REVISION
https://doi.org/10.22239/2317-269X.01741

# Pharmacological treatment for COVID-19 in latin american protocols: A narrative review of the effectiveness and safety

## Tratamiento farmacológico para COVID-19 en protocolos latinoamericanos: una revisión narrativa de la eficacia y seguridad

**Pamela Alejandra Escalante Saavedra**[I,*]
**Martín Cañás**[II]
**Dulce María Calvo Barbado**[III]
**Liliana Barajas Esparza**[IV]
**Mariana Caffaratti**[V]
**Noelia Speranza Mourine**[VI]
**Carlos Alberto Fuentes Martínez**[VII]
**José Julián López Gutiérrez**[VIII]

[I] Centro Brasileiro de Informação sobre Medicamentos, Conselho Federal de Farmácia, Brasília, DF, Brasil.
[II] CIMEFF Área de Farmacología, Federación Médica de la Provincia de Buenos Aires (FEMEBA), La Plata, Argentina
[III] Asesora independiente, Barcelona, España
[IV] Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, Pachuca de Soto, Hidalgo, México
[V] Centro de Información de Medicamentos, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina
[VI] Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay
[VII] Centro de Información de Medicamentos CIME, Acción Internacional por la Salud (AIS Nicaragua), Matagalpa, Nicaragua
[VIII] Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá, Colombia

* **E-mail:** saavedra.pamela.alejandra@gmail.com

Received: 07 Aug 2020
Approved: 13 Aug 2020

## ABSTRACT

**Introduction:** The pandemic caused by SARS-CoV-2 has put the global scientific community in an accelerated pace of research for an effective treatment for COVID-19. **Objective:** To identify and evaluate drugs in Latin American protocols of pharmacological treatment for COVID-19. **Method:** The evidence and mega trial results available to date on the most frequent medications are analyzed. **Results:** The most common Medicines in national protocols are hydroxychloroquine, lopinavir/ritonavir, and remdesivir. None of the drugs that collect the most data from clinical studies, with the except for dexamethasone in a small subgroup of patients, so far showed significant differences in mortality. **Conclusions:** The emerging situation of COVID-19 has determined Rush and controversial decision-making based on questionable and/or low-quality studies. This highlights the provisional nature of the information and the possibility of generating changes as more results become available. Advance medication authorization exposes a known problem. Although regulatory agility is required at this time, speed should not overlap with basic ethical standards and trust in evidence.

**KEYWORDS:** COVID-19; Clinical protocols; Medicaments; Evidence-Based Medicine; Latin America

## RESUMEN

**Introducción:** La pandemia causada por el SARS-Cov-2 ha puesto a la comunidad científica mundial en ritmo acelerado de investigación y busca por un tratamiento efectivo para COVID-19. **Objetivo:** Identificar y evaluar medicamentos en protocolos latinoamericanos de tratamiento farmacológico para el COVID-19. **Método:** Se analiza la evidencia y resultados de mega ensayo disponibles hasta la fecha sobre los medicamentos más frecuentes. **Resultados:** Los medicamentos más frecuentes en protocolos nacionales son hidroxicloroquina, lopinavir/ritonavir y remdesivir. Ninguno de los medicamentos que recopilan mayor cantidad de datos provenientes de estudios clínicos, a excepción de la dexametasona en un subgrupo reducido de pacientes, mostró, hasta el momento, diferencias significativas en la mortalidad. **Conclusiones:** La situación emergente de la COVID-19 ha determinado la toma de decisiones apresuradas y controversiales con base en estudios cuestionables y/o de baja calidad. Esto pone de relieve el carácter provisorio de la información y la posibilidad de generar cambios a medida que se dispongan de más resultados. La autorización anticipada de medicamentos expone un problema conocido. A pesar de que la agilidad regulatoria es necesaria en este momento, la velocidad no debe sobreponerse a los patrones básicos éticos y de confianza en la evidencia.

**PALABRAS CLAVE:** COVID-19; Protocolos Clínicos; Medicamentos; Medicina Basada en Evidencia; Latinoamérica

## INTRODUCTION

The new coronavirus or SARS-CoV-2 causes clinical manifestations as mild, moderate or severe conditions, including pneumonia, acute respiratory distress syndrome (ARDS), sepsis and septic shock. Most of the reported cases begin with mild symptoms[1].

In Latin America, countries have made official pharmacological treatment protocols that include medicines for different clinical conditions of patients (severity) and at different levels of care[2]. However, several of these protocols leave the decision about the pharmacological treatment to be used in each patient to medical criteria, that is, s the doctor must evaluate the benefit/risk ratio and decide based on the available evidence and his personal experience.

Among the drugs included are hydroxychloroquine (HCQ), chloroquine (CQ) (two antimalarial with immunomodulatory effects also used to treat autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis)[3], remdesivir (a nucleotide analog prodrug with antiviral activity by inhibition of polymerase RNA dependent of RNA 96% identical between Middle East respiratory syndrome - MERS, severe acute respiratory syndrome - SARS and COVID-19)[2], lopinavir/ritonavir (LPV/r, combination of antivirals used in the treatment of human immunodeficiency virus - HIV)[2] and more recently dexamethasone (a corticosteroid that may be useful in reducing complications of respiratory distress syndrome acute ARDS) in severe forms of the disease caused by the SARS-CoV-2[4].

In addition to support measures for those patients requiring hospitalization, there is currently no evidence from quality controlled clinical trials, published in peer-reviewed journals, to recommend a specific treatment for the SARS-CoV-2 coronavirus [1,5,6].

Besides, it is analyzed the available evidence until the elaboration date of this article, about the most frequently included medicine in the pharmacological treatment protocols for COVID-19 in Latin America.

## METHOD

A review of the national protocols for COVID-19 in Latin American countries was carried out, which were provided by the information centers belonging to the Network of Drug Information Centers of Latin America and the Caribbean (RED CIMLAC, Spanish abreviattion), as well as the clinical practice guides of the National Institutes of Health (NIH) of United States. Those drugs that represented a different mechanism of action, medicines more referenced in Latin American protocols and international clinical trials, were conveniently included.

In this way, CQ and HCQ were included as representative of the antiparasitics, remdesivir and LPV/r as representatives of the group of antiviral and dexamethasone as representative of corticosteroids.

