Drug repurposing against SARS-CoV-2:

A review based on principal reports

Reposicionamiento de fármacos contra SARS-CoV-2: revisión en base a reportes principales

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Abstract

Despite the measures taken and the molecular advances for the development of new agents for the control of SARS-CoV-2 infection, there is still insufficient development of an effective treatment. The objective of the review was to describe the clinical studies and reported articles on drugs used as possible therapeutic agents for COVID-19 and the main conclusions on their reuse. A non-systematic review through PubMed, ScienceDirect, and clinical trials at ClinicalTrials.gov on original articles and case report in English and Spanish that will report information on COVID-19 treatment and its main conclusions. Articles that were not relevant or that did not mention updated information to that reported in other articles were excluded. A total of 99 bibliographic references were included. COVID-19 appears as a multisystemic disease with variable clinical symptoms. Since no specific treatment is yet known, multiple drugs have been proposed that attack the different pathways of SARS-CoV-2. For severe disease in patients who require hospitalization and oxygen support, the use of remdesivir, dexamethasone, or tocilizumab is recommended if there are patient conditions that apply to use them. The use of ivermectin, colchicine, lopinavir/ritonavir, hydroxychloroquine, and chloroquine have not reported benefits that surpass adverse effects.

Keywords: Coronavirus, Drug Therapy, Repurposing.

Resumen

A pesar de las medidas tomadas y los avances moleculares para el desarrollo de nuevos agentes para el control de la infección por SARS-CoV-2, aún existe un desarrollo insuficiente de un tratamiento efectivo. El objetivo de la revisión fue describir los estudios clínicos y artículos reportados de fármacos utilizados como posibles agentes terapéuticos para el COVID-19 y sus principales conclusiones sobre su reutilización. Se realizó una revisión a través de PubMed, ScienceDirect y ensayos clínicos en ClinicalTrials.gov sobre artículos originales y reportes de casos en inglés y español que reportarán información sobre el tratamiento del COVID-19 y sus principales conclusiones. Se excluyeron los artículos que no fueran relevantes o que no mencionaran información actualizada a lo reportado en otros artículos. Se incluyeron un total de 99 referencias bibliográficas. El COVID-19 se presenta como una enfermedad multisistémica con síntomas clínicos variables. Dado que aún no se conoce un tratamiento específico, se proponen múltiples fármacos que atacan las diferentes vías del SARS-CoV-2. Para enfermedad grave en pacientes que requieren hospitalización y soporte de oxígeno, se recomienda el uso de remdesivir, dexametasona o tocilizumab siempre que existan condiciones del paciente que apliquen para usarlos. El uso de ivermectina, colchicina, lopinavir/ritonavir, hidroxicloroquina y cloroquina no han reportado beneficios que superen los efectos adversos.

Palabras claves: Coronavirus, Tratamiento Farmacológico, Reposicionamiento de Drogas

Introduction

In December 2019, the Wuhan Municipal Health Commission reported the appearance of cases of atypical pneumonia that by March 2020 was declared a pandemic caused by the new coronavirus, SARS-CoV-2 that causes COVID-19, which has caused approximately four million deaths[1]. This has been identified as responsible for producing nonspecific signs and symptoms such as fever, cough, and dyspnea. Most patients present with upper respiratory symptoms; to a lesser extent gastrointestinal symptom; severe acute respiratory syndrome (SARS), and death in the most extreme cases. In addition,

a large number of thrombotic episodes, cardiovascular and kidney diseases, and an immune response called cytokine release syndrome, associated with high mortality, have been reported. Approximately 80% of the cases present mild, 15% moderate, and 5% severe[2]. The forms of transmission of SARS-CoV-2 include transmission by contact (oral, nasal, and ocular mucous membranes) and direct transmission (coughing, sneezing, and inhalation of droplets) and some studies demonstrate the possibility of transmission of SARS-CoV-2 during the asymptomatic incubation period, between 1 and 14 days[3,4].

Despite the studies carried out, specific treatment has not been established, therefore, the objective of this review is to describe the clinical studies and principal reports of drugs used as possible therapeutic agents for COVID-19 and their main conclusions.

Materials and Methods

A narrative review through PubMed, Science Direct, and ClinicalTrials.gov on original articles and case reports between January 2020 and August 2022 in the English language that will include information on the main drugs that have been tested as a possible treatment of COVID-19 and its main conclusions. Subsequently, a brief description of each of these was made. Keywords (MeSH) were used in the initial research: "COVID-19 AND Favipiravir", "COVID-19 AND Hydroxychloroquine", "COVID-19 AND Remdesivir", "COVID-19 AND lopinavir-ritonavir", "COVID-19 AND Arbidol ", COVID-19 AND nafamostat", COVID-19 AND chloroquine", COVID-19 AND tocilizumab, "COVID-19 AND ivermectin", "COVID-19 AND Sotrovimab", COVID-19 "AND Sofosbuvir/velpatasvir", "COVID-19 AND Molnupiravir", "COVID-19 AND Paxlovid", "COVID-19 AND Bamlanivimab/Etesevimab".

