to requiring low oxygen supplementation during the study period. A 3.5-fold increase in remdesivir use outside of criteria was observed after formulary addition when much of the prescribing was shifted from Infectious Diseases (ID) and Pulmonary Critical Care Medicine (PCCM) to the Internal Medicine service. Compared to Pre-formulary patients, Post-formulary patients had lower requirements for oxygen supplementation and more achieved early clinical response with <5 days of remdesivir (29.7% vs. 9.2%, p<0.0001), had significantly shorter time to stability (median 4 vs. 6.5 days, p<0.0001) and length of stay (6 vs. 10 days, p<0.0001), and lower mortality (9.9% vs. 15.5%, p=0.19). None of the patients who achieved early response and received <5 days of remdesivir had a COVID-related readmission or emergency department (ED) visit within 30 days. Potential cost savings per 100 patients is estimated at $35,000 with strict adherence to criteria and an additional $15,444 when treatment duration is shortened to 4 days in the early responders.

Conclusion: Prescribing of remdesivir outside of criteria increased after it was no longer restricted to ID or PCCM specialists upon formulary addition. Provider education is needed to improve adherence to criteria-based prescribing. Shortening treatment duration in early responders can lessen healthcare resource utilization and cost without negatively impacting patient outcomes.

KEYWORDS

COVID-19; SARS-CoV-2; Remdesivir; Resource Allocation; Cost Savings.

Corresponding Author Information

Annie Wong-Beringer
PharmD, FIDSA, University of Southern California, School of Pharmacy, 1985 Zonal Avenue, Los Angeles, CA 90089; Email: anniew@usc.edu.

Received: August 10, 2022; **Accepted:** September 18, 2022; **Published:** September 22, 2022

Citation: Anthony Sophonsri, Pamela Ny, Paul Nieberg, Annie Wong-Beringer. Evolving Pattern of Remdesivir Prescribing During the COVID-19 Pandemic: Outcome and Cost Implications. Advances Infec Diseases Therapy. 2022;1(1):1-7.

Introduction

Coronavirus disease (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first outbreak in Wuhan in 2019, COVID-19 has spread rapidly bringing about a global pandemic. To date, there have been over 160 million confirmed cases with a death toll over 3.3 million worldwide [1]. Of the countries most affected by the pandemic, the United States remains at the top with over 32 million confirmed cases and over 580,000 deaths. Clinical presentation of COVID-19 varies from asymptomatic to severe acute respiratory distress and multiorgan failure–the latter resulting from a dysregulated host immune response [2].

Over the past year, an overwhelming amount of research has been undertaken to understand the pathogenesis and spread of SARS-CoV-2 in search for effective vaccines and treatment options. Several antiviral agents with potential promise from past viral outbreaks have been identified and repurposed for use against SARS-CoV-2 [3]. To date, remdesivir is the only FDA approved agent for the treatment of COVID-19 [4]. It is an antiviral agent first discovered to have activity against the Middle East Respiratory Syndrome (MERS) and first Severe Acute Respiratory Syndrome (SARS) coronaviruses *in vitro* as well as *in vivo* in animal models [5-7]. Results from the Adaptive COVID-19 Treatment Trial-1 (ACTT-1) suggest that remdesivir improves time to recovery by 5 days in patients with COVID-19 (median 10 d vs. 15 d, $p<0.001$), with the greatest benefit in those requiring low oxygen supplementation (not requiring high flow nasal cannula or mechanical ventilation) [8]. Notably, during a time of limited resources with surges in COVID-19 cases requiring hospitalization, the recommended duration of remdesivir therapy was shortened from 10 days to 5 days based on results from the SIMPLE trial indicating no difference in time to recovery or mortality [9]. Remdesivir has been integrated into the standard treatment protocol in patients hospitalized for COVID-19 without severe renal or liver dysfunction. While treatment with remdesivir has been shown to improve recovery time, it lacks survival benefit. Thus, it is unclear whether continuation of remdesivir treatment provides any benefit in patients who achieve early clinical response prior to completion of the 5-day course. Here, we report our evolving experience on remdesivir utilization, its impact on patient outcomes, and cost implications during a period of significant resource scarcity.

