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Real-life use of remdesivir in hospitalized patients with COVID-19

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ABSTRACT

Objective. Controversial results on remdesivir efficacy have been reported. We aimed to report our real-life experience with the use of remdesivir from its availability in Spain.

Methods. We performed a descriptive study of all patients admitted for ≥ 48 hours with confirmed COVID-19 who received remdesivir between the 1st of July and the 30th of September 2020.

Results. A total of 123 patients out of 242 admitted with COVID-19 at our hospital (50.8%) received remdesivir. Median age was 58 years, 61% were males and 56.9% received at least one anti-inflammatory treatment. No adverse events requiring remdesivir discontinuation were reported. The need of intensive care unit admission, mechanical ventilation and 30-days mortality were 19.5%, 7.3% and 4.1%, respectively.

Conclusion. In our real-life experience, the use of remdesivir in hospitalized patients with COVID-19 was associated with a low mortality rate and good safety profile.

Keywords: Antivirals; COVID-19; outcome; remdesivir.

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Uso en vida real de remdesivir en pacientes hospitalizados con COVID-19

RESUMEN

Objetivo. Se han comunicado resultados controvertidos sobre la eficacia de remdesivir. Nuestro objetivo es comunicar nuestra experiencia en vida real con el uso de remdesivir desde su disponibilidad en España.

Métodos. Realizamos un estudio descriptivo de todos los pacientes ingresados durante ≥ 48 horas con COVID-19 confirmado que recibieron remdesivir entre el 1 de julio y el 30 de septiembre de 2020.

Resultados. Un total de 123 pacientes de los 242 ingresados con COVID-19 en nuestro hospital (50,8%) recibieron remdesivir. La mediana de edad fue de 58 años, el 61% eran varones y el 56,9% recibieron al menos un tratamiento anti-inflamatorio. No se registraron acontecimientos adversos que requirieran la interrupción del remdesivir. La necesidad de ingreso en la unidad de cuidados intensivos, la ventilación mecánica y la mortalidad a los 30 días fueron del 19,5%, el 7,3% y el 4,1%, respectivamente.

Conclusiones. En nuestra experiencia, el uso de remdesivir en pacientes hospitalizados con COVID-19 se asoció con una baja tasa de mortalidad y un buen perfil de seguridad.

Palabras clave: Antivirales; COVID-19; resultados; remdesivir

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) emerged at the end of 2019, causing a devastating pandemic and reported one million deaths [1]. Initially, patients with COVID-19 received supportive care to relieve symptoms as well as antivirals according to in vitro data showing activity. However, these drugs failed to prove efficacy [2,3]. On May 1st, 2020, remdesivir received Food and Drug Administration (FDA) emergency use authorization for hospitalized patients with COVID-19 and was officially approved on October 22nd, 2020. Initial clinical trials using a control arm demonstrated the superiority of remdesivir in terms of clinical status improvement at day 28 [4] or at day 11 [5]; however, initial clinical trials performed in China [6] and a recent report from the Solidarity trial [7] did not prove that remdesivir had no benefit [8,9]. Different outcomes and the potential influence of when remdesivir was administered after symptom onset could explain the apparently controversial results in the aforementioned trials [10].

We aim to report our experience using remdesivir from July to September 2020, since the drug was made available in Spain.

METHODS

Study design and patients. This observational cohort study was performed at Hospital Clinic in Barcelona (Spain), a 700-bed university center that provides care for an urban population of 500,000 adults. All patients admitted for ≥ 48 hours with COVID-19 who received remdesivir between July 1st and the September 30th, 2020, were included. All patients had a COVID-19 diagnosis confirmed by real-time reverse-transcription polymerase chain reaction (rRT-PCR) performed on nasopharyngeal throat swabs. The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

During this period, remdesivir treatment had to be approved by the Spanish Ministry of Health and dispensed by the Spanish Agency of Drugs and Health Products. Indication for remdesivir fell under consideration of attending physicians in July; however, beginning August 1st, the Spanish Agency of Drugs and Health Products established common criteria for all institutions in Spain. Criteria to prescribe remdesivir included hospitalized patients with severe pneumonia due to SARS-CoV-2 documented by rRT-PCR, serology or antigen test, and all the following characteristics: 1) aged >12 years and >40 kg; 2) need of supplemental low-flow oxygen; 3) ≤ 7 days from symptom onset to remdesivir prescription; and 4) met at least two of these three criteria: respiratory rate ≥ 24 bpm, oxygen saturation at air ambient $\leq 94\%$, or $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. Exclusion criteria included requirement of supplemental high-flow oxygen, mechanical ventilation, vasoactive drugs, extracorporeal membrane oxygenation (ECMO), or meeting criteria for multiorgan failure. Contraindications included aspartate

amino transferase (ASAT) and alanine amino transferase (ALAT) ≥ 5 times the normal range values, glomerular filtration < 30 mL/min, hemodialysis, or peritoneal dialysis.