To review the articles, the authors read the titles, followed by the abstracts to reduce the number of records per drug search. Articles that were not relevant or that did not mention updated information to that reported in other articles were excluded. A total of 123 references were included, of which 41 were included in Table 1.

Results

Therapeutic alternatives against SARS-CoV-2

In the absence of effective treatment related to difficulties with the development of a safe and selective drug, it is important to consider repurposing drugs. Multiple alternative therapies have emerged that are summarized in **(Table 1),** classified by their mechanism associated with the inhibition of viral replication as nucleoside analogs, functional protease inhibitors, inhibitors of membrane function, and inclusion of therapeutic agents repositioned with different mechanisms and proposed as alternatives for treatment.

Table 1. Studies related to the repurposing of drugs against SARS-CoV-2

Drug	Study methods	Participants	Age (years)	Main findings	Reference
Favipiravir	Prospective, multicenter, open-label and randomized superiority trial	240 (116 with Favipiravir and 120 with Arbidol)	<65 (87) ≥65 (29)	The recovery rate was 55.86% in the FPV group (7 days) (p = 0.0199).	5
	Open, non-randomized study.	80 FVP (n = 35) and LPV/RTV (n = 45)	15–44 (36) 45–64 (33) >65 (11)	FPV showed better therapeutic responses in terms of disease progression and viral shedding.	6
	Open-label, multicenter, single-arm, postmarketing study	1083 patients	The mean 40.59±13.2 years	With use of FVP 95.8% exhibited clinical cure to 14 days. Only 1.4% of patients required O_2.	7
	Randomized, double-blinded, multicentre, and placebo-controlled trial	245 (112: favipiravir and 119: placebo)	Median: 37 years; IQR: 32 - 44 years. 155 were male	This study found no clinical and virological benefit in mild COVID-19 patients with favipiravir.	8
Remdesivir	Double-blind, randomized, placebo-controlled trial	1063 (541 assigned to remdesivir and 522 to placebo)	58.9 ± 15.0	Remdesivir was superior to placebo in the treatment time of those hospitalized with COVID-19 and evidence of lower respiratory tract infection.	9
	A multicenter, randomized, double-blind, placebo-controlled trial	237 (158 with remdesivir and 79 with placebo)	≥ 18	Remdesivir was not associated with statistically significant clinical benefits.	10
	DisCoVeRy was a phase 3, open-label, adaptive, multicentre, randomised, controlled trial	857 participants (remdesivir n=429 or care only n=428)	≥18 years	No clinical benefit with use of remdesivir in patients hospitalized with COVID-19. Symptomatic > 7 days and required oxygen support.	11
	Randomized, double-blind, placebo-controlled trial	562 patients (279 remdesivir and 283 placebo).	Mean age 50 years.	In 3-day of remdesivir had an acceptable safety and 87% lower risk of hospitalization or death.	12