Methods

Study Design

This study was performed at a 625-bed community teaching hospital in Pasadena, CA, USA during the period of March 1, 2020 – December 15, 2020. The study protocol was approved by the institutional review board. Informed consent was waived as this was an observational study. Hospitalized adult patients (≥ 18 years) with COVID-19 pneumonia confirmed by SARS-CoV-2 PCR who received ≥1 dose of remdesivir were eligible for inclusion.

Patients who received remdesivir between March 1 and November 19, 2020 were included in the 'Pre-Formulary' cohort. Patients who received remdesivir from November 20 to December 15, 2020 were included in the 'Post-formulary' cohort. The 'Pre-formulary' cohort received remdesivir under the Expanded Access Program (EAP) or Emergency Use Authorization (EUA). Under the EAP, patients who required invasive mechanical ventilation were eligible for remdesivir on a case by case basis. On May 1, 2020, the Food & Drug Administration (FDA) approved remdesivir for use under an EUA in which patients with O_2 saturation ≤ 94% on room air and required supplemental oxygen support were eligible for remdesivir. During the Pre-formulary period, prescribing of remdesivir under the EAP or EUA was restricted to Infectious Diseases (ID) and Pulmonary Critical Care Medicine (PCCM) specialties. Remdesivir was later added to the hospital formulary on November 19, 2020 for use as a 5-day treatment course in patients who tested positive for SARS-CoV-2 with the same criteria for use as the EUA: 1.) O_2 saturation ≤ 94% on room air and 2.) requiring supplemental oxygen support. Upon formulary addition, prescribing of remdesivir was made available to all specialties.

The medical records of study patients were reviewed for pertinent clinical information: demographics, comorbid conditions, oxygenation status, treatment and clinical response. Duration of hospital stay and disposition at discharge were also recorded. Study data were managed using the REDCap electronic data capture software hosted at the University of Southern California. REDCap is a secure, web-based platform designed for data capture in research studies [10].

Definitions

A clinical response was defined as achieving clinical stability based on resolution of fever, tachycardia, tachypnea, hypotension, and hypoxia without the use of oxygen supplementation, and return of mental status to baseline. Early clinical response was defined as having achieved clinical stability prior to completing a 5-day course of remdesivir. Use of low oxygen supplementation was defined as requiring nasal cannula, oxymizer, or a non-rebreather mask at ≤15L/min. High flow oxygen supplementation was defined as requiring high flow nasal cannula >15L/min. Invasive mechanical ventilation was defined as requiring endotracheal intubation. A COVID-19 related readmission or emergency department (ED) visit was defined as a subsequent hospital admission or an ED encounter for new, persistent, returning, or worsening COVID-19 related symptoms (fever, cough, dyspnea, fatigue, myalgia, rhinorrhea, nausea or vomiting, and altered mental status).

Data Analysis

Overall prescribing details including prescriber specialty and adherence to institutional criteria for use were compared between cohorts. Outcome measures were compared only on patients who met criteria for remdesivir use in the Pre- and Post-formulary groups: time to achieve clinical response, hospital length of stay, mortality, and 30-day COVID-19-related readmissions or ED visit. Cost analysis was performed based on drug acquisition cost alone using a 5-day regimen as the standard duration of remdesivir

therapy. Due to the shortage of hospital beds during the December 2020 surge of COVID-19 cases, additional details on the reason for discharge delay and disposition from the hospital were also compared. Univariate analysis was performed using Mann-Whitney U or Student t-test for continuous data and Fisher's exact or chi-square test for categorical data where appropriate. All statistical tests were 2-tailed and a p-value <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism v9.0 (San Diego, CA, USA).

Results

Study Population

A total of 352 patients received remdesivir treatment between March 1, 2020 and December 15, 2020. Baseline demographics were shown to be similar between the Pre- and Post-formulary groups. (**Table 1**). The median age was 64 years and 56% were male. Overall, 90.9% were admitted from home and 7.4% were from a skilled nursing facility (SNF). The most common comorbid condition was hypertension (50.9%), followed by diabetes (33%), dyslipidemia (26.4%), chronic kidney disease (6.8%), and dementia (5.1%).

