

Effect of co-treatment of COVID-19 with Remdesivir

Efecto del cotratamiento de COVID-19 con Remdesivir

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Abstract:

Background: Due to the COVID-19 pandemic, randomized clinical studies were conducted with Remdesivir in combination with Baricitinib or Dexamethasone, which have shown effectiveness for the treatment of COVID-19.

Objective: We analyzed the effect of co-treatment with Remdesivir in a retrospective in Mexico.

Methods: Thirty-four patients treated with Remdesivir in combination with Baricitinib or Dexamethasone were included. Age, sex, comorbidities, signs, and symptoms were recorded at hospital admission, intubation needs, intensive care unit (ICU) requirements, days of hospital stay and their evolution, as well as laboratory data upon admission and upon admission terminate Remdesivir treatment.

Results: Most were male, with an age of 56.5 years (49 years-60.3 years), whose main comorbidity was obesity. The main symptoms on admission were dyspnea and cough. Thirty-two patients received the short Remdesivir regimen, 22 were co-treated with Baricitinib and 12 with Dexamethasone. Most did not require ICU care, 9 patients died, 19% of those co-treated with Baricitinib and 42% of those co-treated with Dexamethasone. A significant decrease in hemoglobin, protein, albumin and LDH levels was observed.

Conclusion: In this study, we observed lower mortality in patients co-treated with Baricitinib vs those co-treated with Dexamethasone, and a hospital stay similar to that reported in randomized clinical studies.

Keywords: COVID-19, Remdesivir, Baricitinib, Dexamethasone



Resumen

Introducción: Debido a la pandemia de COVID-19, se realizaron estudios clínicos aleatorizados con Remdesivir en combinación con Baricitinib o Dexametasona, que han demostrado efectividad para el tratamiento de COVID-19.

Objetivo: Se realizó un análisis del efecto del co-tratamiento con Remdesivir en una muestra retrospectiva en México.

Métodos: Se incluyeron 34 pacientes tratados con Remdesivir en combinación con Baricitinib o Dexametasona. Se registraron edad, sexo, comorbilidades, signos y síntomas al ingreso hospitalario, necesidades de intubación, requerimientos de unidad de cuidados intensivos (UCI), días de estancia hospitalaria y su evolución, así como datos de laboratorio al ingreso y al ingreso al final del tratamiento con Remdesivir.

Resultados: La mayoría eran varones, con una edad de 56.5 años (49 años-60.3 años), cuya principal comorbilidad era la obesidad. Los principales síntomas al ingreso fueron disnea y tos. Treinta y dos pacientes recibieron el régimen corto de Remdesivir, 22 fueron cotratados con Baricitinib y 12 con Dexametasona. La mayoría no requirió atención en UCI, 9 pacientes fallecieron, 19% de los cotratados con Baricitinib y 42% de los cotratados con Dexametasona. Se observó una disminución significativa en los niveles de hemoglobina, proteínas, albúmina y LDH.

Conclusión: En este estudio observamos una menor mortalidad en los pacientes cotratados con Baricitinib frente a los cotratados con Dexametasona, y una estancia hospitalaria similar a la reportada en estudios clínicos aleatorizados.

Palabras clave: COVID-19, remdesivir, baricitinib, Dexametasona

INTRODUCTION

The SARS-CoV-2 virus infection was described in December 2019 in Wuhan, China, causing the coronavirus disease 2019 (COVID-19). As of September 27, of 2021 an estimated of 231,551,680 infected people have been reported, causing the death of 4,743,708 patients worldwide.⁽¹⁾

The SARS-CoV-2 virus belongs to the beta coronavirus family, it is a positive sense single-stranded RNA envelope virus, from 60 nm to 140 nm, with a spike protein (S) from 9 nm to 12 nm that gives the appearance of a solar corona.⁽²⁻⁴⁾