Ribavirin Lopinarvir/ ritonavir IFN-α2b or IFN-β1b	Multicenter, prospective, open-label, randomized, phase 2 trial	127 (86 were randomly matched groups and 41 were control groups)	>18	The combination of IFN - β1b, LPV / r, and ribavirin was safer and more effective than LPV / r in relieving symptoms. Such as the decrease in hospital stay time.	13
	An open, prospective, single-center, randomized clinical trial	101 (33 to the group treated with RBV + IFN-a, 36 to the group treated with LPV/r + IFN and 32 to the group treated with RBV + LPV/r + IFN)	18-65 (mean 42.5)	There were no statistically apparent differences between the three treatment regimens in terms of antiviral effectiveness in patients with mild to moderate COVID-19.	14
	Cohort retrospective	115 (44 with intravenous ribavirin and 71 for no control group)	18-60 (mean 54.9)	There were no significant differences in laboratory parameters between the two groups after the treatment course.	15
	Cases/control	47	5-68	Combination treatment with LPV/r and adjuvant drugs results in a decrease in body temperature and maintenance of normal mechanisms with a non-adverse response.	16
	A randomized, open-label clinical trial	80 (In the end, 33 in the IFN group and 33 in the control group)	≥18 years	IFN β-1b showed a favorable result during the time of clinical stay without serious adverse events in individuals with severe COVID-19.	17
	Open-label, block randomized, phase 3 clinical trial	66 allocated to the FVP (n = 33) and LPV/RTV (n = 33)	18–80 years	The therapy with FVP did not show a higher efficacy against to the combination of LPV/ RTV	18
	DisCoVeRy is a phase III open-label, adaptive, multicentre, randomized, superiority-controlled trial	603 controls: 148, lopinavir/ritonavir: 145; lopinavir/ ritonavir plus IFN-b-1a: 145, hydroxychloroquine: 145.	≥18 years old median age of 63 years (IQR 54 - 71)	LPV/RTV, LPV/RTV plus, IFN-β-1 and HCQ were not associated with clinical improvement at day 15 – 29.	
Arbidol (Umifenovir)	Cases/control	164 (82 cases in the infected group and 82 uninfected controls)	Me=37	Prophylactic oral arbidol was associated with a lower incidence of SARS-CoV-2 infection, but not with a hospitalization rate among healthcare professionals.	19
	Retrospective multicenter cohort study	141 Arbidol/IFN - α2b (71) IFN - α (70)	≥ 18	Baseline laboratory and clinical characteristics were similar between umifenovir / IFN-α2b and IFN-α.	20
	Randomized, double-blind, placebo-controlled, multicenter, phase III trials	132	18-75 years	Umifenovir show the primary and secondary endpoint criteria and exhibits statistically significant efficacy for Mild-asymptomatic patients. It is tolerated to doses of 800mg (14 days).	21
Nafamostat	phase 2 open-label, randomised, multicentre, controlled trial	108 screened, 104 randomized (nafamostat: 53 and SOC: 51)	Mean: 58.6 years	No significant difference in time to clinical improvement between the nafamostat vs SOC.	22
	phase Ib/IIa open label, platform randomised controlled trial	66 (44 allocated: 23 nafamostat and 21 SOC)		IV nafamostat poorly tolerated. Not support the use of IV nafamostat in COVID-19 patients	23
Hydroxychloroquine/ Azithromycin (HCQ/ AZT)	A randomized, double-blind, placebo-controlled trial	821	HCQ 41 (33–51) Placebo 40 (32–50)	HCQ did not prevent COVID-19 compatible disease or confirmed infection	24
	Cohort	1376 (811 HCQ and 565 without HCQ)	<40 (80) 40–59 (217) 60–79 (367) ≥80 (147)	HCQ did not show a significant association between its use and intubation or death.	25
	Retrospective multicenter cohort study	1438 HCQ (271) HCQ/AZT (735) AZT (211) None (221)	<18 18-30 31-44 45-64 ≥ 65	Treatment with HCQ, AZT, or combined was not significantly associated with differences in hospital mortality.	26
	Retrospective observational multicenter study.	2541	<65 (1278) ≥ 65 (1263)	HCQ alone and in combination with AZT was associated with a reduction in mortality associated with COVID-19	27
	Restrospective	3,737 3,119 (HCQ+AZ) 618 other regimes	(45±17)	HCQ-AZT was associated with a lower risk of transfer to the ICU or death, a lower risk of hospitalization <10 days, and a shorter duration of viral shedding. QTc prolongation (> 60 ms) was observed in 25 patients.	28
	Cross-sectional	8075 4542 (HCQ) 3533 (sin HCQ)	16-≥80		29
	Cohort study, observational, multicenter	1064 HCQ (189) CQ (377) Untreated (498)	≥ 18	No effect of HCQ on mortality outside the ICU.	30
	Retrospective cohort	HCQ (10,703) No-HCQ (21,406)	HCQ (64·8±12.9) No-HCQ (65.4±13.3)	HCQ was not associated with SARS-CoV-2 prophylaxis in patients with rheumatologic conditions	31
	Academic-led, multicentre, double-blind, placebo-controlled randomised tria	1372 (689 HCQ and 683 placebo)	Median age: 45 (36-56) years.	HCQ did not reduce the risk of hospitalization compared to the placebo control.	32
	Placebo-controlled double-blind randomised multicentre trial.	117	65 (52–77) years	AZT and HCQ did not show survival in patients with COVID-19	33