Remdesivir Utilization

An overview of COVID-19 admissions, evolving trends in treatment prescribed, and death rate are depicted in **Figure 1**. The rate of Post-formulary remdesivir utilization coincided with the recent surge in COVID-19 cases and was 1.7-fold higher compared to drug access through EAP or EUA during the Pre-formulary period (61.9%, 104/168 vs. 36%, 248/688). During the Pre-formulary period, remdesivir was exclusively prescribed by ID or PCCM services (**Table 2**). In contrast, the majority of remdesivir orders in the Post-formulary group were prescribed by the Internal Medicine service (76.0%), followed by ID or PCCM (24.0%). At the start of therapy, fewer patients in the Post-formulary group required high-flow nasal cannula (5.8% vs. 16.9%, p=0.0053) or invasive mechanical ventilation (2.9% vs. 19.8%, p<0.0001). Additionally, there were significantly more Post-formulary patients on room air (12.5% vs. 3.6%, p=0.0017) prior to remdesivir initiation, thus not meeting institutional criteria for use. The median duration of therapy was 5 days in both groups.

Nearly all patients in the entire study cohort received concomitant corticosteroids (91.5%, 322/352); however, a significantly greater proportion of patients received corticosteroids in the Post-

Characteristics		Total (N=352)	Pre-formulary (n=248)	Post-formulary (n=104)	p-value
Median [IQR] age, yr		64 [50, 73]	64 [50, 72]	63 [50, 76]	0.48
Male (%)		197 (56.0)	140 (56.5)	57 (54.8)	0.77
Residence prior to admission					
	Home (%)	320 (90.9)	230 (92.7)	90 (86.5)	0.15
	SNF/LTAC (%)	26 (7.4)	14 (5.6)	12 (11.5)	
	Unknown/other (%)	6 (1.7)	4 (1.6)	2 (1.9)	
Comorbidities					
	Hypertension (%)	179 (50.9)	131 (52.8)	48 (46.2)	0.25
	Diabetes (%)	116 (33.0)	85 (34.3)	31 (29.8)	0.42
	Dyslipidemia (%)	93 (26.4)	70 (28.2)	23 (22.1)	0.24
	Chronic kidney disease (%)	24 (6.8)	13 (5.2)	11 (10.6)	0.070
	Dementia (%)	18 (5.1)	9 (3.6)	9 (8.7)	0.051

Note: SNF = skilled nursing facility, LTAC = long-term acute care facility.

Table 1: Patient Demographics.

Characteristics		Total (N=352)	Pre-formulary (n=248)	Post-formulary (n=104)	p-value
Prescribing service					
	Internal Medicine (%)	79 (22.4)	0 (0)	79 (76)	<0.0001
	ID/PCCM (%)	273 (77.6)	248 (100)	25 (24)	
Criteria not met					
	Not requiring O_2 supplementation (%)	22 (6.3)	9 (3.6)	13 (12.5)[a]	0.0017
	SpO_2 >94% on room air (%)	6 (1.7)	4 (1.6)	2 (1.9)	0.84
Oxygenation status at start of therapy[b]					
	Room air (%)	22 (6.3)	9 (3.6)	13 (12.5)	0.0017
	Low O_2 supplementation (%)	222 (63.1)	141 (56.9)	81 (77.9)	0.0002
	High flow O_2 supplementation (%)	48 (13.6)	42 (16.9)	6 (5.8)	0.0053
	Invasive mechanical ventilation (%)	52 (14.8)	49 (19.8)	3 (2.9)	<0.0001
Median [IQR] DOT, days		5 [5,5]	5 [5, 5]	5 [5, 5]	
Concomitant corticosteroids (%)		322 (91.5)	221 (89.1)	101 (97.1)	0.014

NOTE: ID = Infectious Diseases, PCCM = Pulmonary Critical Care Medicine, DOT = duration of therapy.

[a]Services prescribing to patients NOT meeting criteria: Infectious Diseases (4/13), Internal Medicine (9/13)

[b]Oxygen supplementation: nasal cannula, non-rebreather mask, or oxymizer ≤15L/min; High flow oxygen supplementation: high flow nasal cannula >15L/min; Invasive mechanical ventilation: endotracheal intubation

Table 2: Remdesivir Utilization.