Data collection. For all patients hospitalized with COVID-19, high-quality data concerning demographics (age, sex), epidemiology, comorbidities, laboratory tests, microbiological results, treatment and outcomes were collected directly from electronic health records (EHR) using an intelligent system (SILDv1.0 system, S34M[®]) as described elsewhere [11].

Statistical analysis. Qualitative variables are presented as percentages and quantitative variables as median and interquartile range (IQR).

RESULTS

We assessed 242 consecutive adults with COVID-19 at our hospital during the study period. Of these patients, 123 (50.8%) received remdesivir. The median age was 58 years (range 48-69) and 61% were male. Characteristics are detailed in Table 1. Remarkably, remdesivir was used in four patients with chronic kidney disease and in 24 immune-suppressed patients (13 with solid neoplasm, 8 with a hematological disease and 3 with HIV infection). The median (IQR) days from symptom onset to remdesivir prescription was 7 (4-9).

Table 2 shows the treatment options and outcome. In the cohort, 56.9 % of patients received at least one anti-inflammatory treatment, being the most frequent dexamethasone ($n=57$) and/or tocilizumab ($n=33$). Remdesivir was administered at the same time with dexamethasone in 24 patients (24/57; 42%) and with tocilizumab in 19 (19/33; 57%). C-reactive protein median (IQR) values at dexamethasone and tocilizumab administration were 14.3 (13.6-17.4) mg/dL and 13.2 (7.8-16.1) mg/dL, respectively.

The median (IQR) baseline creatinine was 0.86 mg/dL (0.72-1.08); but 6 patients had a creatinine value of >1.5 mg/dL (1.52 to 1.75 mg/dL) when remdesivir was prescribed. All these patients were discharged with a creatinine value of <1.40 mg/dL (0.84 to 1.40 mg/dL). One patient, with an initial creatinine value of 1.39 mg/dL, was discharged with the value at 1.72 mg/dL. The median (IQR) values of ASAT and ALAT at baseline (before starting remdesivir) were 39 (24-64) U/L and 36 (23-61) U/L, respectively. The median values at hospital discharge were 33 (19-57) U/L and 60 (35-97) U/L, respectively. The median (IQR) lymphocyte counts at baseline and at hospital discharge were 1 (0.8-1.3) $\times 10^9$ /L and 1.7 (1.2-2.2) $\times 10^9$ /L, respectively. No adverse events requiring remdesivir discontinuation were reported.

Needs for intensive care unit (ICU) admission and mechanical ventilation was 19.5% and 7.3%, respectively. The 30-day mortality rate was 4.1% (5/123), and 8.3% (2/24) among patients that required ICU admission. All dead patients had ≥ 80 years and all concomitantly received any anti-inflammatory therapy. The 30-day mortality among patients receiving concomitantly remdesivir and dexamethasone was 16.7% and 5.3% with tocilizumab.

Table 1		Clinical characteristics of 123 consecutive adults treated with remdesivir for COVID-19.
Patient characteristics		
Median (IQR) age, in years		58 (48-69)
Age > 65 years (%)		41 (33.3%)
Sex male, n (%)		75 (61%)
Comorbidities (%)		
Hypertension		50 (40.7%)
Diabetes mellitus		27 (22%)
Chronic heart disease		19 (15.4%)
Chronic lung disease		24 (19.5%)
Chronic liver disease		6 (3%)
Chronic kidney disease		4 (3.3%)
Solid neoplasm		13 (10.6%)
Hematological disease		8 (6.5%)
HIV		3 (2.4%)
Median (IQR) days from symptom onset to hospital admission		6 (4-8)
Median (IQR) days from symptom onset to remdesivir		7 (4-9)
Vital signs at admission		
Median (IQR) temperature (°C)		37 (36.5-38)
Median (IQR) respiratory rate (rpm)		20 (18-26)
Respiratory rate > 20 (%)		80 (65%)
Median (IQR) oxygen saturation (%)		94 (93-95)
Oxygen saturation < 94% (%)		48 (39%)
Median (IQR) cardiac rate (rpm)		91 (82-100)
Laboratory at admission, median (IQR)		
Ferritin (ng/mL)		495 (287-1096)
C-RP (mg/dL)		7.99 (4.69-14.47)
D-dimer (ng/mL)		500 (300-900)
LDH (U/L)		323 (265,75-376)
Lymphocyte count (x10 ⁹ /L)		1 (0.7-1.3)
Creatinine (mg/dL)		0.86 (0.72-1.08)
ASAT (U/L)		39 U/L (24-64)
ALAT (U/L)		36 U/L (23-61)