Tocilizumab (TCZ)	Retrospective observational cohort	764	≥18	COVID-19 patients who required ICU support with TCZ had reduced mortality.	34
	Multicenter, open-label randomized clinical trial	131	Mean: 64	In patients who required oxygen support but did not enter the ICU, TCZ did not reduce the WHO-CPS scores below 5 on day 4.	35
	Retrospective cohort	158 TCZ (90) Standard treatment (68)	Standard care: 71 (14.6) TCZ: 62.9 (12.5)	TCZ significantly improved survival compared to standard care	36
	cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized clinical trial	131 (64 TCZ and 67 to UC)	64 (57.1-74.3) years	TCZ did not reduce WHO-CPS scores lower than 5 to 4 days, and might have decreased the risk of NIV or death to 14 days.	37
	Randomised, double-blind, placebo-controlled, phase 3 trial	438 TCZ: 294 (190 to 60 day). Placebo: 144 (96 to 60 day)	≥18 years	Tocilizumab does not benefit the reduction of mortality at 60 days.	38
Ivermectin (IVM)	Double-blind, parallel, randomized, placebo-controlled trial	112	≥18	All patients in the ivermectin group were discharged successfully. Compared to the placebo group.	39
	Randomized, blinded, placebo-controlled trial	363	Mean: 40	Early recovery in mild to moderate COVID-19 infection treated with IVM plus doxycycline.	40
	Comparative study	400	17–74	Probability of safe combination therapy with IVM and doxycycline.	41
	A randomized, double-blind, placebo-controlled study	501 (250 IVM and 251 placebo).	42±15.5 years	IVM had no significant effect on patients with COVID-19.	42
	Randomized, investigator-initiated, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial	93 (placebo: 32; IVM-600 mg: 29 and IVM- 1200 mg: 32)	Median: 47.0 years; IQR: 31.0–58.0.	High-dose ivermectin not evidenced usefulness to reduce viral load.	43
	Open-label randomized clinical trial	490 (IVM: 241 and Control: 249)	mean (SD): 62.5(8.7) years	Ivermectin in early illness did not prevent progression to severe disease.	44

Abbreviations: ANK= Anakinra; AZT= azithromycin; CQ= chloroquine; DXT= dexamethasone; FVP= favipiravir; HCQ= hydroxychloroquine; ICU= Intensive Care Unit; IFN= interferon; IV: Intravenous; IVM: ivermectin; LPV/r= lopinavir-ribavirin; SOC= Standard of care; TCZ= tocilizumab

Nucleoside analogs. Potential COVID-19 treatments include favipiravir, remdesivir, and galidesivir. Favipiravir (FPV) or T-705, exhibits a remarkable antiviral response against multiple RNA viruses. Its intensive use has been reported in antiviral therapy against influenza and Ebola viruses, which have been evaluated both *in vitro* and *in vivo*. Likewise, they have led to the combination therapy between FPV with ribavirin, in which it has been established that ribavirin is capable of increasing FVP activity by an indirect effect on immunomodulatory activities and inhibition of inosine-5′ monophosphate dehydrogenase. However, in individuals infected with SARS-CoV-2, the efficacy of favipiravir has been demonstrated with a rate of around 71% (p = 0.02) and related to patients with comorbidities, where a notable reduction in clinical symptoms such as fever and cough, in short recovery time intervals compared to Arbidol treatment (p = 0.001)[5].On the other hand, remdesivir (RDV) is a drug evaluated *in vitro*, which acts as an analogous inhibitor of RNA-dependent RNA polymerase (RdRps), demonstrating remarkable activity against the Ebola virus, SARS-CoV and MERS[45]. In addition, a study presented by Wang et al. reported that the EC90 was 1.76 μM against SARS-CoV-2 in VeroE6 cells, suggesting the inhibition of SARS-CoV-2 strains and inhibitory capacity reported in human liver cell lines (Huh-7) with probable sensitivity to COVID-19. Likewise, recent reports by Wang et al., have described that RDV inhibits the virus with values of EC50 = 0.77 μM, CC50> 100 μM, SI> 129.87[46,47].

RDV has been reported to be administered in clinical trials at doses of 10 mg/kg (~ 200 mg in humans), before 5 mg/kg daily (~100mg daily x 6 days) included in some monkey trials which demonstrated favorable results and a decrease in viral load in the lower respiratory tract[48]. In clinical studies by Grein et al., they did not demonstrate significant efficacy against the antiviral activity, indicating limitations with sample size and study design modification[49]. Also, it is a nephrotoxic and hepatotoxic agent, the United States Food and Drug Administration (FDA) has allowed its use in severe stages of COVID-19, but the randomized clinical trial has found no significant benefit[50].

