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REVIEW

Pharmacologic treatment in patients with COVID-19: an integrative review

Tratamiento farmacológico en pacientes con COVID-19: una revisión integradora

Tratamento farmacológico em pacientes com COVID-19: uma revisão integrativa

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Abstract

Introduction: Today more than ever human health has been compromised; humanity is suffering from the invasion of the SARS-CoV-2 coronavirus, which has exposed the world to the worst health emergency in this century. Although the scientific community and global health systems are joining efforts in the search for a definitive treatment, to date it is recognized that the therapy is aimed at mitigating the symptoms. **Objective:** Identify scientific evidence on pharmacological treatment for patients with COVID-19. **Methodology:** An integrative review of literature published from December 2019 to October 2020, in the following information systems Clinical Key, Dialnet, EBSCO Host and Scopus was performed using the descriptors Coronavirus Infections, COVID-19, Drug therapy, and pharmacological treatment. The selection criteria were quantitative research articles of any type of design, in English and Spanish, available in full text, obtaining a sample of 24 articles. **Results:** Most of the studies were integrative reviews with a percentage of 66.6 and clinical or in vitro trials with a percentage of 12.5. Nine drugs of major use in COVID-19 were identified in the drug therapy, that is, Hydroxychloroquine/Chloroquine, Lopinavir/Ritonavir, Remdesivir, Azithromycin, Ivermectin, Tocilizumab and Dexamethasone. However, According to the scientific evidence only four drugs showed significant effectiveness. **Conclusions:** Remdesivir demonstrated greater effectiveness and safety during the treatment, and Tocilizumab and Dexamethasone showed favorable results. Nevertheless, the results are not conclusive. The authors pointed out that so far is not possible to conclude there are treatments that effectively fight COVID-19.

Keywords: COVID-19; Coronavirus Infections; Pharmacological Treatment (DeCS, MeSH).

Resumen

Introducción: La salud hoy más que nunca ha sido vulnerada, la humanidad está sufriendo por la invasión del coronavirus SARS-CoV-2, que ha expuesto al mundo a la peor emergencia sanitaria en este siglo. La comunidad científica y los sistemas de salud global conjuntan esfuerzos en la búsqueda de un tratamiento definitivo, a la fecha se reconoce que la terapia está dirigida a mitigar los síntomas. **Objetivo:** Identificar las evidencias científicas sobre el tratamiento farmacológico en los pacientes con COVID-19. **Metodología:** Se realizó una revisión integradora de la literatura publicada de diciembre 2019 a octubre 2020, en los sistemas de información Clinical Key, Dialnet, EBSCO Host y Scopus, mediante los descriptores Coronavirus Infections, COVID-19, Drug therapy, tratamiento farmacológico. Los criterios de selección fueron artículos de investigación cuantitativa de cualquier tipo de diseño, en inglés y español disponibles a texto completo, obteniéndose una muestra de 24 artículos. **Resultados:** La mayoría de los estudios fueron revisiones integrativas con 66.6% y ensayos clínicos o in vitro con 12.5%. Se identificaron en la terapia farmacológica nueve medicamentos de mayor uso en COVID-19: Hidroxicloroquina/cloroquina, lopinavir/ritonavir, remdesivir, azitromicina, ivermectina, tocilizumab y dexametasona, no obstante, solo cuatro fármacos mostraron efectividad significativa según la evidencia científica. **Conclusiones**: remdesivir demostró mayor efectividad y seguridad en el tratamiento, tocilizumab y dexametasona mostraron resultados favorables, sin embargo, los resultados no son contundentes. Los autores señalan que aún no es posible afirmar que se dispone de tratamientos que combata la COVID-19 efectivamente.

Palabras clave: COVID-19; Infecciones por coronavirus; Tratamiento farmacológico (DeCS, MeSH).