To identify the efficacy and safety results of the selected drugs between April and June 2020, the databases of MEDLINE (PubMed search engine), Epistemonikos, EMBASE, Latin American and Caribbean Literature in Health Sciences (LILACS) and *Cochrane* Library were reviewed, in which clinical trials with the selected drugs were identified. The strategy and keywords used in PubMed were the following: (Therapy/Broad[filter]) AND (-drug name-); (Therapy/Broad[filter]) AND (-drug name- AND COVID-19); (Therapy/Broad[filter]) AND (-drug name- AND SARS-CoV-2); (Therapy/Broad[filter]) AND (-drug name- AND coronavirus); ("-drug name-" [Supplementary Concept]) AND "COVID-19" [Supplementary Concept]; (Medical Genetics[-filter]) AND (-name of the drug); (Therapy/Broad[filter]) AND (-drug name- AND efficacy); ("Treatment Outcome"[Mesh]) AND "-drug name-" [Supplementary Concept]); ("-drug name-" [Supplementary Concept]) AND "Drug-Related Side Effects and Adverse Reactions"[Mesh]); (Therapy/Broad[filter]) AND (drug name- AND adverse events).

Additionally, a non-systematic review of institutional repositories of health agencies was carried out, such as the *Food and Drug Administration* (FDA) and the Spanish Agency for Medicines and Health Products (AEMPS), and the project Observatory of Medicine with High Financial Impact (DIME) [7], Library of the University Pablo de Olavide of Spain [8], Institute of Health Carlos III of Ministry of Science and Innovation in Spain [9] and the base *Clinical Trials* of the National Institute of Health of United States[10].

The preliminary results of study *Randomised Evaluation of COVID-19 Therapy* (RECOVERY), a multicenter randomized controlled trial (RCT) opened with six treatment arms, were reviewed: LPV/r, HCQ, dexamethasone, azithromycin, convalescent plasma and tocilizumab[11].

Analytical observational studies and clinical trials, as well as preliminary results and case series of the selected drugs, were included for analysis.

## RESULTS

### Chloroquine and hydroxychloroquine

According to the results of Wang et al.[12], Yao et al.[13] and Mc Intosh[14], CQ and HCQ inhibit the replication of SARS-CoV-2 *in vitro* although HCQ appears to have more potent antiviral activity. Based on these *in vitro* studies, the National Health Commission of China was the first to include the use of CQ in its treatment guidelines[14,15].

In Table 1, there are eight RCTs and several observational studies of CQ and HCQ. The RECOVERY study is the one that provides the most evidence and concludes that no differences in mortality were observed when patients were treated with HCQ. Evidence from clinical trials thus far has not shown benefits, either as a treatment or as prophylaxis.

**Table 1.** Clinical and observational trials with hydroxychloroquine and chloroquine in COVID-19 (main efficacy and safety results).

| Authors | Description | Main results |
|---|---|---|
| | Randomized clinical trials | |
| Chen et al.[16] | Thirty hospitalized patients with moderate infection, without significant comorbidities (mean age 50 years, 70% men). The treatment group received HCQ 400 mg/day and the control group received standard treatment for five days. All patients received other treatments concomitantly. | No differences were found between the groups in nasopharyngeal viral clearance on day 7, or in length of hospital stay or complications.<br>RAM: There were no differences in adverse events between the groups. There were no deaths. |
| Chen et al.[17] | In 62 patients hospitalized with pneumonia, without critical condition (average age 45 years). Treatment group received 200 mg every 12 hours of HCQ for five days in addition to supportive treatment, and the control group only supportive treatment. | HCQ modestly accelerates the disappearance of symptoms (fever and cough) and radiological improvement.<br>They do not present the results of the main variable of the original protocol: viral clearance and T-cell recovery time.<br>The study has serious limitations and was not peer-reviewed, so the results should be interpreted with caution. |
| Tang et al.[18] | Intermediate results of RCTs with 150 patients in a 1:1 relationship with mild to moderate COVID-19 and with an average age of 46 years. 75 patients were assigned to treatment with HCQ 800-1,200 mg/day plus standard care and 75 patients only to standard care. The average duration between the onset of symptoms and treatment with HCQ or standard care was 16 days. 63% of the patients in both groups received other antiviral treatments. | Administration of HCQ did not result in a significantly higher probability of negative CRP conversion at 28 days of treatment.<br>RAM: Adverse events were higher in the HCQ group (30% vs 8.8%). |
| Borba et al.[19] | RCT with preliminary findings on efficacy and safety of two CQ regimens in 81 patients with severe COVID-19. Mortality of 39.0% (16/41 patients) was evidenced in the high-dose group versus 15.0% (6/40) in the low-dose group (log-rank, −2,183; P = 0.03). | They concluded that CQ should not be recommended for critically ill COVID-19 patients due to its potential safety risks, especially when taken concurrently with azithromycin and oseltamivir.<br>Study limitations: lack of a placebo control group, small sample size, absence of exclusion criteria based on QTc interval at baseline.<br>RAM: Elevated QTc (11/73) due to high doses. Mortality (16/41) due to high doses. |
| Boulware et al.[20] | RCT post-exposure prophylaxis to COVID-19, 441 patients with HCQ versus 407 with placebo (n = 407); median age with HCQ 41 years, with placebo 40 years; 48.2% men. | No deaths in either group; incidence of diseases compatible with COVID-19 without significant differences between participants who received HCQ (49 of 414 [11.8%]) and those who received placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval −7.0 to 2.2; P = 0.35).<br>RAM: With HCQ the effects were not serious, there were no arrhythmias. There were no deaths. |
| Chen et al.[21] | RCT, 48 patients of which 18 with HCQ, 18 with CQ and 12 with placebo; mean age CQ 45.2 years, HCQ 45.7 years, placebo 51.3 years; 46% men. | The CQ group achieved a shorter time to clinical recovery (CRT) than the control group (P = 0.019). There was a trend towards reduced CRT in the HCQ group (P = 0.049). The time to reach viral RNA negativity was significantly faster in the CQ group and HCQ group than in the control group (P = 0.006 and P = 0.010, respectively). The median number of days to reach RNA negativity in the CQ, HCQ and control groups was 2.5 (IQR: 2.0-3.8) days; 2.0 (IQR: 2.0-3.5) days and 7.0 (IQR: 3.0-10.0) days, respectively. The CQ and HCQ groups also showed trends toward improvement in length of hospitalization and findings on lung computed tomography (CT). |
| Horby et al.[22] | Open RCT. HCQ arm: 1,542 patients assigned to HCQ (2,000 mg on the first day, 400 mg in the next 24 hours, and 800 mg/day for nine days) and 3,132 patients assigned to standard care. Main variable: mortality. Secondary endpoints: length of hospital stay, need for ventilation, need for renal replacement therapy, and appearance of serious arrhythmias (included in a protocol modification). Patients receiving remdesivir were not excluded. | Preliminary results only from the HCQ branch. There were no significant differences in the primary variable of mortality at 28 days (25.7% for HCQ versus 23.5% for standard care (HR = 1.11; 95% CI 0.98-1.26; P = 0.10). There was also no evidence of beneficial effects on length of hospital stay or other outcomes. |
| Skipper et al.[23] | RCT Post-exposure prophylaxis to COVID-19. HCQ 800 mg once, followed by 600 mg over 6 to 8 hours, then 600 mg daily for 4 more days, or masked placebo.<br>In 491 randomized patients, 423 completed. HCQ 212 vs placebo 211. 56% (236 out of 423) signed up within 1 day of the onset of symptoms. | No differences in the severity of symptoms at 14 days (difference in symptom severity: relative 12%; absolute 0.27 points [CI95% -0.61 to 0.07 points]; P=0.117).<br>At 14 days, 24% (49 out of 201) of participants receiving HCQ had continuous symptoms compared to 30% (59 out of 194) who received placebo (P=0.21). |