Protease inhibitors. LPV/r is a conjugated molecule used in antiretroviral therapy against HIV. However, classified in the group of protease inhibitors, ritonavir is a CYP3A4 inhibitor that stimulates lopinavir decreased metabolism. Despite the limited evidence of the action of LPV/r in the treatment of SARS CoV, Cao et al.,[51] conducted a randomized controlled trial, with a sample of 199 adult patients hospitalized with SARS-CoV-2. They were divided into two groups with a 1: 1 ratio at random and the results shown did not observe any benefit beyond standard care. It should be noted that a systematic review showed that the antiviral activity of LPV/r is based on early application to reduce patient mortality; however, the loss of an early therapeutic window results in significant ineffectiveness[52]. Zhou et al, determined that LPV/r antiviral treatment could inhibit the virus by 21% in survivors

with a median time to start treatment between 0 and 14 days, and a median duration of viral clearance of 22 days. Current evidence has shown that LPV/r is not associated with a reduction in 28-day mortality, length of hospital stay, or risk of progression to mechanical ventilation[53]. It is important to indicate that this therapy has been combined and compared with other reference drugs such as Arbidol, RBV, interferons, and HCQ. Which, variability in the clinical response of patients has been evidenced[54].

Membrane fusion inhibitors. Arbidol is a broad-spectrum molecule that has shown activity against DNA and RNA viruses. Its action is micromolecular because it inhibits viral fusion to the cell membrane, thus interrupting the entry of the virus into the cell. Its inhibitory activity is EC_{50} = 10.57 ± 0.74 to 19.16 ± 0.29 μM[55]. In cohort studies in patients with moderate COVID-19, it was established that around 120 individuals underwent treatment with Arbidol, obtaining recovery rates of 55.86%. However, the clinical behavior of these individuals was less effective when they were subjected to favipiravir [5]. In the studies by Yang et al., it showed that oral Arbidol was related to a lower viral infection but not with health professionals. Arbidol was found to be a safe drug and is associated with a higher negative CRP rate on day 14 in adult COVID-19 patients; however, it cannot shorten the time to negative nucleic acid conversion, improve symptoms, or decrease the risk of disease progression[56].

Interlucin-6 receptor antagonist. The Acute Respiratory Distress Syndrome is one of the most serious complications of SARS-C V-2, its pathophysiology has been related to elevated levels of intralucin-6 (IL-6) that is associated with the Cytokine Release Syndrome[57]. This could be the reason why TCZ has been shown to be an effective treatment in patients with severe COVID-19. TCZ is a recombinant humanized monoclonal antibody of the IgG1 subtype, its main indications are for the treatment of rheumatoid arthritis, giant cell arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis[58]. TCZ binds to both forms of the IL-6 receptor (IL-6R), the transmembrane form, and the soluble form (sIL-6R), inhibiting classical signal transduction of the IL-6 signal and may inhibit SRC[59]. Although some studies described in Table 1 reported reduced mortality and positive outcomes to avoid the use of invasive mechanical ventilation, a meta-analysis found that TCZ could not provide any additional benefit for severe COVID-19 clinical outcomes[60]. This suggests that randomized controlled trial studies are still needed to be sure of the benefit that TCZ could provide. Capra et al., [61] found in their study that respiratory function improved in 64.8% of patients with TCZ who were still hospitalized, while 100% of controls worsened and required mechanical ventilation. IL-6 levels are directly related to more severe lung damage, therefore, pending the best treatment to prevent higher mortality rates, as seen so far, the use of TCZ is suggested in critically ill patients. with COVID-19 with significantly elevated IL-6 [59]. The National Health Commission and the State Administration of Traditional Chinese Medicine recommend a dose of 400 mg (4-8 mg/kg), if the initial medication is not effective, an additional administration can be administered after 12 hours. The maximum single dose is 800 mg and it is not indicated in patients with active infections such as tuberculosis[61].

Other possible therapeutic agents

Nafamostat. It has been proven as a potent MERS-CoV inhibitor, influencing the correct fusion of the membrane, and specifically inhibiting TMPRSS2, favoring a significant reduction in viral production. In tests against COVID-19 strains, it showed promising inhibitory activity with EC50 = 22.50 µM, CC50> 100 µM, SI> 4.44[62]. Another possible candidate within the classification of serine protease inhibitors is Camostat, which shows potential antiviral activity and could be an alternative in the treatment against SARS-CoV-2[63]. Osawa et al.[64] evaluated the coagulation status of patients with COVID-19, who were classified into three groups (low, intermediate, and high risk). Therefore, patients with lower risk had low levels of D-dimer; however, individuals classified as intermediate and high risk showed dynamic changes in fibrinogen and D-dimer levels, indicating that they were not totally conclusive due to the size of the sample obtained. However, the structured clinical studies to date are developed by the RACONA study, INGYU BAE sponsored by the Gyeongsang National University Hospital and the Institute Pasteur of Dakar, in which samples between 84-256 adult individuals have been selected and maintaining its development in phase 3[65,66].