Abstrato

Introdução: Hoje, mais do que nunca, a saúde humana foi comprometida; a humanidade está sofrendo com a invasão do coronavírus SARS-CoV-2, que expôs o mundo à pior emergência sanitária deste século. Embora a comunidade científica e os sistemas globais de saúde estejam unindo esforços na busca por um tratamento definitivo, até o momento é reconhecido que a terapia visa mitigar os sintomas. Identificar evidências científicas sobre o tratamento farmacológico de pacientes com COVID-19. **Objetivo:** Identificar evidências científicas sobre o tratamento farmacológico para pacientes com COVID-19. **Metodologia:** Foi realizada uma revisão integrativa da literatura publicada de dezembro de 2019 a outubro de 2020, nos seguintes sistemas de informação Clinical Key, Dialnet, EBSCO Host e Scopus utilizando os descritores Coronavirus Infections, COVID-19, Drug therapy, and pharmacological treatment. Os critérios de seleção foram artigos de pesquisa quantitativa, de qualquer tipo de delineamento, nos idiomas inglês e espanhol, disponíveis na íntegra, obtendo-se uma amostra de 24 artigos. **Resultados:** A maioria dos estudos foram revisões integrativas com percentual de 66,6 e ensaios clínicos ou in vitro com percentual de 12,5. Nove medicamentos de maior uso no COVID-19 foram identificados na terapia medicamentosa, ou seja, Hidroxicloroquina/Cloroquina, Lopinavir/Ritonavir, Remdesivir, Azitromicina, Ivermectina, Tocilizumabe e Dexametasona. No entanto, de acordo com as evidências científicas, apenas quatro medicamentos mostraram eficácia significativa. **Conclusões:** De acordo com as evidências científicas, apenas quatro medicamentos mostraram eficácia significativa. Conclusões: Remdesivir demonstrou maior eficácia e segurança durante o tratamento, e Tocilizumabe e Dexametasona apresentaram resultados favoráveis. No entanto, os resultados não são conclusivos. Os autores apontaram que até o momento não é possível concluir que existam tratamentos que combatam efetivamente o COVID-19.

Palavras-chave: COVID-19; Infecções por Coronavírus; Tratamento Farmacológico (DeCS).

Introduction

In the international context, it is recognized that the health situation today is very complex. This situation has been intensified by the impact of the COVID-19 pandemic that has exposed the world to the worst health emergency of this century, which has caused great human, economic and social costs [(1)]. The acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2), better known as COVID-19, began in Wuhan, China, in December 2020. Since that date, COVID-19 has spread globally and on March 11, 2021 [(2)] the World Health Organization (WHO) declared it a pandemic. The Emergency Committee on COVID-19 [(3)] held its fifth meeting in October 2020 where the situation and its progress were reviewed, repeating that the pandemic was a Public Health emergency of international importance, reporting to date 44 million cases, 28.2 million people recovered and just over 1.1 million deaths from COVID-19 [(2-4)]. Several countries joined forces to reduce and contain the spread of the virus, and made multiple

efforts to discover a definitive treatment that would improve the health conditions of the population. Until that time, it was directed towards the management and containment of symptoms, through antiviral therapy and plasma transfusion, because at that time specific drugs and vaccines against the virus had not yet been discovered (3-5).

Coronaviruses belong to a large family of viruses called *Coronaviridae*, which continuously circulate among the human population and typically target the upper respiratory tract causing symptoms similar to the common cold. Most people with COVID-19 had mild (40%) or moderate (40%) disease, but some developed severe (15%) and critical (5%) disease with complications such as respiratory failure, acute respiratory syndrome, sepsis, thromboembolism and multiorgan failure that could lead to death. In severe disease, smoking, advanced age and comorbidities such as high blood pressure, heart disease, diabetes and cancer have been identified as risk factors [(5, 6)].

Currently, no convincing results from randomized clinical trials regarding a therapy that improves outcomes in suspected or confirmed cases of COVID-19 have yet been found [(4, 7, 8)]. More than 300 active treatment clinical trials have been conducted with evidence-based findings regarding the major treatments proposed suggest the use of antiviral therapies including monoclonal antibodies and antiviral peptides that act on the viral tip glycoprotein, as well as viral enzyme inhibitors, viral nucleic acid synthesis inhibitors, and inhibitors of other viral proteins. Other therapies include agents that potentiate the host interferon response or affect signaling pathways in viral replication [(6-9)]. Therefore, antiviral drugs (Remdesivir, Ribavirin, Lopinavir-Ritonavir, Favipiravir, Oseltamivir, Umifenovir), antimalarials (Chloroquine [CQ] and Hydroxychloroquine [HCQ]), immunomodulatory agents (Tocilizumab [TCZ] interferons, plasma transfusions) and coadjuvant agents (Azithromycin [AZI], Corticosteroids [CST]), are currently used, among others. Action mechanisms and further pharmacological measures should be analyzed in the light of clinical trial results, especially with regard to the safety and performance of each drug [(7-12)].

Some recent reports have shown therapeutic effects against COVID-19 infection, such as the use of HCQ [10, 11], AZI [11,12] and Ivermectin [13]; however, there are still no consistent data on which drug has greater efficiency compared to another or if the combination of them can preserve life [3, 8, 14-17].

Since the nurse is the main human resource in the health system that provides 24-hour care and administers the various treatments to patients with COVID-19, it is vitally important to keep up to date with the most widely used international pharmacological treatments. This review aims to answer the question: Which are the pharmacological treatments and its outcome/effectiveness in the control, recovery and survival of patients with COVID-19? Therefore, the purpose is to identify scientific evidence on pharmacological treatments for patients with COVID-19.