Continue

Continuation

| Authors | Description | Main results |
|---|---|---|
| | Observational Studies | |
| Gautret et al.[24] | In 36 patients with HCQ (200 mg three times daily for ten days). | HCQ use was associated with a higher rate of undetectable SARS-CoV-2 RNA in nasopharyngeal samples on day 6 compared to no specific treatment (70.0% versus 12.5%). The use of azithromycin in combination with HCQ seems to have an additional benefit. Limitations: internal validity (uncontrolled, non-randomized, unmasked, excluding patients without proper justification). The primary variable without optimal clinical duration or relevance which limits its external validity. |
| Rosenberg et al.[25] | In 1,438 patients hospitalized with COVID-19 treated with HCQ, azithromycin or both, compared to neither treatment. | It was not significantly associated with differences in hospital mortality or alterations in ECG in the adjusted analysis (HR x 1.08 IC95% 0.63-1.85; HR = 0.56 IC95% 0.26-1.21 and HR = 1.35 IC95% 0.76-2.40, respectively), in any of the treatment groups. |
| Geleris et al.[26] | In 1,376 patients with COVID-19, HCQ administration, versus control group. | It was not associated with a significantly higher or lower risk of intubation or death (HR = 1.04; IC95% 0.82 to 1.32) in the adjusted analysis. |
| Magagnoli et al.[27] | In 368 male patients, median 69 years old, treated with HCQ plus support treatment. The outcome variables were mortality and need for mechanical ventilation. | The mortality rate was 27.8% in those treated with HCQ, 22.1% in those treated with HCQ and azithromycin and 11.4% in those not treated with HCQ. Ventilation rate was (13.3%), (6.9%) and (14.1%), respectively. The use of HCQ alone (but not the use of HCQ and azithromycin) was associated with an increase in overall mortality compared to support treatment, while the use of HCQ with or without azithromycin did not reduce the risk of mechanical ventilation. |
| Mahévas et al.[28] | In 181 patients requiring oxygen treated with HCQ. The use of HCQ 600 mg per day versus standard support treatment was compared. Primary variable: survival without the need for admission to intensive care within seven days of evolution or death. | This result was 20.5 versus 22.0%, (16 versus 21 events, RR = 0.93; 95% CI 0.48–1.81). Eight patients out of 84 who received HCQ had ECG modifications that required discontinuation of treatment. RAM: Electrocardiographic modifications (8/84), QT interval extension corrected >500 ms (1 patient), first degree atrioventricular blockage (1 patient). |
| Gautret et al.[29] | Retrospective, observational and uncontrolled study with 80 patients who were treated with HCQ (200 mg 3 times daily for ten days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). | In 93% of patients PCR was negativized on the eighth day of treatment. Most patients had mild to moderate pictures, and even four were asymptomatic. Since there was also no control group, it prevents us from knowing what its spontaneous evolution would have been and what the usefulness may be in patients with more severe conditions. |
| Million et al.[30] | Retrospective observational study without control group, with 1,061 positive SARS-CoV-2 patients, regardless of the presence of symptoms. 95.0% of patients had mild infection. | Clinical improvement and viral clearance were observed in 10 days in 91.7% of the patients. Five continued to be interned at the time of completion of the study. RAM: Mild adverse events (2.3%) gastrointestinal and skin in nature. |
| Molina et al.[31] | Prospective cohort of 11 hospitalized (uncontrolled) patients. All patients received the same dose and duration of HCQ as the Gautret et al.[24]study. | The HCQ and azithromycin regimen did not produce rapid viral clearance or provide clinical benefit in severe patients. |

Source: Own authorship with data from the studies cited, 2020.
RAM: Adverse Drug Reactions; RCT: Randomised clinical trial; HCQ: Hydroxychloroquine; CQ: chloroquine; ECG: electrocardiogram.

Regarding the adverse events that occurred with the use of CQ and HCQ, several clinical and observational studies add evidence that this treatment is associated with cardiac adverse effects, such as prolongation of the QT interval. The main reports are described in Table 1.

The following summarizes the recommendations and warnings that scientific societies, organizations and health agencies have made in recent months, to reduce the risk of arrhythmias in patients being treated for COVID-19 with CQ or HCQ[28,32,33,34]:

I. Monitor the electrocardiographic/QT interval.

II. Correct hypokalemia (at values greater than 4 mEq/L) and hypomagnesemia (at values greater than 2 mg/dL).

III. Use with caution in patients with heart and kidney disease. An initial assessment of these factors and ongoing monitoring should be conducted.

IV. Do not combine with other drugs that share the risk of prolonging the QT interval of the electrocardiogram (ECG). The

risk increases with high doses of HCQ and when administered with other medicines that also share this potential risk, such as azithromycin.

