

Current pharmacological treatments for COVID-19: A narrative review

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ABSTRACT

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The coronavirus disease 2019 (COVID-19) pandemic has lasted more than one year. The number of daily cases and the number of deaths is still changing dynamically. As of this writing, specific drugs for COVID-19 are not yet available. This review aims to describe the key clinical evidence in pharmacological treatments for COVID-19. The article search process was carried out on the PubMed database with a combination of keywords ((“COVID-19”) OR (“SARS-CoV-2”)) AND ((“treatment”) OR (“therapy”)). In this article, there were six drugs reviewed that is corticosteroids, remdesivir, lopinavir-ritonavir, hydroxychloroquine, ivermectin, and interleukin-6 (IL-6) receptor blockers. Hydroxychloroquine, lopinavir-ritonavir, remdesivir, and ivermectin were not recommended for COVID-19 treatments regardless of disease severity and duration of symptoms. Therefore, they were excluded from the list of drugs for the treatment of COVID-19 by World Health Organization (WHO) stated strong recommendations in favor of two drugs, namely systemic corticosteroids and IL-6 receptor blockers namely tocilizumab or sarilumab. Both of them are recommended for the treatment of patients with severe and critical covid-19 so they are included in the list of COVID-19 therapeutic drugs by WHO.

ABSTRAK

Pandemi coronavirus disease 2019 (COVID-19) telah berlangsung lebih dari setahun. Jumlah kasus harian dan jumlah kematian masih berubah secara dinamis. Sampai tulisan ini dibuat, obat spesifik untuk COVID-19 belum tersedia. Makalah ini bertujuan menunjukkan bukti klinis untuk pengobatan COVID-19. Proses penelusuran artikel dilakukan pada database PubMed dengan kombinasi kata kunci ((“COVID-19”) OR (“SARS-CoV-2”)) AND ((“treatment”) OR (“therapy”)). Dalam artikel ini, ada enam obat yang ditelaah yaitu kortikosteroid, remdesivir, lopinavir-ritonavir, hydroxychloroquine, ivermectin, dan penghambat reseptor IL-6. Hidroksiklorokuin, lopinavir-ritonavir, remdesivir, dan ivermectin tidak direkomendasikan untuk terapi pasien COVID-19 pada semua tingkat keparahan penyakit dan durasi munculnya gejala sehingga dikeluarkan dari daftar obat untuk pengobatan COVID-19 oleh *World Health Organization* (WHO). Selanjutnya, WHO menyatakan rekomendasi kuat yang mendukung dua obat, yaitu kortikosteroid sistemik dan penghambat reseptor IL-6 yaitu tocilizumab atau sarilumab. Kedua obat ini direkomendasikan untuk pengobatan pasien COVID-19 derajat berat dan kritis sehingga masuk dalam daftar obat untuk pengobatan COVID-19 oleh WHO.

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INTRODUCTION

The World Health Organization (WHO) on March 11, 2020, has declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic.¹ COVID-19 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that was first identified in Wuhan, Hubei province, China, in December 2019.²

As of 17th September 2021, WHO reported 4.6 million deaths worldwide.³ The number of confirmed cases varies widely between countries. Although some areas in the world are seeing a drop in cases, some countries are experiencing a significant surge in COVID-19 cases. Indonesia reported a total of 4,185,144 cumulative confirmed case on September 17th, 2021 with 140,138 cumulative death (case fatality rate/CFR=3.3%).⁴

The transmission of SARS-CoV-2 is believed to be through aerosols and respiratory droplets. When an infected person coughs, sneezes, or talks, aerosols, and droplets containing the virus particles are generated. Besides the infected person, there are other sources of aerosol and droplets such as some medical and surgical procedures, toilet flushes, and running tap water.⁵ It has been speculated that environmental factors such as crowding, adequacy of ventilation, indoor or outdoor setting, and size of the indoor space may be related to the virus spread.^{6,7}

The common symptoms of SARS-CoV-2 infection are fever (83%-98%), cough (50%-82%), fatigue (25%-44%), shortness of breath (19%-55%), and myalgia (11%-44%).⁸ Loss of the sense of smell (anosmia) or loss of taste sensation (ageusia) in conjunction with respiratory symptoms has also been reported.^{9,10} Study from Alene *et al.*¹¹ reported that one-fourth of SARS-CoV-2 infections remained asymptomatic throughout the course of infection.