Methodology

Integrative review of the literature applying critical reading [18,19], the PICO methodology was used, which means: Patient (Patient/P): Adults diagnosed with COVID-19; Intervention or Treatment (Intervention/I): Pharmacological treatment used; Comparison (Comparison/Treatment groups/C): Comparison between the different drugs; Expected Outcomes (Outcomes/O): Control, recovery, survival of the patients. Therefore, a plan was implemented to search for information in studies of any type of research design, published from December 2019 to November 2020, in the databases and information systems EBSCO-Host, Scopus, Clinical Key and Dialnet. Keywords extracted from Descriptors of Health Sciences of the Latin American and Caribbean Center (DeCS) (20): Coronavirus infections, COVID-19, drug therapy, drug treatment, and from the Medical Subject Heading of the National Library of Medicine (MeSH) (21): COVID-19 drug treatment, coronavirus disease 2019 drug treatment, (term introduced in March 2020), were used. Other terms used in the search were COVID-19, SARS-CoV-2, drug therapy, COVID-19 drug effectiveness, treatment coronavirus, coronavirus pharmacotherapy, COVID-19, effective pharmacological treatment in COVID-19, and the combined Boolean operators AND and OR.

The search for information produced 13,382 articles published in English (91.6%) and Spanish (8.4%) (Table 1). Those available in full text in both languages that addressed the study variables in adult population were selected; 13,358 repeated articles and those in which the full text document was not found were eliminated.

Table 1. Information system and search strategy for articles on pharmacological treatment in patients with COVID-19, (*n=13,382*).

Database information system	Search strategy	Articles
Clinical Key	1. COVID AND tratamiento (treatment).	1. Spanish: 305; English: 5531
	2. Coronavirus tratamiento (treatment)OR COVID SAR2.	2. Spanish: 366; English: 6265
	3. COVID AND Pharmacotherapy.	3. Spanish: 12; English: 83
EBSCO Host	1. COVID - 19 AND tratamiento (treatment).	1. Spanish: 190
	2. COVID - 19 AND drugs.	2. English: 152
SCOPUS	1. SARS-CoV-2 AND farmacoterapia (pharmacotherapy).	1. Spanish: 26
	2. SARS-CoV-2 AND pharmacotherapy OR COVID-19 treatment.	2. Spanish: 137
Dialnet	1. COVID AND tratamiento (treatment).	1. Spanish: 211
	2. SARS-CoV-2 AND tratamiento (treatment).	2. Spanish: 4

Source: Own development.

After the critical reading and in accordance with the criteria established to answer the PICO research question, the sample finally consisted of 24 articles. In the collection, analysis and presentation of data, we used tables presenting information on the selected studies, such as authors, year, country, objective, methods, results and conclusions.

Results

The literature consulted was published in 2020 and belonged to the USA (20.8%), Spain (12.5%), China, Ecuador, Colombia and Peru with 8.3% each, and other countries such as India, Arabia, England, Portugal, Cuba and Mexico with 4.2%. Regarding the language of publication, 54.2% were in Spanish and 45.8% in English. In terms of research design, 66.6% was an integrative review, 12.5% were clinical or in vitro trials, 8.3% were systematic reviews and meta-analyses, and the remaining 4.2% corresponded to other types of design.

According to the critical reading, pharmacological treatment against COVID-19 was classified into groups according to their effect and potency, with the following groups being considered: various antiviral drugs by themselves or in combination, including Remdesivir, Rivafarin, Lopinavir/Ritonavir, Faviparir, Oseltamivir, Umifenovir, Emtricitabine/Tenofovir/Alafenamide [5,16,17, 25-28, 30, 31, 33, 35-37]. Other drugs such as antimalarials, antiparasitic and antibacterial with antiviral effect in SARS-CoV-2 were: CQ, HCQ alone or combined with AZI and Ivermectin [5, 14, 23, 25, 28, 29, 32, 34-36], Nitazoxanide, Teicoplanin, Azithromycin and Ceftriaxone [5, 14, 23]. Anti-inflammatory drugs such as Corticoids, Methylprednisolone, Dexamethasone and Prednisone [5, 17, 22, 24, 28]. Immunomodulatory drugs, TCZ, Interferons, Immunoglobulin and convalescent plasma [5, 21, 22, 27, 31, 35, 37-39], and also anticoagulant drugs such as Heparin and Enoxaparin [35].

From all the studies according to the scientific evidence, only four drugs showed significant effectiveness, Remdesivir showed greater effectiveness and safety in the treatment; Tocilizumab and Dexamethasone showed favorable results. Nevertheless, the results are not conclusive. The most relevant information from the analysis of the selected studies is shown below (Table 2).

Table 2. Pharmacological treatment for patients with COVID-19, (*n = 24*).