DISCUSSION

This is the first report to assess the efficacy and tolerability of remdesivir in a real-life cohort of patients with COVID-19, including those with cancer or hematological disease. Our results documented a low mortality rate (4.1%) in hospitalized patients receiving remdesivir for severe pneumonia due to SARS-CoV-2. This rate is in line with that reported in the ACTT-1 study that randomized patients to remdesivir or placebo [4]. Our patients mainly correspond to those in the

Table 2		Concomitant treatment and outcomes of 123 consecutive adults treated with remdesivir for COVID-19.
Treatment		
Other drugs with potential antiviral effect		
Lopinavir/ritonavir (%)		1 (0.8%)
Anti-inflammatory effect		
Tocilizumab (%)		33 (26.8%)
Anakinra (%)		7 (5.7%)
Methyl-prednisolone (%)		14 (11.4%)
Dexamethasone (%)		57 (46.3%)
Prednisone (%)		24 (19.5%)
Antibiotic treatment		
Ceftriaxone (%)		52 (42.8%)
Ceftaroline (%)		16 (13%)
Outcomes		
Median (IQR) of length of hospital stay		8 (6-12)
ICU admission (%)		24 (19.5%)
Need of mechanical ventilation (%)		9 (7.3%)
30-day mortality (%)		5 (4.1)

ACTT-1 study with a baseline ordinal score of 5 (hospitalized patients requiring supplemental oxygen) who had a mortality rate of 3.8% in the remdesivir arm versus 12.3% in the control arm. The total number of patients in this study subgroup was 435 (232 and 203 in each arm), being the largest group. This is reasonable since this is the most common type of patients requiring hospital admission in the daily practice, therefore, our results enlarge the experience in this important subgroup.

The most severe patients required co-administration of an anti-inflammatory therapy, and as expected they had the highest mortality rate. Interestingly, the concomitant use of remdesivir and tocilizumab was associated with the lowest mortality rate in this group (5.3%), in line with the recent report showing better outcomes among patients receiving remdesivir plus baricitinib [12]. Both immune-modulators inhibit specific pathways of inflammatory cascade instead of the broad-spectrum inhibition induced by steroids with potential harmful consequences [13].

The optimal timing for remdesivir treatment remains to be clarified. SARS-CoV-2 shedding from the respiratory tract peaks during the first 2-3 days from clinical symptom onset and rapidly decreases [14], consistent with a brief window of clinical benefit from antiviral drugs. In this scenario, prompt initiation of antiviral treatment may be the key point to improve outcomes of patients with COVID-19. Such approach has been documented in other respiratory virus such as the influenza, with the use of neuraminidase inhibitors [15]. In our cohort, remdesivir was administered earlier than in the ACTT-1

study (median of 7 vs. 9 days from symptom onset to remdesivir) [4]. Such early drug administration could explain the shorter length of hospital stay (8 vs. 12 days) and lower need of mechanical ventilation (7.3 vs. 12.9%). A prior trial [6] failed to demonstrate any benefits from remdesivir treatment in patients with COVID-19; however, the median days from symptom onset to remdesivir was 11 and, indeed, 37 of the 196 (19%) patients had undetectable viral RNA on nasopharyngeal and oropharyngeal swabs obtained at baseline. Considering all together, this data suggests that patients included in this study were in a late stage with low viral load and, therefore, the expected benefit of an antiviral in this population is minimal.

The impact of remdesivir on reducing viral shedding has been reported in macaques [16]. Information about viral shedding in humans receiving remdesivir treatment is, however, lacking. Such information is important to define the duration of transmissibility and the potential consequences on the isolation measures.

Our cohort supports the good tolerability profile of remdesivir, presenting with no serious adverse events and, in particular, no alterations in liver enzymes. No patient required discontinuation of the drug.

The main limitation of this study was its retrospective nature and a possible underreporting of adverse events. However, we were able to closely monitor laboratory parameters to minimize this problem. However, the strength of our study is that the Spanish Ministry of Health perfectly defined the indication for remdesivir and our results support such current indication.

We conclude that the use of remdesivir in hospitalized patients with pneumonia due to SARS-CoV-2 is associated with a low mortality rate and has a good safety profile.

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