V. Use HCQ only in the hospital setting or in the context of a clinical trial, due to its potential serious cardiac adverse effects and the need to correct electrolyte alterations, in addition to monitoring and evaluating liver and kidney functions.

VI. If a patient is treated out-of-hospital, inform patients about the risk of heart rhythm disturbances, their symptoms, and the need to consult a doctor in case they appear.

## Remdesivir

According to the NHI *Clinical Trials* database, at the time of writing this article, there are at least 15 ongoing RCTs with standard treatment in patients with moderate and severe COVID-19 (nine of them in phase 3)[2], all with no published results yet. Table 2 describes the published results of the most relevant studies and reported adverse events.

Based on the study by Beigel *et al.* [36], FDA granted emergency use authorization to remdesivir in hospitalized patients with severe COVID-19[40]. This is the one that provides the most evidence so far; their preliminary results showed that the average recovery time was 11 days in the remdesivir group, compared to 15 days in the placebo group. However, no statistically significant differences were observed in mortality.

Furthermore, the results of the Goldman *et al.*[39] study with remdesivir and an accompanying editorial note that at current times of limited supplies of remdesivir, for patients in the early stages of severe disease, priority should be given to a five-day treatment[41].

**Table 2.** Clinical and observational trials with remdesivir in COVID-19 (main efficacy and safety results).

| Author | Description | Main results |
|---|---|---|
| Wang et al.[35] | Randomized, double-blind, placebo-controlled and multicenter clinical trial.<br>237 hospitalized patients, with oxygen saturation <95% or PaO2/FiO≤2300 mmHg and radiologically confirmed pneumonia. Treatment group: remdesivir (n = 158). Control group: placebo (n = 79). Both groups were allowed the concurrent use of corticosteroids, interferons and LPV/r. Main variable: time to clinical improvement, being monitored for 28 days. | It ended prematurely due to recruitment difficulties.<br>No differences were found between remdesivir and placebo in the main variable (HR = 1.23; IC95% 0.87-1.75), or secondary variables, including mortality. Treatment with remdesivir was not associated with statistically significant benefits.<br>RAM: Hypotension, nausea, vomiting, diaphoresis and tremors. |
| Beigel et al.[36] | RCT, double-blind, placebo-controlled with 1,059 hospitalized patients randomized to receive remdesivir (n = 538) or placebo (n = 521). Patients had at least one of the following infection criteria: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2 ≤ 94%) in ambient air, or supplemental oxygen requirement, mechanical ventilation or oxygenation by extracorporeal membrane.<br>The percentage of patients in mechanical ventilation at the time of randomization was 23.1% in the remdesivir group and 28.2% in the placebo group. Excluding patients with ALT or AST levels > 5 times the normal upper limit, with renal impairment, need for hemodialysis or hemofiltration. Mean duration of symptoms before the onset of remdesivir was nine days. Main variable: time to clinical improvement. | The average recovery time was 11 days in the remdesivir group, compared to 15 days in the placebo group (HR = 1.32; IC95% 1.12 - 1.55; p < 0.001). There was also a trend towards lower mortality that was not statistically significant; 7.1% in the remdesivir versus 11.9% placebo group (HR = 0.70; CI95% 0.47-1.04).<br>According to the authors, the percentage of mortality in the remdesivir group is high despite treatment, so it is likely that as a future strategy the combination of remdesivir with other antiviral treatments can be evaluated to improve the results in patients with COVID-19.<br>Remdesivir showed an improvement in recovery time of four days compared to support treatment. This finding, although it could be considered beneficial by some in the context of a pandemic, has little clinical relevance.<br>RAM: Serious adverse events were reported at 21%, anemia or decreased hemoglobin, acute renal injury, decreased estimated glomerular filtration rate, increased blood creatinine, pyrexia, hyperglycemia and increased levels ALT, AST or both. |
| Grein et al.[37] | A series of cases, including 61 hospitalized patients with oxygen saturation of 94% or less, who initiated treatment with remdesivir (compassionate use). Of these, eight were excluded for data loss, eventually analyzing 53 patients. Mean duration of symptoms before the onset of remdesivir was twelve days. | During a median follow-up of 18 days, two-thirds of cases treated with remdesivir showed clinical improvement; but the absence of controls prevents estimating actual efficiency.<br>RAM: Hypotension (8%). |
| Antinori et al.[38] | In study (prepress) which included 35 patients hospitalized in a hospital in Milan (Italy), with oxygen or mechanical fan requirements, which were monitored during compassionate use of this drug. Patients with ALT or AST levels greater than five times the upper limit of normal and creatinine purification <30 mL/min were excluded. The primary result of the study was clinical improvement of patients on day 10 and 28. | Ten patients had clinical improvement on the tenth day and 22 to twenty-eighth; 14 died.<br>RAM: eight patients left the study due to adverse events: four due to renal failure (three died), three due to increased hepatic transaminases and one for severe maculopapular rash. |
| Goldman et al.[39] | In open study it included 397 hospitalized patients who were randomly assigned to 5 versus 10 days of remdesivir (load dose of 200 mg on day 1, followed by 100 mg daily). The study compared the clinical improvement of patients in both groups. Hospitalized patients with confirmed SARS-CoV-2 infection, 94% or less oxygen saturation while breathing ambient air and radiological evidence of pneumonia were included in the study. | The results did not show a significant difference between the two regimens, in patients with severe COVID-19 who do not require mechanical ventilation. |

Source: Own authorship with data from the studies cited, 2020.
RAM: Adverse reactions to medicinal products; ALT: alanine aminotransferase AST: aspartate aminotransferase.

### Lopinavir/ritonavir

LPV/r is a combination of antivirals for HIV, where lopinavir is the active agent that inhibits the protease activity of the coronavirus, while ritonavir increases the half-life of lopinavir. This association showed activity *in vitro* in SARS-CoV and MERS-CoV, for which its use was postulated as part of the treatment of COVID-19[42]. Table 3 describes the most relevant results. The RECOVERY study, which provides the most evidence to date, did not show a benefit on the progression of the disease to the need for mechanical ventilation or on the length of hospital stay.

In addition, regarding safety, it is reported that LPV/r causes adverse gastrointestinal effects (diarrhea, nausea, vomiting)[44,46] and also upper respiratory infection[46], dyslipidemia, dysglycemia, QT prolongation and has the potential to interact with a large number of medications[47].