Authors	**Country**	**Objectives**	**Methods**	**Main results**	**Conclusions**
Choudhary R, Sharma AK. [14]	India	To present insights from major research on the drugs Ivermectin, HCQ and AZI in the context of the current health emergency.	Integrative Review. Sample not specified.	Clinical trials revealed the potential effect of HCQ in acute respiratory syndrome due to coronavirus, Ivermectin showed inhibition of viral replication. In in vitro assays it reduced the virus 5000-fold in 48 hours. AZI showed high therapeutic potency and may act as a prophylactic to decrease the infection rate of COVID-19.	HCQ, Ivermectin and AZI have potential effect against coronavirus infection; however, their efficiency should be studied in detail in larger clinical trials.
Fan L, Jiang, S, Yang X, Wang Z. [22]	China	To examine the drugs used for the emerging treatment of COVID-19 in China.	Integrative Review. Sample not specified.	There are 23 different drugs used in the treatment of COVID-19, based on symptomatology: Chemical drugs (Rivafirin, Lopinavir/Ritonavir, Arbidol, Darunavir, Remdesivir, CQ phosphate, Favipiravir, HCQ combined with AZI, Emtricitabine, Tenofovir/Alafenamide). Biologic	There are still no specific antiviral drugs for COVID-19. The drugs being used are based on the experiences of previous treatments in viruses such as SARS, MERS and

				drugs (interferon, TCZ, convalescent plasma therapy, glucocorticoids). Another drug, intravenous immunoglobulin indicated in systemic inflammation in critically ill patients.	others. The efficiency and safety of the drugs need to be investigated with further clinical trials.
Tzu-Han Y, Chian-Ying C, Yi-Fan Y, Chian-Shiu C, Aliaksandr AY, Tzu-Ying Y, Cheng-Hsuan L, et al. [23]	China	To show the pharmacological effectiveness of Hydroxychloroquine/Chloroquine (HCQ/CQ) against COVID-19.	Systematic review and meta-analysis, n=9 trials including 4,112 patients. Analysis in groups with different disease stage and period (≤ 14 days, > 14 days), as well as HCQ doses, ≤ 400 mg/day) and > 400 mg day).	The combination of HCQ-AZI in patients with COVID-19 showed greater benefits in virus elimination (OR 27.18, 95% CI: 1.29-574.32), relative to the increment in mortality rate (OR 2.34, 95% CI: 1.63-3.36). The treatment could reduce the mortality rate and progression to severe disease in severely infected COVID-19 patients (OR 0.27, 95% CI: 0.13-0.58). A lower risk of mortality was observed in the stratified group in the >14-day period (OR 0.27, 95% CI 0.13-0.58) vs. the ≤14-day follow-up group, which conversely showed increased mortality rate (OR 2.09, 95% CI 1.41-3.10).	HCQ-AZI showed benefits associated with virus elimination in patients, and decreased mortality rate for COVID-19. More rigorous, large-scale studies with longer follow-up periods in patients with COVID-19 are required.
Reina J. [26]	Spain	To demonstrate the antiviral efficiency of Remdesivir.	Integrative Review. Sample not specified.	Remdesivir showed in vitro and in animals a high capacity to block viral infection and replication with concentrations achievable in human plasma. All studies were performed with SARS-CoV-2 and MERS-CoV. It seems that by virological and functional analogy, Remdesivir is one of the few that have demonstrated efficiency.	Remdesivir could be the antiviral hope against SARS-CoV-2. It is suggested that this drug be administered in the first 48 hours to shorten viral replication and decrease transmissibility.
Wayah S, Auta R, Waziri P, Haruna E. [16]	Nigeria	To probe drugs targeting host cell surface receptors required for SARS-CoV-2 infection and to examine drugs that can modify the host immune response to achieve virus elimination	Integrative Review. Sample not specified.	Groups of drugs with various effects are discussed: Host receptor drugs or enzymes in the virus cell, angiotensin 2 enzyme (ACES-2), those acting on transmembrane proteases (TMPRS2) or effective systemic antibacterials. Drugs acting on host cell gangliosides to reduce viral load, such as CQ, HCQ, even more potent. Drugs that inhibit viral RNA validated in various trials such as Remdesivir. Others such as antibody therapy, immunomodulators and	In COVID-19, no single therapeutic approach is sufficient to mitigate the disease. It requires the use of combination drugs with diverse effects. The most potent drugs in viral reduction were HCQ (better than Lopinavir and Ritonavir) but surpassed by Remdesivir,