The SARS-CoV-2 virus uses the spike protein to bind to receptors for angiotensin converting enzyme 2 (ACE2) to enter cells. The host cell transmembrane serine protease type 2 (TMPRSS2) promotes the activation of protein S and its anchorage with the ACE2 receptor, mediating the entry of the coronavirus into the host cell.¹ This virus uses RNA-dependent RNA polymerase to replicate genomic RNA and produce small sub genomic RNAs that are used to synthesize spike, envelope, membrane and nucleocapsid structural proteins so that the virus can exit and repeat the cycle in other cells.^(4,5)

Most patients infected with SARS-CoV-2 do not require hospitalization, however, in some patients, especially with risk factors such as advanced age, obesity, hypertension, diabetes and chronic kidney disease, the disease progresses to the forms severe or critical and require hospitalization, develop complications such as acute respiratory distress syndrome (ARDS), multisystem disease up to death.^(6,7)

Disease progression is the result of multiple pathophysiological mechanisms including the cytopathic effect of SARS-CoV-2; dysregulation of the renin-angiotensin-aldosterone system due to the decrease in ACE2 and the decrease in the inactivation of des-Arg9-bradykinin; dysregulation of the immune response leading to a “cytokine storm”; coagulopathy associated with the exocytosis of procoagulant factors, thrombotic microangiopathy (probably caused by virus-induced endothelial damage), complement activation and the effects of cytokines, generating “immunothrombosis” and autoimmunity.⁽⁸⁾

Due to the pathophysiology, the design of treatments has been complex; various clinical studies of pharmacological agents have been developed in the world, some to mediate the immune response and other antiviral agents such as Remdesivir, this is an antiviral that has shown in vitro inhibition of the RNA-dependent RNA polymerase (RdRp) of SARS- CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV).⁽⁹⁾

Remdesivir is a monophosphate prodrug, which is metabolized to its active triphosphate form, acting as a substrate for RpRp in coronaviruses and blocking the synthesis of viral RNA. Double-blind studies have shown a faster recovery by reducing the days of hospital stay.⁽¹⁰⁾

Since October 2020, the US Food and Drug Administration (FDA) approved the antiviral Remdesivir for the treatment of COVID-19, and in Mexico since March 12, 2021, the Federal Commission for Protection against Health Risks (COFEPRIS) authorized its emergent use in hospitalized patients in the initial phase of the disease.^(11,12)

Despite its authorization and recommendations by different national and international organizations, there is still controversy about its effectiveness since in the study ACTT-1 (Adaptive COVID-19 Treatment Trial) demonstrated a decrease in morbidity, mortality and days of hospital stay, however, the Solidarity study, funded by the World Health Organization (WHO), did not show benefits in the mortality but a reduction in severity and hospital stay; highlighting that most of the studies included mainly white population, and only 11% to 20% of black race and 17% to 23% of Latin American patients.⁽¹³⁾

Since November 2020, the FDA approved the combination of Remdesivir with Baricitinib, for the treatment of COVID-19 in patients who require supplemental oxygen or mechanical ventilation, since a decrease in recovery time was demonstrated. Baricitinib is a Janus kinase (JAK) 1 and 2 inhibitors, related to the production of pro-inflammatory cytokines such as IL-2, IL-6, IL-10, gamma interferon, and macrophage colony stimulating factor and granulocytes.⁽¹⁴⁾

In randomized clinical studies such as RECOVERY, the effectiveness of dexamethasone was evaluated, which has been shown to reduce mortality in patients who require treatment with supplemental oxygen or mechanical ventilation.⁽¹⁵⁾

In this study, we evaluated the effects of Remdesivir with Baricitinib and Remdesivir with Dexamethasone co-treatment in patients hospitalized in a tertiary hospital, in Mexico, with moderate or severe SARS-CoV-2 disease.

MATERIALS AND METHODS

This study was observational, retrospective, longitudinal in a tertiary hospital in Mexico City, Mexico. The records of hospitalized patients who were treated with Remdesivir from February to May 2021 were reviewed. Only patients with laboratory data prior to treatment and at the end of treatment were included. This study was approved by the Research Committee of the institution with number of Registry 091/2021, this study does not include data that allow the identification of patients and is attached to the guidelines of the Declaration of Helsinki.

Age, sex, comorbidities, symptoms, and signs were collected at hospital admission, as well as laboratory data prior to treatment and at the end of treatment with Remdesivir, follow-up on intubation needs, intensive care unit requirements (ICU), the days of hospital stay and its evolution.