### Dexamethasone

Regarding dexamethasone, the studies found are described in Table 4.

The strongest evidence so far comes from the RECOVERY[49]clinical trial, preliminary results show that in critically ill hospitalized

**Table 3.** Observational and clinical trials with lopinavir / ritonavir in COVID-19 (main efficacy and safety results).

| Authors | Description | Main results |
|---|---|---|
| Cao et al.[43] | Open, randomized and open trial in 199 hospitalized patients with severe infection (difficulties maintaining O saturation$_2$>94%). There were 99 patients to receive LPV/r (LPV 400 mg/100 mg orally/12 days) and 100 for standard care, for 14 days. The primary result was clinical improvement at 2 points on a 7-point ordinal scale, or hospital discharge, whichever occurred first. | No differences were found between the two groups in the primary result. Viral debugging was no different between groups. Mortality was lower in the treatment arm, but was not statistically significant. In 14% of patients in the treatment group, intervention had to be discontinued due to adverse effects such as gastrointestinal intolerance and laboratory abnormalities. |
| Hung et al.[44] | Open, randomized, phase 2 trial, 127 patients with mild to moderate disease were randomized (2:1), a triple combination of LPV/r (400 mg + 100 mg, 12 hours, 14 days), ribavirin (400 mg every 12 hours) and interferon beta-1b (three doses of 8 million IU, on alternate days) or the LPV/r control group (400 mg + 100 mg, every 12 hours, 14 days). The main outcome variable was time to obtain a negative nasopharyngeal swab by RT-PCR therapy. They were only given interferon if they appeared within seven days of the onset of symptoms. | The primary variable was significantly shorter in the combination therapy group (7 versus 12 days; HR = 4.37; IC95% 1.86–10.24). The combination group also had better clinical results, including a shorter time for symptom relief (4 versus 8 days) and a shorter median hospital stay (9 versus 15 days). |
| Recovery[45] | Open RCT. LPV/r branch 4,972 patients. There were 1,596 patients assigned LPV/r and 3,376 patients assigned to support treatment. | Of the total number of patients tested (n = 4,972), 26% did not require any respiratory support, 70% required supplemental oxygen and 4% received mechanical ventilation upon entering the study. There was no effect on mortality at 28 days (LPV/r = 353 (22.1%); control = 719 (21.3%), RR = 1.04 IC95% 0.91- 1.18). No benefits in the progression of the disease, in the need for mechanical ventilation and in the duration of hospital stay (no association measures are presented for these outcomes). |

Source: Own authorship with data from the studies cited, 2020.
LPV/r: lopinavir/ritonavir; RT-PCR: reverse transcription followed by polymer chain reaction.

**Table 4.** Randomized clinical trials with dexamethasone in COVID-19 (main efficacy and safety results).

| Authors | Description | Main results |
|---|---|---|
| Villar et al.[48] | RCT that included 277 patients with SDRA in 17 intensive care units in university hospitals across Spain. 139 were randomized in the dexamethasone group and 138 in the control group. The main study variable was the number of days the patient remained alive and fanless, from the day of their randomization to the 28th. | For patients in the dexamethasone group, the average number of days was greater than that of the control group (difference between groups 4.8 days [IC95% 2.57 to 7.03]; p < 0.0001). The second measured variable corresponded to all causes of death within 60 days of randomization. It was observed that 29 (21%) patients in the dexamethasone group and 50 (36%) patients in the control group had died (difference between groups -15.3% [95% CI -25.9 to -4.9]; p = 0.0047). RAM: Hyperglycemia, new infections, barotraumas. There were no differences in adverse events between the groups. |
| Recovery[49] | The dexamethasone arm included 2,104 patients randomized to dexamethasone 6 mg once daily (orally or IV) for 10 days, compared with 4,321 patients randomized to standard treatment. | Dexamethasone reduced deaths in 1/3 in ventilated patients (frequency ratio 0.65; CI95% 0.48 to 0.88; p = 0.0003), and in 1/5 in other patients receiving oxygen only (frequency ratio 0.80; CI95% 0.67 to 0.96; p = 0.0021). No benefit was found in patients who did not need respiratory assistance (frequency ratio 1.22; CI95% 0.86 to 1.75; p = 0.14), and it is mentioned that the results are consistent with possible damage to this group. In general, dexamethasone reduced the mortality rate to 28 days by 17%, p = 0.0007. |

Source: Own authorship with data from the studies cited, 2020.
ARDS: acute respiratory distress syndrome.

patients, dexamethasone reduced deaths by 1/3 in ventilated patients and by 1/5 in other patients who received oxygen only. No evidence of benefit was found in hospitalized patients who did not require oxygen, and the results are consistent with possible harm in this group.

It should be noted that the authors of the Spanish multicenter RCT concluded that the early administration of dexamethasone could reduce the duration of mechanical ventilation and overall mortality in patients with established moderate to severe ARDS, with no significant difference in the proportion of adverse events in both groups[48].

On the other hand, a systematic review based on observational studies and a small cohort with data in patients with COVID-19, published in May 2020, indicates that corticosteroids can reduce mortality in patients with COVID-19 and ARDS, but that in for severe COVID-19 patients without ARDS, the evidence on the benefit was inconsistent and of very low quality[50].

Based on this, as diffuse inflammation and alveolar damage with hemophagocytosis occur in SARS, MERS and COVID-19 infections, it is expected consistent with the clinical phases of the disease and histopathology that the use with corticosteroids (for example, dexamethasone), could have a role in suppressing lung inflammation[51,52,53].

The benefit in critically ill patients who require oxygen, seen in the recently published RECOVERY trial, added to its known safety profile, low cost, and high accessibility, possibly lead to its adoption as part of the protocols in this group of patients[49].

## DISCUSSION

This review consolidates the data from available clinical studies about most frequently cited medicines in COVID-19 in the protocols of Latin America and from those positioned as candidates for inclusion. The Latin American context with its welfare, social and economic characteristics and the existence of regulatory authorities with less force in their decisions, complicates the application of the best available evidence.