				anticoagulants to stimulate host response.	supported in type III clinical trials, widely used in China and USA.
Marto N, Monteiro E.[25]	Portugal	To analyze the positioning of health agencies around the world regarding off-label use of reused drugs or new investigational drugs to treat coronavirus disease.	Integrative Review. Sample not specified.	China was the first country to develop clinical guidelines for the treatment of COVID-19, including Lopinavir/Ritonavir (LPV/r), Remdesivir, Rivafirin, interferon beta, CQ, HCQ, TCZ, plasma and immunoglobulin. Due to the urgency of the pandemic and the limited evidence in several countries, protocols for the use of these drugs have been issued. The available evidence indicates that the drugs that reduce disease progression and mortality rate are, above all, Remdesivir, CQ, HCQ, LPV7r, and TCZ.	The importance of administering off-label and investigational drugs in clinical trials or at least in standardized settings to generate as much scientific knowledge as possible is emphasized. Remdesivir is considered the best antiviral due to its broad spectrum and clinical safety.
Crespillo C, Moreno S.[5]	Spain	Review the drugs used and under investigation for the treatment of COVID-19.	Integrative Review. Sample not specified.	Various drugs used with in vitro activity such as: Lopinavir/Ritonavir, CQ/HCQ, AZI, Betaferon. Remdesivir is in clinical trials, with encouraging preliminary results. Anti-inflammatory and immunomodulatory drugs have been extensively investigated. Glucocorticoids at low doses for a few days have shown a reduction in the mortality rate, although the results are not yet definitive. TCZ has been widely used, with positive effects in observational studies.	Currently no drug has been shown to be effective against coronavirus in humans, although several drugs with in vitro activity have been used.

Tlayjeh H, Mhish O, Enani M, Alruwaili A, Tleyjeh R, Thalib L.[24]	Saudi Arabia	To review the literature on the association between systemic therapy with CST and COVID-19 patients' outcomes.	Systematic review and meta-analysis. Included observational studies and randomized clinical trials (RCTs) evaluating patients with COVID-19 treated with CST. Diverse samples	The effect of systemic therapy with CST on short-term mortality was examined in 16,977 hospitalized patients (1 RCT and 19 cohorts) and in other studies with 10,278 patients (1 RCT and 8 cohorts). The pooled adjusted RR was 0.92 (95% CI: 0.69 to 1.22, I2=81.94%). Four cohort studies examined the effect of CST on the combined outcome of death, ICU admission, and need for mechanical ventilation. The pooled adjusted RR was 0.41 (0.23-0.73, I2=78.69%). Six cohorts examined the effect of CST on delayed viral clearance. The pooled adjusted RR was 1.47 (95% CI 1.11-1.93, I2=43.38%).	Not in all studies, CSTs were associated in reducing short-term mortality, but changes in the time to viral clearance were observed in hospitalized COVID-19 patients with different severity.
Díaz E, Amezaga-Menéndez R, Vidal-Cortés P, Escapa MG, Subeviola B, Serrano-Lázaro A et al. [27]	Spain	To provide an update on the therapy that is currently being applied.	Integrative review. Diverse samples in different studies.	Several therapies with different actions are used. Antiviral effect: Lopinavir/Ritonavir, Remdesivir, HCQ and AZI, Interferon B, Remdesivir, overall mortality was 18% (13% with mechanical ventilation, 5% not ventilated). It was not associated with clinical improvement. TCZ is indicated in patients with moderate disease and not in severe cases. The National Health Commission of China and other experts recommend its use in critically ill patients with IL-6 elevation. The evidence for anti-inflammatory treatment with TCZ is very limited. We observed that the anticoagulant was associated with decreased mortality (HRa 0.86, per day, 95% CI 0.82-0.89, p<0.001).	The lack of proven therapies and the need for clinical trials to establish clear and objective treatment guidelines are highlighted. Different therapies are used with rapid modifications in the protocols.
Gonzales-Zamora J, Quiroz T, Vega A. [28]	USA	To present a case study of a male patient with COVID-19-associated pneumonia.	Case study.	Patient with SARS-CoV-2, initially received Ceftriaxone and AZI, the latter replaced by HCQ, when he did not improve, Remdesivir was indicated at a dose of 200 mg IV daily and then 100 mg IV daily for 4 days, combined with Prednisolone for IL-6 increase. The patient improved significantly.	The combination of Remdesivir and Methylprednisolone should be considered in cases of severe COVID-19 pneumonia to fight viral damage and control inflammation.