Statistical analysis

For statistical analysis, qualitative data are expressed in frequencies and percentages, qualitative data were tested for normality, data that complied with normality are expressed as mean and standard deviation, the rest are expressed as median and range interquartile (IQR). To analyze the changes before and after the treatment, the paired Student's T test or the Wilcoxon test was performed according to the normality of the data. Data analysis was performed using the Statistical Package for Social Sciences software, version 20.0 (SPSS; IBM, Armonk, New York, USA).

RESULTS

This study included the data of 34 patients with moderate to severe COVID-19 disease according to the NIH (National Institutes of Health) classification,⁽¹⁶⁾ hospitalized and treated in a tertiary hospital, most of them male, with an age range of 19 to 85 years and obesity as the main comorbidity (Table 1).

Table 1. Sociodemographic data, signs, and symptoms at hospital admission

Sex	n (%)
Male	23 (67.6)
Female	11 (32.4)
Age median (IQR)	56.5 (49-60.3)
Comorbidities	n (%)
Obesity	11 (32.4)
Hypertension	8 (23.5)
Overweight	7 (20.6)
Diabetes	6 (17.6)
Asthma	1 (2.9)
Chronic kidney disease	1 (2.9)
Symptoms	n (%)
Dyspnea	19 (55.9)
Cough	18 (52.9)
Myalgia	15 (44.1)
Fever	13 (38.2)
Arthralgia	13 (38.2)
Headache	4 (11.8)
Odynophagia	4 (11.8)
Rhinorrhea	4 (11.8)
Signs	Median (IQR)
Saturation (%)	91 (89, 94)
PaO ₂ /FiO ₂	431 (406, 448)
Respiratory rate (Rpm)	20 (19, 22)
Heart rate (Bpm)	74 (68, 97)
Systolic pressure (mmHg)	127 (111, 140)
Diastolic pressure (mmHg)	73 (65, 81)
Size (m)	1.67 (1.61, 1.71)
Weight (kg)	74 (65.5, 91)
BMI (kg/m ²)	26.8 (24.2, 32.8)

BMI: body mass index.

Bpm: beats per minute

IQR (interquartile range)

Rpm: breaths per minute

BMI: body mass index, Bpm: beats per minute, IQR (interquartile range), Rpm: breaths per minute.

According to the Massachusetts Severity Risk Classification,⁽¹⁷⁾ only 2 patients were in category 2 (5.9%) and 32 were in category 3 (94.1%) at hospital admission, the signs and symptoms on admission are shown in Table 1.

The majority (32 patients) received the short treatment regimen (5 days) and 2 patients received the long regimen (10 days). The treatment combinations are shown in Table 2. All patients were co treated with dexamethasone. None of the patients presented side effects that caused the early termination of treatment. At admission the oxygen requirement was 12.5 L (3L,15 L), the beginning of treatment with remdesivir was at 15 days $\pm$ 7.8 days after beginning of symptomatology, while the beginning of treatment was 8.3 days $\pm$ 6 days after admission at hospital, there are not significant differences between the groups.