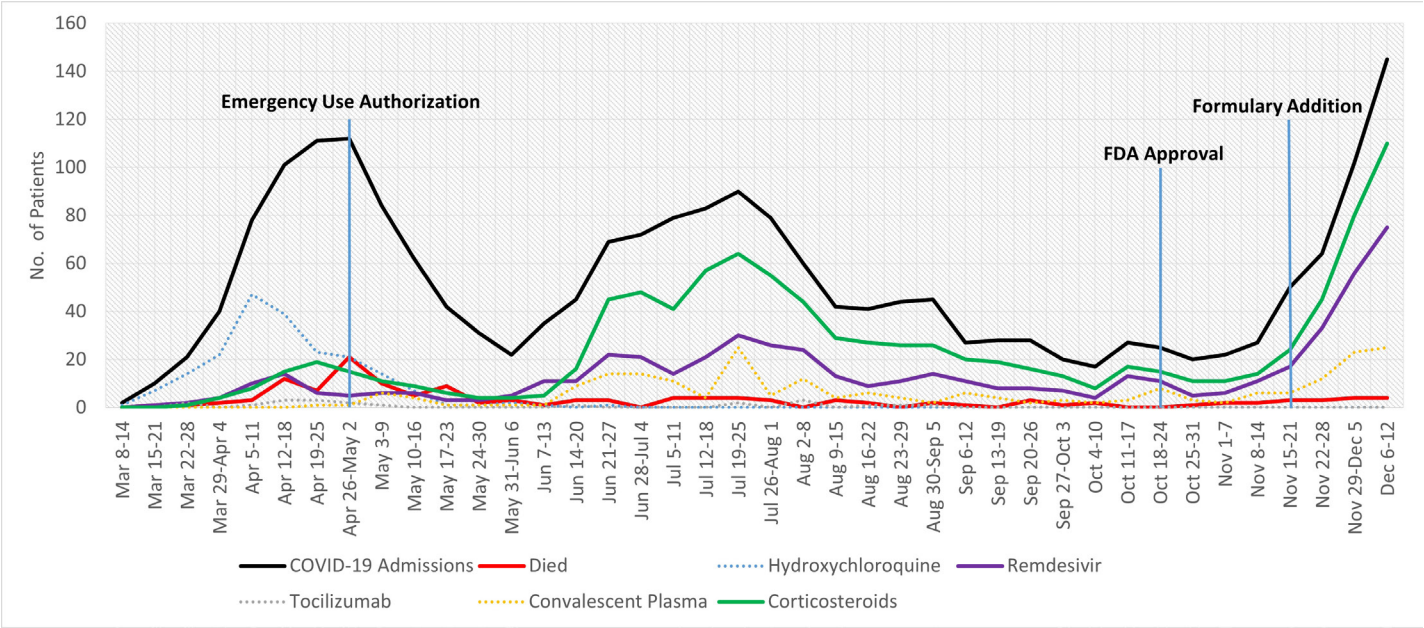

Figure 1: Overview of COVID-19 Admissions, Treatments, and Death Rate Between March and December 2020.

COVID-19 cases surged in March, June, and December 2020. Prior to May 1, 2020, remdesivir was only available through the Expanded Access Program (EAP) wherein only invasive mechanically ventilated patients could apply for compassionate use. Since then, remdesivir was approved for Emergency Use Authorization (EUA) where all patients with $SpO_2 \leq 94\%$ on room air and requiring oxygen supplementation could receive remdesivir. On October 22, 2020, remdesivir was approved by the FDA for use in all hospitalized patients with COVID-19. Remdesivir was added to the hospital formulary on November 19, 2020 for the treatment of COVID-19 in hospitalized patients with $SpO_2 \leq 94\%$ on room air and requiring oxygen supplementation.

compared to Pre-formulary group (97.1% vs. 89.1%, p=0.014) as well as in the subset of patients who met criteria (97.8% vs. 89.5%, p=0.014). Notably, in an exploratory subanalysis of Pre-formulary patients, corticosteroid administration was significantly higher among patients admitted after release of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial preliminary results on June 16, 2020 which showed survival benefit with dexamethasone administration compared to those admitted pre-release (98.4% vs. 53.2%, p<0.0001) and was associated with lower mortality (11.5% vs. 31.9%, p=0.0005).