Pan American Health Organization (OPS), OMS. [29]	USA	Recommend the use of Ivermectin for the treatment of COVID-19.	Rapid integrative review of all human in vitro (laboratory) and in vivo (clinical) studies of COVID-19. Sample not specified	The Expert Committee statement on Ivermectin emphasized its efficiency in reducing viral load in laboratory cultures, at dosage levels well above those approved by FDA in the treatment of parasitic diseases in humans. This body pointed out insufficient evidence for Ivermectin to reduce viral load in patients with COVID-19.	The studies of Ivermectin present high bias, very little certainty of the evidence and the existing evidence is insufficient to reach a conclusion on its benefits and harms. The Pan American Health Organization does not recommend the use of Ivermectin in the treatment for COVID-19.
Cao B, Wang D, Liu Wen, Wang J, Fan J, Ruan L, et al. [30]	England	Evaluate the efficiency of Lopinavir/Ritonavir, according to time and clinical improvement.	Randomized controlled trial. Adult patients hospitalized with COVID-19 (99 experimental group and 100 control group). Measurements 14 and 28 days.	Treatment with Lopinavir-Ritonavir (400 and 100 mg) 2/day for 14 days was not associated with clinical improvement versus standard care HR 1.24 (95% CI, 0.90 -1.729). Patients at the 28-day measurement had significant clinical improvement in less time than that observed with standard care 1.39 (95% CI, 1.00-1.91). Mortality at 28 days was similar in both groups (19.2% vs. 25%; difference, -5.8 percentage points (95% CI, -17.3-5.7).	In adult patients with severe COVID-19, treatment with Lopinavir/Ritonavir at 28 days significantly accelerated clinical improvement and did not reduce mortality.
Sanders J, Monogue M, Jodlowski T, Cutrell J. [31]	USA	To review the evidence for the main proposed new or experimental treatments for COVID-19.	Integrative review, documents published by March 25, 2020. Sample not specified.	Remdesivir is the drug with potent in vitro activity against SARS-CoV-2, but there is not yet conclusive evidence. There is no high-quality evidence on the efficiency of CQ/HCQ in SARS or MERS. Lopinavir/Ritonavir data indicate that it has a limited role in the treatment of COVID-19. Interferons are not recommended because of conflicting data on their action. Nitazoxanide is relatively favorable, but further study is required. Convalescent plasma and immunoglobulin was associated with a reduction in mortality OR 0.25 (95% CI, 0.14-0.45).	Further quality studies on treatment for COVID-19 are required. To date, no therapy has been shown to be effective, except convalescent plasma and immunoglobulin are slightly associated with decreased mortality.

Rosenberg E, Dufort E, Udo T, Wilberschied L, Kumar J, Tesoriero J, et al.[32]	USA	To describe the association between the use of HCQ with or without AZI, clinical outcomes, and in-hospital mortality among patients with COVID-19.	Multicenter cohort study. Sample 1,438 patients from 25 hospitals in New York. Groups: 1) HCQ +AZI, n=735; 2) HCQ, n=271; 3) AZI, n= 211 and 4) none of the drugs, n=221.	In all groups of patients hospitalized with COVID-19, using Cox proportional hazards adjustments, no significant differences in the potential mortality rate were observed. HCQ-AZI (HR, 1.35 (95% CI, 0.76-2.40); HCQ (HR, 1.09 (95% CI, 0.63-1.85) or AZ (HR, 0.56 95% CI, 0.26-1.21). Cardiac arrest was significantly more likely in patients receiving HCQ-AZI (adjusted OR, 2.13(95% CI, 1.12-4.05), but was not significant in HCQ (adjusted OR, 1.91, 95% CI, 0.96-3.81) or AZ (adjusted OR, 0.64, 95% CI, 0.27-1.56).	Among COVID-19 patients hospitalized in the New York area, differences in mortality were not significant with HCQ-AZI, HCQ, and AZ treatment compared to those with no treatment. However, interpretation of results is limited by the type of study design.
Spinner C, Gottlieb R, Criner G, Arribas J, Cattelan A, Soriano V, et al.[33]	USA	To determine the efficiency of 5 or 10 days of treatment with Remdesivir compared to standard care, on clinical status on the 11th day after initiation of treatment.	Randomized trial in 105 hospitals in the USA, Asia and Europe. Sample n=596 randomized patients. Groups: Remdesivir for 10 days (197), those who received Remdesivir for 5 days (199), and standard care (200).	533 patients completed the trial. The median duration of treatment was 5 days and 6 days in the 10-day Remdesivir group. At day 11, patients in the 5-day Remdesivir group had significant clinical improvement compared with those receiving standard care (OR 1.65; 95% CI, 1.09-2.48; p=.02). On day 11, the distribution in clinical status of those who received Remdesivir on day 10 and the standard care group had no significant difference, p=.18.	Patients with COVID-19 with moderate and low severity with Remdesivir at 5 days had significant clinical changes with respect to those with standard care. At longer treatment time there were no significant changes.
Jimbo-Sotomayor R, Gómez-Jaramillo A, Sánchez X, Moreno-Piedrahita F. [34]	Ecuador	To know the effectiveness of Ivermectin for the treatment of patients with COVID-19.	Integrative review. Included case-control and observational studies. Sample not specified.	Ivermectin acts against SAR-CoV-2 in vitro, decreases the binding of hypoxia-induced transcription factors (HIF-1 α). Mortality was lower in the Ivermectin group (7.3% versus 21.3%), overall mortality rates were lower at 1.4% versus 8.5%; HR 0.20, 95% CI, 0.11-0.37, p<0.0001), however phase 3 clinical trials are needed to confirm these findings.	Ivermectin has demonstrated antiviral activity against SARS-CoV-2; however, there are still no human clinical trial results to support its use.