Effective treatments for COVID-19 patients are urgently needed. The rising number of research and clinical trials

for COVID-19 has burdened healthcare providers and policymakers to stay up to date.

MATERIALS AND METHODS

This review aims to describe the key clinical evidence in pharmacological therapies for COVID-19. The article search process was carried out on the PubMed database with a combination of keywords ((“COVID-19”) OR (“SARS-CoV-2”)) AND ((“treatment”) OR (“therapy”)). We strived to obtain high quality evidence in the form of randomized control trials (RCT). However, non-clinical studies (both in experimental animals and *in vitro*) are also used as a reference to enrich the discussion of this narrative review. The writing of this review only includes articles that are available in English.

DISCUSSION

Corticosteroids

Corticosteroids are a class of steroid hormones released by the adrenal cortex, which includes glucocorticoids and mineralocorticoids. The term “corticosteroids” is generally used to refer to glucocorticoids. It is one of the most widely prescribed drugs in the world due to its prominent immunomodulatory actions.¹² Glucocorticoids have been widely used in syndromes closely related to COVID-19, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), severe influenza, and community-acquired pneumonia. The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support in the form of non-invasive oxygenation and invasive mechanical ventilation. The incidence of death in the dexamethasone group was lower compared to the usual care group on subject who receive invasive mechanical

ventilation (29.3% vs 41.4%; RR = 0.64; 95% confidence interval [CI] 0.51-0.81) and on subject with non-invasive oxygenation (23.3% vs 26.2%; RR = 0.82; 95% CI 0.72-0.94). On the other hand, the incidence of death is higher in the dexamethasone group compared to the usual group among patients who were not receiving any respiratory support (17.8% vs 14.0%; RR = 1.19; 95%CI 0.91-1.55).¹³ Another clinical trial in Brazil, the COVID-19 Dexamethasone (CoDEX) Trial found that intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of mechanical ventilation over 28 days. Patients in the dexamethasone group had a mean 6.6 ventilator-free days (95% CI 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95%CI 2.9-5.4) in the standard care group (difference, 2.26; 95% CI 0.2-4.38; $p = 0.04$).¹⁴

Another prematurely closed trial found that the short-term early use of corticosteroids could suppress the immune cells, which may prolong SARS-CoV-2 shedding in patients with COVID-19 pneumonia.¹⁵ This study highlights the concerns of balancing benefit and harm on treating patients with systemic corticosteroids. Another important point is that this trial used methylprednisolone, while the RECOVERY Trial and CoDEX Trial in Brazil utilizes dexamethasone. Another study in Iran compares methylprednisolone and dexamethasone in patients hospitalized with COVID-19 who receive supplemental oxygen, they found that methylprednisolone demonstrated better results compared to dexamethasone. Those who received methylprednisolone ended up with significantly better clinical status compared to the dexamethasone group at day 5 (4.02 vs. 5.21, $p = 0.002$) and day 10 (2.90 vs. 4.71, $p = 0.001$) of admission. The mean length of hospital stay was 7.43 ± 3.64 and 10.52 ± 5.47 days in the methylprednisolone and dexamethasone groups, respectively ($p = 0.015$).

Another corticosteroid drug used in the pharmacological treatment for COVID-19 was hydrocortisone. The REMAP CAP trial which involves eight countries found that among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority concerning the odds of improvement in organ support-free days within 21 days. Organ support-free days defined as days alive and free of ICU-based respiratory or cardiovascular support within 21 days. However, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority.¹⁶

The rationale behind systemic corticosteroid use is to mitigate inflammatory organ injury in viral pneumonia caused by SARS-CoV-2. However, the benefit of corticosteroid use is only found in patients with COVID-19 on oxygen supplementation or respiratory support.¹³ WHO recommend systemic corticosteroid for the treatment of patients with severe and critical COVID-19. On the other hand, WHO suggests not to use corticosteroids in the treatment of patients with non-severe COVID-19.^{17,18}

Remdesivir

Remdesivir is a novel monophosphoramidate nucleoside prodrug, which is when metabolized to its active compound, inhibits viral RNA synthesis.¹⁹ Remdesivir has been observed to have an *in vitro* and *in vivo* antiviral activity against SARS-CoV-2.²⁰