Clinical Outcomes for Patients Meeting Criteria for Use

A lower proportion of patients met criteria for remdesivir use in the Post- compared to the Pre-formulary group (87.5%, 91/104 vs. 96.4%, 239/248, respectively, p=0.0017). Those patients not meeting criteria were excluded from the following analyses. Outcomes appeared more favorable in the Post- compared to the Pre-formulary group (**Table 3**): more patients achieved early clinical response (defined as achieving clinical stability prior to completion of 5 days of remdesivir therapy) (29.7% vs. 9.2%, p<0.0001), shorter median time to stability (TTS) (4 days vs. 6.5 days, p<0.0001) and length of stay (6 days vs. 10 days, p<0.0001), and a trend towards lower mortality (9.9% vs. 15.5%, p=0.19). When patients were stratified by their residence prior to admission, mortality was 8 times higher for patients who presented from a skilled nursing facility compared to those presenting from home (50.0% vs. 10.8%, OR 8.3, 95% CI 3.3-20.4, p<0.0001) despite receiving remdesivir therapy.

Among all survivors, more Post-formulary patients achieved clinical stability (51.6% vs. 40.2%, p=0.06) by the time of hospital discharge. For those who did not achieve clinical stability, nearly all required oxygen supplementation on the day of discharge (92.9%, 130/140). Discharge disposition was similar between groups; most were discharged to home (73.3%), followed by SNF/long-term acute care facility (LTAC) (8.8%) (**Table 4**). The proportion of patients who experienced discharge delays despite achieving clinical stability were similar between the Pre- and Post-formulary groups (20.2% vs. 28.8%, p=0.0761). A majority of the discharge delays were due to completion of remdesivir therapy in the Post-formulary group (73.3% vs. 32.0%, p=0.0003) whereas, discharge planning accounted for a greater proportion of discharge delays in the Pre-formulary group (20.0% vs. 0.0%, p=0.0088). Rates of COVID-19-related readmissions or ED visits within 30 days were relatively low during both Pre- and Post-formulary periods (6.1% vs. 9.4%, p=0.36) (**Table 3**). Notably, in the subset of survivors (n=15) who achieved early clinical response and received <5 days of remdesivir, none were readmitted or required ED visits within 30 days.

Cost Analysis in Post-formulary Patients

In the 12.5% (n=13) of patients who did not meet criteria for use, 13 loading doses (200 mg) and 44 maintenance doses (100 mg) were administered at a drug acquisition cost of $520 per 100 mg vial, totaling $36,400 during this study period. A projected savings of $35,000 per 100 patients receiving remdesivir was estimated if remdesivir were prescribed for patients meeting criteria. Considering that 30% of Post-formulary patients achieved early

Outcomes	Total N=330 (%)	Pre-formulary N=239 (%)	Post-formulary N=91 (%)	p-value
Clinical response (%)	143 (43.3)	96 (40.2)	47 (51.6)	0.060
Early response (%)	49 (14.8)	22 (9.2)	27 (29.7)	<0.0001
Median [IQR] TTS, days	6 [4, 10]	6.5 [5,12]	4 [2, 6]	<0.0001
Expired (%)	46 (13.9)	37 (15.5)	9 (9.9)	0.19
LOS, median [IQR], d	8 [6, 14]	10 [7, 17]	6 [5, 8]	<0.0001
O_2 supplementation at discharge, non-responders (%)	130/140 (92.9)	96/106 (90.6)	34/35 (97.1)	0.21
Home O_2 supplementation at discharge (%)	115/284 (40.5)	86/202 (42.6)	29/82 (35.4)	0.26
30-day COVID-related readmission/ED visit (%)[a]	24/284 (8.5)	19/202 (9.4)	5/82 (6.1)	0.36
30-day COVID-related readmission/ED visit in early remdesivir discontinuation (%)	0/15 (0)	0/4 (0)	0/11 (0)	

NOTE: TTS = time to stability, LOS = length of stay.

[a]Pre-formulary group: 16 readmissions, 3 ED visits; Post-formulary group: 2 readmissions, 3 ED visits.

Table 3: Clinical Outcomes for Patients Meeting Criteria for Use.