Santillán A, Palacios E. [9]	Ecuador	To know the treatment currently available to treat COVID-19.	Integrative Review. Sample not specified.	Current studies indicate that HCQ or CQ as well as Lopinavir/Ritonavir are not effective drugs in reducing mortality in patients with COVID-19. Remdesivir aids clinical improvement, was associated with a 5-day reduction in median time and virus elimination.	There are no conclusive results on the effectiveness of drugs against COVID-19.
Huamán-Sánchez K. [35]	Peru	To synthesize the available evidence on the effectiveness and safety of TCZ in the treatment of COVID-19.	Integrative review. 16 observational studies	The dose of TCZ is variable according to the person's weight and the severity status. In relation to mortality, 15 studies reported this outcome; five suggest that its use could possibly decrease mortality due to COVID-19; of this group, only three studies adjusted for other baseline variables or comorbidities. TCZ showed no effect on clinical improvement, HR 1.01; 95% CI, 1.00-1.02; p<0.006.	The evidence of the effectiveness of TCZ is of very low quality due to methodological limitations.
Pareja-Cruz A, Luque-Espino J. [36]	Peru	To review the current knowledge regarding therapeutic alternatives for COVID-19.	Integrative Review. Sample not specified.	Therapeutic alternatives with possible efficiency against COVID-19 are antiviral drugs (Arbidol, Remdesivir, Favipiravir, Lopinavir/Ritonavir), drugs that have usually been used as antiparasitics (CQ and HCQ) and antibacterials (Teicoplanin and AZI).	Treatment for COVID-19 requires further controlled trials to prove its efficiency. In Peru, the following scheme is used: CQ, HCQ, and HCQ/AZI.
Benavides V. [17]	Colombia	Describe the repositioning treatments against the virus.	Integrative Review. Sample not specified.	Antimalarial antiviral drugs, antibiotics, glucocorticoids, monoclonal antibodies and others are being studied; their findings, although preliminary, indicate that they improve virus elimination. The repositioning treatments were HCQ, AZI+HCQ.	Combination treatments when used together improve virus clearance. There is still no definitive conclusion.
Moneriz C, Castro-Salguedo C. [37]	Colombia	Recognize the available information on potential drugs for the treatment of patients with COVID-19.	Integrative review, 90 articles were selected.	The drugs against COVID-19 with positive results were Remdesivir and CQ. Lopinavir showed no difference between combination therapy and standard therapy in terms of clinical improvement and mortality. The effectiveness of TCZ is related to the degree of disease severity. It is suggested that Interferon, Arbidol and Teicoplamine may be useful.	Anti-COVID-19 drugs are used in the treatment of symptoms and as support in severe cases. Several studies show benefits without statistical significance. Clinical trials are required.
Caly L, Druce J, Catton M, Jans D, Wagstaff K.[13]	Australia	Report the antiviral effect of Ivermectin.	Invitro assay of SARS-CoV-2 virus cell culture and treatment.	In the laboratory, epithelial cells used in culture (Vero-hSLAM) were infected with the Australia/VIC01/2020 isolate, and after 2 hours, serial dilutions of Ivermectin were used. After 48 hours, tissue was sampled and	The study demonstrated the broad-spectrum in vitro antiviral effect of Ivermectin against SARS-CoV-2 strains. A single dose of 5

				analyzed by PCR assay, a >5000-fold decrease in viral RNA (99.9%) was observed in samples treated with 5 µM of Ivermectin.	µM controlled virus replication within 24-48 hours.
Santos S, Salas C. [39]	Mexico	Establish a framework for the taxonomic classification of SARS-CoV-2, detection methods and potential treatment.	Integrative Review. Sample not specified.	Potential treatment against SARS-CoV-2 in Vero E6 cells was Remdesivir with 90% effect. CQ works in contagion and in later stages of COVID-19; it has antiviral and immunomodulatory effects.	It cannot be affirmed that treatments that efficiently and reliably combat SARS-CoV-2 are available.
Gómez T, Diéguez G, Pérez A. [38]	Cuba	To describe the therapeutic alternatives for COVID-19, according to the pathophysiological mechanisms described so far.	Bibliographic review of 31 references.	Treatments against COVID-19 are: Viral envelope membrane fusion inhibitors (Arbidol), endothelial membrane protein protease inhibitors (TMPRSS2), Camostat and Nafamostat, entry and endocytosis inhibitors (CQ and HCQ), 3-chymotrypsin inhibitors, antiviral drugs of this enzyme (Lopinavir and Ritonavir, Darunavir, Kalectra) effective only during the replication phase, RNA polymerase inhibitors, Ribavirin, Favipiravir, Remdesivir. Another antibacterial drug used was AZI.	Several drugs are used that have shown effectiveness in the viral cycle phase. The authors suggest focusing on HCQ, AZI, Kaletra and Remdesivir with their respective combinations. In Cuba, CQ is part of the treatment protocol and its use has had effective results.