Nitazoxanide. It's mainly antiprotozoal agent with antiviral potential against a wide range of viruses, such as Ebola and including coronaviruses present in humans and animals with vitro activity[67]. Nitazoxanide interfere with the production of cytokines that promote inflammatory processes and the production of mediators of the immune response such as interleukins 6 (IL-6). According to Calderon et al.[68], a phase 4 clinical study was carried out, in which they declared the implementation of treatments based on hydroxychloroquine and nitazoxanide in patients with SARS-CoV-2. The report states the use of trial therapy of hydroxychloroquine 400 mg oral/12 hours for two days and 200 mg oral/12 hours for four days + nitazoxanide 500 mg oral/6 hours with food, for seven days. While, Rocco et al. have evidenced that patients with mild COVID-19 treated with nitazoxanide and placebo not differ significantly instead early nitazoxanide might reduced viral load[69].

Chloroquine and Hydroxychloroquine. Both are widely known in the treatment of protozoa as antimalarials and present a cost-effectiveness balance that makes them viable as an alternative in therapy. Sinha and Balayla et al.[70], established that weak bases have the ability to act on the enzyme systems of the acid vesicles of the virus, conditioning the effector capacity and viral entry with possible pH alterations. On the other hand, the possible inhibition of glycosyltransferases that CQ/HCQ could inhibit viral entry by blocking the biosynthesis of sialic acids, which are relevant in the recognition of the virus-host cell, has been described [71]. Some predictive models have studied the link between sialic acid and inhibition by CQ/HCQ, showing in the first instance that sialic acids and gangliosides have high affinity, integrating it into the viral mechanism related to protein S domains, such as 111-158

are critical for viral entry. In this way, it was concluded that HCQ derivatives influence the binding of glycosides[71].

These findings led China to include CQ in the recommendation for the prevention and treatment of pneumonia[72]. Furtado et al. in a randomized open-label clinical trial enrolled 447 patients and reported that the addition of azithromycin and hydroxychloroquine as treatment did not improve clinical outcomes in patients with severe COVID-19[73]. Mainly, from clinical studies that were not totally consistent, it has been stated that the effectiveness in cases of infected patients was not significant compared to controls. However, the important data that were established present a relatively small population and this allows maintaining a variability of opinion regarding the effectiveness of the treatment. On the other hand, its toxicity is demonstrated in cardiovascular disorders and is a possible cause of retinopathy[74].

Interferons. Type 1 interferons such as IFN-β, IFN-ε, IFN-κ, IFN-ω, and 12 IFN-α subtypes (IFN-α2b, IFN-α2a and IFN-α1b subtypes approved for clinical use) [75]. A group of pleiotropic cytokines evoking various physiological responses including antiviral, antiproliferative, immunomodulatory, developmental, and cytotoxic activities[76–78], have been used primarily for the treatment of myelofibrosis, multiple sclerosis, Kaposi's sarcoma in the HIV/AIDS, Hepatitis B and C, Shingles, and Hairy Cell Leukemia. IFN-α2b and IFN-β1b are currently being studied to treat SARS-CoV-2 infection. They were used as a treatment for MERS-CoV infection in combination with other drugs such as ribavirin that reduce virus replication[79,80]. Its mechanism of action consists mainly of an immunomodulatory effect involved in the signaling of the JAK/STAT pathways that would favor the response of inhibition of replication. Viruses by activating endoribonucleases that cut RNA, inhibiting the translation of viral proteins [81], have shown an inhibitory effect on MERS-CoV and SARS-CoV [82]. It has been proposed as an element in the treatment of COVID-19 in doses of 5 million units twice daily by inhalation, given together with LPV/r [83].

The Chinese National Health Commission recommended IFN-α spray inhalation as a potential alternative to subcutaneous administration, as it has higher activity and may also enhance the specific cytotoxic effect of macrophages and lymphocytes by regulating immune function and stop the invasion and infection of the virus effectively[84]. In addition, IFN inhalation could reduce the adverse reactions of flu-like symptoms seen with subcutaneous administration; however, other adverse effects to be concerned about include nausea, fatigue, weight loss, hematologic toxicities, elevated transaminases, and psychiatric problems (eg, depression and suicidal ideation)[85]. The minimum inhalation dose that can induce biological effects without side effects is 3.0×10^6 IU/day. Wang et al. reported that the combination of IFN with LPV/r or Arbidol was not associated with variations in hospital discharge or improvement in computed tomography compared to LPVr or UFV alone[86] and Hao et al described that aerosol inhalation did not shorten the dissemination time of the SARS-CoV 2 virus in hospitalized patients[84]. IFN-β1b is better tolerated than interferon alpha[87]. The side effects include dermatologic manifestations at the injection site such as painful erythema, life-threatening skin necrosis, fever, chills, myalgia, and headache[88]. Like IFN-α, early administration of IFN-β1b was also shown to reduce mortality (OR, 13.5; 95% CI, 1.5 to 118) but did not change the time to reach clinical response[89]. Even so, the COVID-19 Treatment Guidelines Panel reported that there is low data to recommend the use of IFN-β for the treatment of mild and moderate COVID-19[90].