The Information Centers of the region, have compiled this information and made recommendations based on the analysis of the benefits and risks of the drugs that are included in the therapeutic actions against COVID-19 in the region. In this sense, it may be noted that information from randomized clinical trials is limited, including the investigation of different outcomes, which makes difficult any comparison or grouping, as well as statistical analysis that reinforces or refutes the findings.

The drugs most frequently present in national protocols and with the most data from clinical studies are HCQ, LPV/r, and remdesivir. None showed, so far, significant differences in mortality.

In the case of CQ and HCQ, most of the studies prior to the dissemination of the RECOVERY study results were inconclusive and with questionable quality. When considering the available evidence, it is clearly - that these drugs are not effective in the treatment of COVID-19, and their use exposes patients to worrisome cardiac events. Thus, CQ and HCQ should not be recommended in national or institutional protocols in the countries where they are being used to treat COVID-19.

A fact that deserves attention and that has put scientific communication on guard, was the great repercussion of the study by Mehra et al.[54], which, at the date of this article, is the one -with the largest sample of patients and suggested a higher mortality associated with the use of HCQ and CQ in the context of COVID-19 infection. However, after significant doubts were raised regarding the integrity of the database, one of the most renowned scientific journals, *The Lancet*, first issued a note of concern and subsequently the retraction of the study, to which three of the four authors joined.

This review shows that the studies of both remdesivir and LPV/r have not shown any benefit on mortality in COVID-19. The remdesivir case shows another of the complicated edges of the management of the present epidemic. The advance authorization (emergency use) of remdesivir by the FDA highlights the emerging commercial influence and pressure regulation of drugs in pandemic situations[55]. The interruption of the trial, the change in the final variable, from mortality to symptomatic recovery time and the dissemination of the results initially through press releases, exposes this long-standing problem and the vulnerability of ministerial and health institutions in the face of the commercial influence. Although regulatory agility is necessary at this time, speed should not exceed basic ethical standards and trust in the evidence [56,57].

On the other hand, according to the data from the RECOVERY study, the use of corticosteroids in the small group of patients who meet the criteria of this study makes it one of the therapies considered promising.

The debate on the National Treatment Guidelines is important, because the fact that a drug is included can encourage self-medication and the search for these drugs indiscriminately by the population for uses not included in the protocols, for example, prophylactic uses, in addition to generating a false illusion of prevention and protection at a time when the use of masks, hand washing and social distancing are essential. On the other hand, the massive consumption of drugs in use off label such as those used in COVID-19, whether with or without a prescription or guidance from a health professional, can lead to an increase in serious adverse events such as those mentioned above.

This work, carried out independently, may be useful to support regulatory institutions and ministries of health in the definition of care protocols with robust and impartial evidences-. Drug information centers as well as pharmacology and therapy committees are important allies in these contexts of early, partial, variable quality and excessive amounts of information. In addition, the protocols require constant review to follow changes in the evidence and its adequate communication through official channels.

This is mainly because the pandemic has taught us how important randomized clinical trials are to support decisions in public health. The challenge was, and continues to be, to reconcile the urgency to act with the generation of new knowledge and its applicability. Any experimental use of drugs should be carried out in a research setting, with a defined protocol, and rigorous data collection and interpretation, and within the framework of a clinical trial[57].

Among the desirable lessons that the scientific community can draw from this particular case are the need for comprehensive transparency in the data that support the publications, the risk of speeding up the publication process, the caution to be observed in relation to the expectations placed on the big data technology or the necessary co-responsibility of the authors of an article with the databases of their own studies[54.58]. The information available in a massive way, through the pre-publication platforms and preliminary results, amplified by the media, social networks and political leaders, have exaggerated the magnitude and feasibility of applying the results, generating a lot of pressure on the professionals of the health and health decision-makers[59].

In this sense, it is necessary to separate data from research *in vitro* and data from small series of cases, in addition to reinforce the need to avoid biases, as far as possible, in the scenario of the research from clinical practice itself and to be aware of the safety data of the new therapies proposed with their inclusion when recommendations are suggested in the clinical guidelines. Thus, it is necessary that RCTs contemplate internal analyzes, adaptive protocols and other strategies in this regard to give more robustness and security to the information obtained from them, with external reviewers who continuously monitor its evolution[60]. Finally, the need to provide the healthcare professional in the region with more reliable and valid sources of information.

The negative influence of social networks and the media on the general population makes necessary to develop understandable information proposals, wiht message based on evidence understandable to this type of audience for reducing self-medication.

The establishment of intensive pharmacovigilance programs that supervise the safety of drugs off label use and in very heterogeneous patients is seen as a need not sufficiently reflected in the facts. Having a multicenter repository of all adverse events that have occurred due to the treatments used, with records from any country, would allow in-depth and representative analyzes of them, and can be a safe strategy that deserves to be evaluated by health authorities of the region.

Finally, in the COVID-19 scenario, new actors from the political sphere have joined, which has promoted and implemented strategies without considering the technical opinion of health institutions; this has further complicated decision-making by regulatory authorities that appear not to be totally independent. In this particular, providing regulatory authorities with quality scientific information should be one of the essential objectives of those that produce it in the region, where drug information centers play a leading role in achieving this purpose.

## CONCLUSIONS:

None of the drugs that collect the most data from clinical studies, with the exception of dexamethasone in a small subgroup of patients with severe COVID-19, have shown, until this moment, significant differences in mortality so far.

To date, no studies have been published comparing the different treatments. There are several clinical studies in progress, which will provide more evidence and which must be taken into consideration for the therapeutic management of the disease once critically analyzed.

The currently available evidence does not allow for recommendations on the specific treatment of COVID-19.

The emerging situation of COVID-19 has led to rush and controversial decision making based on questionable and/or low-quality studies. The evidence from clinical studies has important limitations, different outcomes are investigated, and often does not allow for comparison or pooling and statistical analysis to reinforce the findings. This highlights the provisional nature of the information and the possibility of generating changes as more results become available.

Advance authorization of drugs exposes a known problem. Although regulatory agility is necessary at this time, speed should not outweigh basic ethical standards and reliance on evidence.