Outcomes	Total N=352 (%)	Pre-formulary N=248 (%)	Post-formulary N=104 (%)	p-value
Delays in discharge	80 (22.7)	50 (20.2)	30 (28.8)	0.076
Treatment completion	38 (47.5)	16 (32.0)	22 (73.3)	0.0003
Extended monitoring	15 (18.8)	12 (24.0)	3 (10.0)	0.12
Comorbidities	12 (15.0)	8 (16.0)	4 (13.3)	0.75
Discharge planning	10 (12.5)	10 (20.0)	0 (0)	0.0088
Co-infections	5 (6.3)	4 (8.0)	1 (3.3)	0.40
Discharge disposition				
Home	258 (73.3)	176 (71.0)	82 (78.8)	0.13
SNF/LTAC	31 (8.8)	24 (9.7)	7 (6.7)	0.37
Other acute care facility	14 (4.0)	10 (4.0)	4 (3.8)	0.94
Unknown	3 (0.9)	1 (0.4)	2 (1.9)	0.16

NOTE: SNF = skilled nursing facility, LTAC = long-term acute care facility.

Table 4: Discharge Outcomes.

clinical response prior to completion of remdesivir 5-day therapy, a reduction in treatment duration from 5 days to 4 days yielded a projected cost savings of an additional $15,444 for every 100 patients receiving remdesivir.

Discussion

We herein described an evolving pattern of remdesivir prescribing during the COVID-19 pandemic with outcome and cost implications. This retrospective analysis identified a 3.5-fold increase in non-evidence based use of remdesivir after formulary addition in patients not requiring supplemental oxygen, when prescribing was no longer restricted to ID or PCCM specialists. Of the patients whose use met criteria during the Post-formulary period, nearly a third had achieved clinical stability in less than 5 days. Despite early clinical response, a notable portion of patients (21.2%, 22/104) remained hospitalized to complete the 5-day treatment course resulting in delays in discharge in the Post-formulary group. On the other hand, it is notable that in a small subset of early responders, a treatment course of less than 5 days did not result in any COVID-19-related readmissions or ED visits within 30 days. Our findings suggest that it is reasonable to shorten the duration of remdesivir in patients with early clinical response to facilitate prompt discharge during a surge without impacting clinical outcomes. Additionally, restricting use of remdesivir to the approved criteria and shortening treatment duration in early responders could have implications in cost reduction and effective resource allocation.

Although remdesivir has been approved for all hospitalized patients with COVID-19, a subgroup analysis of the ACTT-1 trial showed that remdesivir was only effective in patients requiring low oxygen supplementation [4,8]. Results of this trial provided the basis for our institutional use criteria which reserved the use of remdesivir for patients with an O_2 saturation ≤ 94% on room air and requiring oxygen supplementation. However, once remdesivir was added to the institution's formulary and specialties outside of ID and PCCM were given authorization to prescribe remdesivir, we observed a 3.5-fold increase in remdesivir utilization in patients not requiring oxygen supplementation, thus not meeting criteria. Of the 13 Post-formulary patients who did not meet criteria for use, 12 (92.3%) remained on room air throughout their entire hospital stay. The increase in remdesivir use outside of the approved criteria temporally corresponded to the shift in prescribing towards the Internal Medicine service. Our findings highlight the necessity of provider education on prioritizing patients on low oxygen supplementation as the group most likely to benefit from remdesivir. In particular, at a time when resources are scarce, adherence to the approved criteria would allow institutions to maximize the benefits of the medication for the greatest number of patients.

It is important to note that the criteria for use of remdesivir changed in the first 2 months of the Pre-formulary period from EAP to EUA. Prior to the EUA in May 2020, only patients needing invasive mechanical ventilation could receive remdesivir under the EAP. Although the criteria for use under the EUA and Post-formulary addition were identical, the requirement for needing invasive mechanical ventilation for use of remdesivir under EAP early during the Pre-formulary period likely accounted for the disparities in disease severity between groups. As new evidence emerged, trends in treatment modalities have evolved as well (**Figure 1**). With the release of preliminary results from the RECOVERY trial (June 16, 2020) showing reduction in 28-day mortality with dexamethasone, use of corticosteroids has since increased [11-13]. Among patients who met criteria in the Pre-formulary group, corticosteroid use became significantly more prevalent following release of the RECOVERY trial results (98.4% vs. 53.2%, p<0.0001) which also coincided with lower mortality (11.5% vs. 31.9%, p=0.0005). We also observed a higher prevalence of corticosteroid use in the Post- compared to the Pre-formulary group among patients who met criteria (97.8% vs. 89.5%, p=0.014). Thus, the favorable outcomes seen in the Post-formulary group were likely a consequence of both differences in disease severity and the evolving evidence establishing corticosteroids as the backbone of therapy. Our findings are consistent with current evidence surrounding the efficacy of remdesivir in reducing time to recovery in patients requiring low oxygen support. Thus, it is unclear whether subsequent days of therapy beyond the achievement of clinical stability provides additional benefit [8].