Sotrovimab (VIR-7831). It is a human monoclonal antibody, which is part of the so-called "superantibodies", and was recently authorized for emergency use by the FDA to neutralize SARS-CoV-2. The parental form of Sotrovimab, S309, was isolated from a survivor of the SARS[91]. Gupta et al reported in preliminary results of their multicenter, double-blind, phase 3 trial in outpatients with symptomatic COVID-19 and at least one risk factor for disease progression that this drug reduced progression of COVID-19 in patients with mild/moderate disease[92]. It has been suggested that they should have an advantage over COVID-19 due to their broad neutralization capacity against emerging virus variants[93].

Dexamethasone. Corticosteroid with anti-inflammatory and immunosuppressive action. It has been used in different diseases such as arthritis, blood disorders, hormonal disorders, allergic reactions, skin diseases, eye disorders, respiratory diseases, and disorders of the immune system[94]. Although some studies concluded that methylprednisolone was better than dexamethasone in hospitalized individuals [95,96], the sample in these was small compared to the 2,104 patients in the RECOVERY (Randomized Evaluation of COVID-19 Therapy), study who were administered dexamethasone 6 mg once daily for 10 days and reduced deaths by a third in ventilated patients and by a fifth in other patients receiving oxygen therapy[97]. These latest findings led to the FDA's approval of the use of dexamethasone in conditions of hospitalization and need of oxygen support. Hormonal imbalance, fluid retention, weight gain, anxiety, and disturbed sleep patterns are considered the most common risks associated with dexamethasone.

Sofosbuvir/velpatasvir. Sofosbuvir (SOF) is based on a nucleotide analog that influences the inhibition of the NS5B polymerase of the viral agent that causes hepatitis C. On the other hand, velpatasvir (VEL) is classified as an inhibitor of the non-structural protein NS5A. Therefore, the combined use of SOF/VEL demonstrates its efficiency in various phenotypes including genotype 3 (GT3), which was described in the ASTRAl-3 study. Currently, it has been implemented as a repositioning tool for patients associated with COVID-19, of which it has been shown in multicenter case-control studies that the clearance of SARS-CoV-2 registered values of 83% once started. treatment compared to controls clearance which reached only 13%; additionally, records were reached in a median of 14 to 22 days[98]. Likewise, it has been shown that it seems to indicate safety, however, no clear conclusions are presented regarding the clinical status and mortality reduction in patients with moderate to severe presence of COVID-19[99].

Molnupiravir. It is a prodrug classified as a β-d-N4-hydroxycytidine (NHC) ribonucleoside analogue, which is metabolized in plasma to NHC, activating in the form of 5′-triphosphate. Some studies have evaluated the possible clinical efficacy at a dose of 800 mg from the administration of 200 mg capsules, it has been shown that oral administration could be effective in the treatment of COVID-19 and mainly within 5 days after development of signs and symptoms for non-hospitalized[100]. Likewise, an attempt was made to evaluate the clinical efficacy in patients with mild to moderate COVID-19, where doses of 800 mg every 12 h for 5 days have been used as standard, evidencing improvements in respiratory function markers and indicating a lower need for of respiratory interventions with respect to placebo groups, additionally, they suggest that it could contribute to clinical benefits in hospitalizations or death of patients[101]. However, is necessary more studies according to parameter as efficacy and safety.

Nirmatrelvir/Ritonavir (Paxlovid). Coronavirus M pro is a three-domain cysteine protease characterized by a Cys145-His41 catalytic dyad in the cleft between domains I and II. SARS-CoV-2 M pro is critical in viral replication. From an evolutionary perspective, the amino acid sequence and 3D structure of Mpro are highly conserved among the coronavirinae subfamily. Nirmaterlvir might inhibit the major SARS-CoV-2 protein (Mpro), preventing viral replication. Ritonavir has no activity against the microorganism; however, it increases serum levels of nirmaterlvir by inhibiting its metabolism by CYP3A[102–104].