## REFERENCES

1. Ministerio de Sanidad, Consumo y Bienestar Social (ES). Documento técnico: manejo clínico del COVID-19: atención hospitalaria. Madrid: Ministerio de Sanidad, Consumo y Bienestar Social; 2020[acceso 18 jun 2020]. Disponible en: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCovChina/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf
2. Red de Centros de Información de Medicamentos de Latinoamerica y el Caribe - CIMLAC. Tratamiento farmacológico para COVID-19: ¿cuál es la evidencia existente? Washington: Red de Centros de Información de Medicamentos de Latinoamerica y el Caribe; 2020[acceso 15 mayo 2020]. Disponible en: https://web2.redcimlac.org/images/files/tratamientos_farmacologicos_final.pdf
3. Cennimo D, Windle M, Bronze M. Coronavirus disease 2019 (COVID-19) treatment & management. Medscape. 23 mar 2020[acceso 24 mar 2020]. Disponible en: https://emedicine.medscape.com/article/2500114-treatment

4. Randomised Evaluation of COVID-19 Therapy – RECOVERY. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. London: University of Oxford; 2020[acceso 16 jun 2020]. Disponible en: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-toone-third-in-hospitalised-patients-with-severe-respiratory-complications-of-COVID-19
5. Kalil AC. Treating COVID-19: off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA. 2020;323(19):1897-8. https://doi.org/10.1001/jama.2020.4742
6. Paumgartten FJR, Delgado IF, Pitta LR, Oliveira ACAX. Drug repurposing clinical trials in the search for life-saving COVID-10 therapies: research targets and methodological and ethical issues. Vigil Sanit Debate. 2020;8(2):39-53. https://doi.org/10.22239/2317-269x.0159
7. Decisiones Informadas en Medicamentos – DIME. Observatorio de medicamentos de alto impacto financiero. Bogotá: Decisiones Informadas en Medicamentos; 2020[acceso 16 jun 2020]. Disponible en http://www.proyectodime.info/informacion-regional/informacion-seleccionada-sobre-COVID-19/
8. Universidad Pablo de Olavide. Biblioteca/CRAI. La Biblioteca/CRAI durante la COVID-19: informaciones básicas y recursos de información durante la crisis del coronavirus. Guias y tutoriales de la Biblioteca/CRAI. 2020[acceso 16 jun 2020]. Disponible en: https://guiasbib.upo.es/biblioteca_covid_19/articulos
9. Ministerio de Ciencia e Innovación (ES). Guía COVID-19: información para profesionales sanitarios. Madrid: Ministerio de Ciencia e Innovación; 2020[acceso 16 jun 2020]. Disponible en: https://www.isciii.es/QueHacemos/Servicios/Biblioteca/Paginas/Gu%C3%ADa-COVID-19.-Informaci%C3%B3n-para-profesionales-sanitarios.aspx
10. US National Library of Medicine – NLM. Clinical trials. Washington: US National Library of Medicine; 2020[acceso 16 jun 2020]. Disponible en: https://clinicaltrials.gov/ct2/results?recrs=ab&cond=COVID-19&term=&cntry=US&state=&city=&dist=
11. US National Library of Medicine – NLM. Randomised evaluation of COVID-19 therapy (RECOVERY). Clinical trials. 3 jun 2020[acceso 3 jun 2020]. Disponible en: https://clinicaltrials.gov/ct2/show/NCT04381936
12. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020;30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Clin Infect Dis. 2020;71(15):732-9. https://doi.org/10.1093/cid/ciaa237
14. McIntosh K. Coronavirus disease 2019 (COVID-19). Wolters Kluwer Uptodate. 13 mar 2020[acceso 23 mar 2020]. Disponible en: https://www.cmim.org/PDF_covid/Coronavirus_disease2019_COVID-19_UpToDate2.pdf
15. The Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Chin J Tuberc Respir Dis. 2020;43(3):185-8. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.009
16. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Zhejiang Da Xue Xue Bao Yi Xue Ban. 2020;49(2):215-9. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03
17. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRvix. 2020:1-11. https://doi.org/10.1101/2020.03.22.20040758
18. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:1-11. https://doi.org/10.1136/bmj.m1849
19. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GS, Brito M et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):1-14. https://doi.org/10.1001/jamanetworkopen.2020.8857
20. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med. 2020;383:517-25. https://doi.org/10.1056/NEJMoa2016638
21. Chen L, Zhang ZY, Fu JG, Feng ZP, Zhang SZ, Han QY et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. MedRxiv. 2020:1-27. https://doi.org/10.1101/2020.06.19.20136093
22. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR el at. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. MedRxiv 2020:1-27. https://doi.org/10.1101/2020.07.15.20151852
23. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med. 2020. https://doi.org/10.7326/M20-4207
24. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):1-6. https://doi.org/10.1016/j.ijantimicag.2020.105949
25. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA. 2020;323(24):2493-502. https://doi.org/10.1001/jama.2020.8630

26. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;382:2411-8. https://doi.org/10.1056/NEJMoa2012410
27. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. MedRvix. 2020:1-27. https://doi.org/10.1101/2020.04.16.20065920
28. Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ. 2020;369:1-9. https://doi.org/10.1136/bmj.m1844
29. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020;34:1-7. https://doi.org/10.1016/j.tmaid.2020.101663
30. Million M, Lagier JC, Gautret P, Colson P, Fournier P-E, Amrane S et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1.061 cases in Marseille, France. Travel Med Infect Dis. 2020;35:1-9. https://doi.org/10.1016/j.tmaid.2020.101738
31. Molina JM, Delaugerre C, Goff J, Mela-Lima D, Ponscarme D, Goldwirt L et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020;50(4):382-7. https://doi.org/10.1016/j.medmal.2020.03.006
32. Red Argentina de Centros de Información de Medicamentos – RACIM. Ficha técnica RACIM: hidroxicloroquina, sulfato de. Córdoba: Centros de Información de Medicamentos; 2020[acceso 3 mayo 2020]. Disponible en: http://cime.fcq.unc.edu.ar/wp-content/uploads/sites/15/2020/05/RACIM-Hidroxicloroquina-versi%C3%B3n1-03.05.2020.pdf
33. Caffaratti M. Precaución con el uso de hidroxicloroquina en pacientes con enfermedad cardiovascular y COVID-19. Córdoba: Centro de Información de Medicamentos; 2020[acceso 25 abr 2020]. Disponible en: http:cime.fcq.unc.edu.ar/wp-content/uploads/sites/15/2020/04/Informe-CIME-uso-HCQ-v.final.pdf
34. Agencia Española de Medicamentos y Productos Sanitarios – AEMPS. Cloroquina e hidroxicloroquina: precauciones y vigilancia de posibles reacciones adversas em pacientes con COVID-19. Madrid: Agencia Española de Medicamentos y Productos Sanitarios; 2020[acceso 16 mayo 2020]. Disponible en: http://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2020-seguridad-1/cloroquina-hidroxicloroquina-precauciones-y-vigilancia-de-posibles-reacciones-adversas-en-pacientes-con-COVID-19
35. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78. https://doi.org/10.1016/S0140-6736(20)31022-9
36. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zigman BS, Kalil AC. Remdesivir for the treatment of COVID-19: preliminary report. New Engl J Med. 2020:1-12. https://doi.org/10.1056/NEJMoa2007764
37. Grein J, Ohmagari N, Shin D, Díaz G, Asperges E, Castagna A et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med. 2020;382:2327-36. https://doi.org/10.1056/NEJMoa2007016
38. Antinori S, Cossu M, Ridolfo A, Rech R, Bonazzetti C, Pagani G et al. Compassionate remdesivir treatment of severe COVID-19 pneumonia in intensive care unit (ICU) and non-ICU patients: clinical outcome and differences in post treatment hospitalisation status. Pharmacol Res. 2020;158:1-6. https://doi.org/10.1016/j.phrs.2020.104899
39. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med. 2020:1-11. https://doi.org/10.1056/NEJMoa2015301
40. US Food and Drug Administration – FDA. Fact sheet for health care providers: emergency use authorization (EUA) of remdesivir (GS-5734). Washington: US Food and Drug Administration; 2020[acceso 1 mayo 2020]. Disponible en: https://www.fda.gov/media/137566/download
41. Fundación Instituto Catalán de Farmacología - FICF. Sistema de información esencial en terapéutica y salud (Sietes): Ref ID 103634. Barcelona: Fundación Instituto Catalán de Farmacología; 2020[acceso 27 mayo 2020]. Disponible en: http://www.sietes.org/buscar/cita/103634
42. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):1-14. https://doi.org/10.1038/s41467-019-13940-6
43. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020;382:1787-99. https://doi.org/10.1056/NEJMoa2001282
44. Hung IFN, Lung KC, Tso EYK, Liu R, Chung TWH, Chu MY et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695-70. https://doi.org/10.1016/S0140-6736(20)31042-4
45. Randomised Evaluation of COVID-19 Therapy – RECOVERY. Statement from the chief investigators of the randomised evaluation of COVID-19 therapy (RECOVERY) trial on lopinavir-ritonavir. London: University of Oxford; 2020[acceso 29 jun 2020]. Disponible en: https://www.recoverytrial.net/files/lopinavir-ritonavir-recovery-statement-29062020_final.pdf
46. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020:323(15):1488-94. https://doi.org/10.1001/jama.2020.3204

47. Agencia Española de Medicamentos y Productos Sanitarios – AEMPS. Tratamientos disponibles para el manejo de la infección respiratoria por SARS-CoV-2. Madrid: Agencia Española de Medicamentos y Productos Sanitarios; 2020[acceso 9 jul 2020]. Disponible en: https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/

48. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-76. https://doi.org/10.1016/S2213-2600(19)30417-5

49. Randomised Evaluation of COVID-19 Therapy – RECOVERY. Dexamethasone in hospitalized patients with COVID-19: preliminary report. New Engl J Med. 2020:1-11. https://doi.org/10.1056/NEJMoa2021436

50. Ye Z, Wang Y,Colunga-Lozano LE, Prasad M, Tangamornsuksan W et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ. 2020;192(27):E756-67. https://doi.org/10.1503/cmaj.200645

51. Nicholls JM, Poon LLM, Lee KC, Ng WF, Lai ST, Leung CY et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet. 2003;361(9371):1773-8. https://doi.org/10.1016/S0140-6736(03)13413-7

52. Nicholls J, Dong XP, Jiang G, Peiris M. SARS: clinical virology and pathogenesis. Respirology. 2003;8(supl 1):s6-s8. https://doi.org/10.1046/j.1440-1843.2003.00517.x

53. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Hearth Lung Transplant. 2020;39(5):405-7. https://doi.org/10.1016/j.healun.2020.03.012

54. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Retracted: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020:1-10. https://doi.org/10.1016/S0140-6736(20)31180-6

55. Mak TK, Lim JCW, Thanapholler P, Mahlangu GN, Cooke E, Lumpkin MM. Global regulatory agility during COVID-19 and other health emergencies. BMJ. 2020;369:1-2. https://doi.org/10.1136/bmj.m1575 pmid:32340997

56. Durán C, Cañás M, Chistiaens T. EMA and FDA decisions based on flawed evidence to approve new cancer drugs negatively affect Latin American patients. BMJ. 2019;367. https://doi.org/10.1136/bmj.l6017

57. Cañás M, Urtasun MA. La evidencia en tiempos de coronavirus (COVID-19). Evid Actual Pract Ambul. 2020;23(2):1-5.

58. Fernández LCS. Cloroquina e hidroxicloroquina como potenciales terapias frente al COVID-19. Madrid: Centro Cochrane Iberoamericano; 2020[acceso 5 jun 2020]. Disponible en: https://es.cochrane.org/sites/es.cochrane.org/files/public/uploads/COVID- 19/cochrane_navarra_COVID-19_cloroquina_hidroxicloroquina.pdf

59. Cañás M, Urtasun MA. Entre la ilusión y la ciencia. Revista Mestiza. 2020[acceso 27 abr 2020]. Disponible en: https://revistamestiza.unaj.edu.ar/entre-la-ilusion-y-la-ciencia/

60. Ferner RE, Aronson JK. Remdesivir in COVID-19: a drug with potential: dont´t waste time on uncontrolled observations. BMJ. 2020;369:1-2. https://doi.org/10.1136/bmj.01610

## Contribution of the Authors

Saavedra PAE, Cañás M, Barbado DMC, Esparza LB, Caffaratti M, Speranza N, Martínez CF, Gutiérrez JJL- Conception, planning (study design), acquisition, analysis, interpretation of data and writing of the work. All authors will approve the final version of the work.

## Conflict of Interest

The authors inform that they do not have any potential conflict of interest with peers and institutions, politicians or financers of this study.