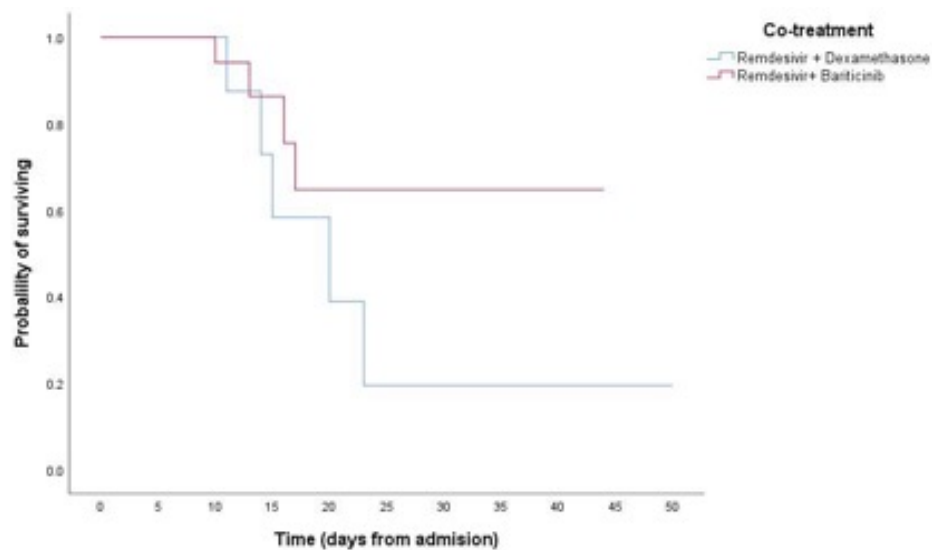
Most of the 24 patients (70.6%) did not require ICU care, 9 patients (26.5%) required mechanical ventilation, the beginning was at 2 days after beginning treatment (0 days, 5.5 days), and 9 patients (26.5%) died, the distribution according to the treatment combinations is shown in Table 2.

Table 2. Treatment and evolution schemes

Remdesivir	+ Baricitinib	+ Dexamethasone
n (%)	22 (64.7)	12 (35.3)
Days of hospital stay (days)	13 (10, 20) ^a	12.5 (9, 19) ^a
Days of hospital stay in recovered (days)	12 (8, 30) ^a	9 (8, 14.5) ^a
Days of hospital stay in patients who died	14.5 (11.5, 16.5) ^a	15 (14, 20) ^a
Mechanic ventilation n (%)	6 (27)	3 (25)
ICU n (%)	7 (32)	3 (25)
Death n (%)	4 (19)	5 (42)

^a median (interquartile range)

The days of hospital stay were 13 days (9 days -20 days), the majority were discharged due to improvement (25 patients) with a hospital stay of 11 days (8 days, 20 days). Mortality of 42% was observed in patients co-treated with Dexamethasone and 19% in those co-treated with Baricitinib (Table 2); Kaplan-Meier analysis showed a mean survival of 33 days in patients co-treated with Baricitinib, and 23 days in patients co-treated with Dexamethasone, without significant differences $X^2 = 1.81$, $p = 0.179$, as shown in Figure 1.

Figure 1.

A decrease in hemoglobin, total proteins, albumin, and LDH was observed; the rest of the parameters were not significantly altered (Table 3).

Table 3. Laboratories

	Initial	End	p
Hematic biometry			
Haemoglobin (g/dL) ^a	15.07 ± 1.76	14.01 ± 2.10	<0.001
Platelets (10 ³ /mL) ^a	250.79 ± 96.45	264.82 ± 119.2	0.547
Leukocytes (10 ³ /mL) ^b	7.34 (4.75, 11.56)	7.39 (5.96, 10.65)	0.489
Lymphocytes (10 ³ /mL) ^b	0.79 (0.45, 1.43)	1.06 (0.64, 1.51)	0.057
Neutrophils (10 ³ /mL) ^b	5.9 (3.58, 5.96)	5.56 (3.53, 9.07)	0.694
Index N/L ^b	7 (4, 11)	4 (3, 14)	0.665
Blood chemistry			
Glucose (mg/dL) ^a	149.70 ± 74.33	161.7 ± 93.28	0.506