A study by Owen, et al. described the high inhibitory potential of Paxlovid for all types of human-infectious coronavitus, including beta-coronaviruses (SARS-CoV-2, SARS-CoV-1, HKU1, OC43, and MERS-CoV), as well as alpha-coronaviruses (229E and NL63), however, they did not observe inhibitory ejectors against cysteine, serine, and aspartyl proteases[105]. For other hand, the studies described show that Paxlovid in the first 5 days of infection is associated with a lower rate of mortality and progression of severe COVID-19, as well as a lower rate of hospital admissions. The rebound rate at 7 and 30 days after Paxlovid treatment was 3.53% and 5.40% for SARS-CoV-2 infection[106–109]. Recent studies demonstrate high utility in preventing progression of severe COVID-19 if administered within the first 3 days of symptom onset, regardless of the patient's vaccination status, however, it has been described as having a high potential for causing drug-drug interaction (DDI) damage with other drugs metabolized through this pathway. Options to mitigate the risk of DDI with nirmatrelvir/ritonavir are limited due to the clinical disease, the short window for intervention and the related difficulty of implementing clinical monitoring or dose adjustment of the medication as in the case of oxycodone which in the presence of ritonavir causes depression resporia[110].

Bamlanivimab/Etesevimab. (BAM/E) bind to distinct but overlapping sites on the receptor-binding domain of the SARS-CoV-2 spike protein, blocking its binding to the human ACE2 receptor[111]. It has been described that the BAM/E combination reduces the hospital instance rate, ICU admissions and hospitalization in patients with non-severe COVID-19, this combination proves to be superior to casirivimab-imdevimab, however, it reduces its *in vitro* activity in the presence of variants such as Beta, Gama and Omicron[112–114]. According to Juan C. Almagro, et al. (2022) The incidence of COVID-19-related hospitalization at 30 days was similar among patients receiving monotherapy with BAM or BAM/E (7.8% and 7.2%, respectively)[115]. The FDA recommended revocation of bamlanivimab monotherapy due to increased resistance of the circulating variant in the U.S. by January 24, 2022, limited the use of bamlanivimab/etesevimab due to reduced activity against Omicron[116].

Discussion

This review briefly describes the clinical studies and their main conclusions on the use of drugs for SARS-CoV-2. The great number of articles about COVID-19 treatment published in these past two years is very high however only a few holds enough evidence on whether we should use some drug or not. To choose wisely, the severity of the patient must be considered to propose the treatment scheme since studies continue to be reported with both the first drugs that were mentioned as possible alternatives to treat COVID-19 plus the new ones that are being proposed, this leads to confusions regarding when to start treatment and even in many cases, prescriptions when is not even indicated.

Despite this, there is a clearer picture regarding the adults and the severity of the disease, at mild levels, treatment is only needed when there are symptoms, in moderate and severe disease, the severity and need must be considered hospitalization. Because the latter are the ones of greatest concern due to high morbidity and mortality, based on published articles, the National Institutes of Health (NIH)[117] guide reports a scheme for the management of hospitalized adults in which remdesivir, dexamethasone, and tocilizumab are the drugs that have shown better outcomes in a certain group of patients with very specific clinical characteristics that the patient must verify before starting any treatment and that have shown improvement if they are used in the correct therapeutic windows. On the other hand, other drugs such as IVM and colchicine have not reported a benefit greater than risk and therefore should only be used in research studies[118,119]; however, some authors have evaluated colchicine for clinic importance[119]. CQ, HQC, and LPV/r should not be used in COVID-19. The adverse risks of these in observational and clinical studies outweigh the clinical benefit[120–122].

Conclusion

The new coronavirus appears as a multisystemic disease with variable clinical symptoms. Since no specific treatment is yet known, multiple drugs are proposed to attack the different pathways of SARS-CoV-2. The use of ivermectin, colchicine, lopinavir/ritonavir, hydroxychloroquine, and chloroquine have not reported benefits superior to adverse effects at any level of severity. For severe disease in patients

requiring hospitalization and oxygen support, the use of remdesivir, dexamethasone, or tocilizumab is recommended as long as there are patient conditions that apply to use them. Likewise, the inclusion of new treatments has been showed its usefulness in patients with moderate to severe COVID-19 as molnupiravir, sofosbuvir/velpatasvir, nirmatrelvir/Ritonavir and bamlanivimab/etesevimab. Likewise, the new therapeutics implemented such as molnupiravir, sofosbuvir/velpatasvir, nirmatrelvir/Ritonavir and bamlanivimab/etesevimab, are presented as important strategies in the treatment of patients with mild to severe COVID-19, clinical studies have shown varied pharmacological efficacy, with results not completely conclusive due to limitations in the studies. However, more studies with a larger number of patients, highly determined inclusion criteria, and a higher level of scientific evidence are needed.

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