Source: Own development.

Discussion

Based on the findings and analysis of the most up-to-date scientific evidence, the drugs that have shown favorable activity against COVID-19 are antiviral, antibacterial, anti-inflammatory and immunomodulatory drugs. It was seen that the strategy with the best results, less time and greater safety is "Drug Repurposing", which refers to the new use of previously approved drugs for events other than the original therapeutic indication, such as, for example, the use of HCQ, which is widely used in systemic autoimmune diseases. Additionally, the combination of various antiviral drugs versus the use of a single antiviral has better controlled the infection, viral replication and with less use of corticosteroids. However, most of the literature that was assessed pointed out the absence of robust studies and the need to carry out larger clinical trials with high scientific validity [6, 8, 9, 14, 15, 17, 25].

According to different reports, it appears that in the treatment of COVID-19 with Remdesivir, a nucleotide analog drug that interferes with the polymerization of the RNA of the virus, with in vitro activity in coronavirus, has shown greater significant benefits in adult patients infected with the virus in the different stages of the evolutionary process of the disease, patients recovered faster than with the use of other drugs, more favorable results were reported in relation to the safety response and efficiency of its application; its use was included in the NIH COVID-19 Treatment Guidelines [5, 16, 17, 22, 25-28, 31, 33, 37, 38, 40, 41].

Moreover, the immunosuppressive drug TCZ, an interleukin-6 (IL-6) inhibitor, included in the treatment of SARS-CoV-2 by the National Health Commission of China, showed benefits in patients, decreased hospitalization time and complications with doses of TCZ in early vs. late stage of the disease, although it had not yet received the approval of the health authority in any country and there was no solid clinical evidence regarding its safety and efficiency [5, 35, 39].

Likewise, it was found in the literature that Hydroxychloroquine/Chloroquine (HCQ/CQ) used from December 2019 to December 2020, showed positive results by reducing viral load in patients in pre- and post-infection stages, anyhow, in addition to having scientific evidence, its application cannot yet be affirmed in an efficient and reliable manner for COVID-19 [10, 11, 17, 23, 24, 32, 40].

The use of AZI, a macrolide antibiotic used effectively in respiratory tract infections, is was also mentioned [14]. In addition, the Mexican Ministry of Health and the Undersecretariat for Health Sector Integration and Development used the drug AZI combined with HCQ to treat certain patients with COVID-19; however, there are mixed reports of its effectiveness when used together with other drugs in patients with pneumonia side effects [42].

Ivermectin, whose main action is broad-spectrum antiparasitic, is also referred to by some authors, because its effectiveness in in-vitro conditions inhibited viral replication of SARS-CoV-2 [13, 14, 34, 43], but recent research of the OPS (Pan American Health Organization) questioned the reports of the studies citing bias, low certainty of evidence and insufficient evidence to reach a valid conclusion about its benefits [2, 8, 13, 29]. The inclusion of other complementary therapies, such as convalescent plasma from patients, has been noted in the treatment for COVID-

19, as well as in other viral infections, due to the existence of the hypothesis of clinical improvement. Nonetheless, there is currently insufficient evidence to recommend or advise against the use of convalescent plasma to patients with COVID-19 [22, 23, 25, 26, 31].

Conclusions

Based on the integrative review that identified scientific evidence on pharmacological treatment of patients with COVID-19, it can be concluded that the drug that showed the greatest benefit to COVID-19 infected patients in the different stages of the evolutionary process of the disease was Remdesivir, which demonstrated the best safety response and efficiency of its treatment. Also, TCZ and glucocorticoids showed favorable results. However, these are still under study to corroborate their pharmacological effectiveness for patients with COVID-19. AZI is currently indicated in the treatment to COVID-19 along with other drugs, as prophylaxis. Hydroxychloroquine/Chloroquine (HCQ/CQ), despite presenting positive results in studies and being the drug with the most scientific evidence, its use cannot yet be claimed as efficient and reliable. To date, several RCTs are being carried out with the aforementioned drugs. Despite this, several authors have pointed out that it is not yet possible to state that COVID-19 treatments are available in an effective and efficient manner.

This research allows updating and broadening nursing knowledge by becoming familiar with the various pharmacological therapies currently available to contribute to improving clinical conditions in patients with COVID-19 in the different degrees of severity of the disease. Likewise, it facilitates the nursing professional to recognize in the scientific literature which are the most effective drugs and the desirable and side effects that, surely, in the clinical practice such knowledge will help in the implementation of timely and effective interventions that will contribute to the patient recovery.

Conflict of interest

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