Creatinine (mg/dL) ^a	0.84 ± 0.23	0.86 ± 0.59	0.823
BUN (mg/dL) ^a	19.88 ± 9.54	22.73 ± 14.60	0.202
Liver function tests			
Total bilirubin (mg/dL) ^b	0.99 (0.81, 1.31)	0.95 (0.74, 1.33)	0.695
Direct bilirubin (mg/dL) ^b	0.61 (0.43, 0.73)	0.51 (0.34, 0.82)	0.321
Indirect bilirubin (mg/dL) ^b	0.47 (0.35, 0.57)	0.48 (0.36, 0.58)	0.604
ALT (U/L) ^b	46 (26.5, 73)	51 (28.5, 73.5)	0.537
AST (U/L) ^b	41.5 (37.5, 51.3)	34 (25.8, 51.3)	0.313
Alkaline phosphatase (U/L) ^b	100.5 (69.5, 125.5)	82.5 (73.5, 112.3)	0.252
Proteins (g/dL) ^a	6.23 ± 0.87	5.64 ± 0.93	0.002
Albumin (g/dL) ^a	3.37 ± 0.66	2.96 ± 0.70	<0.001
Biochemical markers			
CRP (mg/L) ^b	67 (20.4, 134.5)	17.8 (10.4, 200)	0.837
LDH (U/L) ^b	283.5 (218, 398.3)	251 (194.5, 320)	0.001
D-dimer (ng/mL) ^b	581 (422, 784)	498 (218, 1194)	0.191
Procalcitonin (ng/mL) ^b	0.11 (0.05, 0.17)	0.06 (0.03, 0.18)	0.808
Ferritin (ng/dL) ^b	850 (618, 1256)	657 (413, 1030)	0.136

^a mean ± standard deviation, paired Student's t test^b median (interquartile range), Wilcoxon test

DISCUSSION

Currently, there is no effective treatment for all phases of COVID-19 due to its complex pathophysiology,⁽⁸⁾ within clinical studies the effectiveness of Remdesivir in phase 1 of COVID-19 has been observed.⁽⁷⁾

In this study, all the patients met the criteria of the national or hospital guidelines for the use of Remdesivir,^(8,18) and had risk factors for developing severe disease;^(6,17) the main treatment scheme used in this study was 5 days, as in most reports, the ACCTT-1 study demonstrated the effectiveness with a 10-day treatment schedule, and similar efficacy has been observed between the 5 and 10-day treatment schedules, in open-label studies a significant improvement in disease severity was associated with the 5-day schedule and not with the 10-day scheme.⁽¹³⁾

All patients received co-treatment, 22 patients were given the combination of Remdesivir with Baricitinib, Kalil et al. demonstrated that this combination reduces the recovery time from 18 days in patients treated with Remdesivir alone to 10 days in the combination and accelerates clinical improvement after 15 days.⁽¹⁹⁾ In this study, patients who recovered treated with this combination had their stay hospital stay was 12 days.

Remdesivir was combined with dexamethasone in 12 patients, Lee et al. Using a Bayesian analysis, they showed that Remdesivir treatment has a low probability of reducing mortality, except in patients requiring supplemental oxygen who do not require mechanical ventilation. While corticosteroids may be more effective in patients who require supplemental oxygen and mechanical ventilation.⁽²⁰⁾ In this study, it was observed that recovered patients who received co-treatment with Remdesivir and Dexamethasone, the days of hospital stay were 9 days similar to that reported with Remdesivir alone for 8 days.⁽¹⁹⁾ However, in the study by Garibaldi et al. showed that there was no benefit of the combination between Remdesivir and corticosteroids in mortality at 28 days. In this study, a mortality of 42% was observed in this combination with a hospital stay of 15 days.

A significant decrease in LDH was found, which is a marker of disease progression, suggesting its effectiveness in the evolution of the disease.⁽²⁰⁾

The main adverse effects reported in patients treated with Remdesivir are gastrointestinal and elevated liver enzymes, as well as reactions at the site of the application.⁽¹⁰⁾ In this study, no elevation of liver enzymes was observed, but there was a decrease in the levels of haemoglobin, total proteins, and albumin.⁽⁹⁾ At the end of the treatment, these adverse effects were previously reported, being similar in the control groups vs the treated with Remdesivir.⁽⁹⁾

COCLUSION

In conclusion, in this study, the administration of Remdesivir in co-treatment adhering to the national and international guidelines for the treatment of COVID-19, a decrease in LDH levels was observed, and without side effects that caused the interruption of treatment, the main side effects were decrease in haemoglobin, total proteins and albumin. Mortality in patients treated with Remdesivir plus Baricitinib was 19%, lower than in those co-treated with Dexamethasone (42%). The days of hospital stay were similar to those previously reported. The main limitation of the study is its retrospective nature and the

size of the sample. Therefore, it is necessary to evaluate the effect of these combinations in prospective, randomized comparative studies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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