As the number of COVID-19 cases requiring admission surpasses hospital capacity during times of surging cases, it is crucial for institutions to evaluate the utilization of vital resources and implement strategies to optimize resource allocation. Our study suggests that patients who achieve early clinical response do not need to remain in the hospital to complete their 5-day course of remdesivir. None of the early responders who received less than 5 days of remdesivir therapy had a COVID-19-related readmission or ED visit within 30 days. Early discontinuation when clinically appropriate could facilitate prompt discharge which would reduce medication cost as well as free up other vital resources including hospital beds and nursing personnel.

The projected cost of prescribing remdesivir outside of the established criteria was $35,000 per 100 patients receiving remdesivir. It is evident that there is significant cost savings when remdesivir prescribing is restricted to the evidence-based approved criteria. We also estimated an additional reduction in drug spending by $15,444 per 100 patients receiving remdesivir when treatment duration is reduced from 5 to 4 days in the 30% of early responders. Additionally, 28.8% (n=30) of the Post-formulary group had delays in discharge for reasons including completion of the full 5-day treatment course for remdesivir despite achieving clinical stability. Although we are not proposing that a shortened course of therapy for early responders be adopted into common practice, it is a reasonable consideration when healthcare systems are overburdened. Further prospective studies are needed to demonstrate the effectiveness of a shorter treatment course individualized based on patient's response.

Study Limitations

Our study had several limitations. Due to its observational design, we were not able to control for treatment bias and confounding factors from concomitant therapies or supportive care measures, which have evolved over the course of the pandemic. This was notably evident within the Pre-formulary group in which our exploratory subanalysis found differences in mortality and corticosteroid utilization upon release of the RECOVERY trial results. Despite being an observational study, our groups were well balanced on baseline characteristics. However, the difference in oxygen support at start of therapy between groups likely affected outcomes – a consequence of selection bias due to the evolving criteria for remdesivir use from EAP (requiring mechanical ventilation) to EUA (any level of supplemental oxygen support). We acknowledge that the Post-formulary group is comprised of patients who were hospitalized during the December 2020 surge when resources were scarce. The remdesivir prescribing pattern and observed outcomes described in this analysis may not necessarily reflect clinical practice during times when the COVID-19 case burden is manageable, but does provide insight on resource optimization and planning for subsequent surges.

Conclusion

Criteria for remdesivir use evolved from requiring mechanical ventilation Pre-formulary to requiring low oxygen supplementation Post-formulary addition. We observed a 3.5-fold increase in remdesivir use outside of criteria after formulary addition when much of the prescribing was shifted from ID and PCCM to the Internal Medicine service. Among early responders, receiving less than the 5-day treatment did not result in COVID-related readmissions or ED visits within 30 days. Both stricter adherence to prescribing criteria and a shortened duration of therapy could significantly reduce treatment costs and increase availability of hospital beds and other vital resources in times of surging cases.

Acknowledgments

This work was supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. WHO coronavirus diseases (Covid-19) dashboard. World Health Organization. Updated May 18, 2021. Accessed May 18, 2021. https://covid19.who.int/
2. Hojyo S, Uchida M, Tanaka K, et al. How Covid-19 induces cytokine storm with high mortality. Inflamm Regen. 2020; 40:37.

3. Consortium, W.H.O.S.T. et al. Repurposed antiviral drugs for Covid-19 — interim WHO Solidarity Trial results. N Engl J Med. 2021; 384:497-451.
4. Gilead Sciences, Inc. Veklury (remdesivir) prescribing information. Accessed May 18, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf
5. De Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020; 117(12):6771-6776.
6. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East Respiratory Syndrome coronavirus. J Biol Chem. 2020; 295(15):4773–4779.
7. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017; 9(396):eaal3653.
8. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 – final report. N Engl J Med. 2020; 383:1813-1826.
9. Goldman, JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020; 383:1827-1837.
10. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCAP)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42(2):377-381.
11. RECOVERY Collaborative Group, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021; 384:693-704.
12. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with Covid-19: a meta-analysis. JAMA. 2020; 324(13):1330–1341.
13. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA. 2020; 324(13):1307-1316.