Remdesivir showed some beneficial effects toward ameliorating the conditions in patients with COVID-19, such as shortening of time to recovery^{21,22} or clinical status.²³ A scoping review of 17 empirical studies and 23 clinical trial registrations concluded that remdesivir might shorten time to clinical improvement in adults with severe COVID-19, with a similar proportion

of adverse events in both therapy and control groups.²⁴ A systematic review with network meta-analysis of five RCTs concluded that remdesivir could help improving the clinical outcome of hospitalized patients with COVID-19, with a 5-day regimen might be sufficient compared to a 10-day regimen.²⁵ As a combination, baricitinib and remdesivir for COVID-19 patients were superior to remdesivir alone in reducing recovery time and accelerating clinical status.²⁶ Remdesivir appeared to be as tolerable as other comparators or placebo,²⁵ such as in COVID-19 patients on hemodialysis.²²

Some studies reported no significant effect observed with remdesivir usage. NOR-Solidarity trial reported that remdesivir did not affect viral clearance in hospitalized COVID-19 patients.²⁷ In a combination, one study found no difference in mortality outcome between remdesivir-tocilizumab therapy compared to tocilizumab alone. Some minimal/non-use of ventilation benefit was even observed in the tocilizumab alone group, compared to the combination.²⁸ One systematic review with meta-analysis and trial sequential analysis of five RCTs with 7540 participants reported an unclear to high-risk bias with most studies. It was then concluded that there was insufficient evidence to support the use of remdesivir for COVID-19 treatment, as more high-quality RCTs are needed for stronger evidence.²⁹

WHO recommends against administering remdesivir in addition to usual care. The recommendation is conditional, that is if remdesivir is considered, it is contraindicated in those with liver (ALT >5 times normal baseline) or renal (eGFR <30 mL/min) dysfunction. The recommendation for remdesivir was published as early as 20 November 2020, on its second living guideline, following the WHO SOLIDARITY trial, in which the treatment with remdesivir, hydroxychloroquine, and lopinavir-ritonavir for patients with COVID-19 was reported. Since then, the

recommendation remained unchanged until the 6th version of the living guideline. The recommendation was based on the lack of evidence found by the WHO Guideline Development Group (GDG). The low certainty evidence that remdesivir improved the outcomes of COVID-19 patients included, but was not limited to, reduced mortality, the need for mechanical ventilation, and time to clinical improvement. There was, however, no evidence of increased severe adverse events found from the trials. The overall credibility of the subgroup effect was also judged to be insufficient to make subgroup recommendations. Considering the overall low certainty evidence of remdesivir benefit and harm, driven by the risk of bias and imprecision limitations of the included studies, it was interpreted that remdesivir possibly had little to no benefit compared with usual care and further pharmacovigilance was needed, even though this did not prove that remdesivir is ineffective.^{17,18}

Lopinavir-ritonavir

Lopinavir and ritonavir are antiviral drugs with protease inhibitor activity that have been established as antivirals for HIV-1 and 2.³⁰ The combination of both drugs increases their plasma half-life. Interests in lopinavir for COVID-19 therapy were based on its antiprotease activity for SARS coronavirus (SARS CoV), which is proved in vitro against SARS-CoV, SARS-CoV-2, and MERS-CoV.³¹⁻³³

In one trial, the lopinavir-ritonavir treatment showed no benefit beyond standard care, though the standard care group experienced a more serious adverse event, while gastrointestinal adverse events were observed in the lopinavir-ritonavir group. Due to the adverse events, however, lopinavir-ritonavir treatment had to be stopped early for 13 patients.³⁴ Another trial randomized 694 COVID-19 patients into receiving lopinavir-ritonavir, hydroxychloroquine, a combination of both, or no antiviral therapy as control. The trial concluded that lopinavir-ritonavir

alone, hydroxychloroquine alone, or in combination worsened the outcomes compared to control.³⁵ DisCoVeRY trial, conducted as an add-on to the Solidarity Trial, reported no improvement of clinical status nor SARS-CoV-2 clearance for patients with lopinavir-ritonavir therapy, or in its combination with IFN- β -1a and hydroxychloroquine.³ For early treatment of COVID-19, a trial of 685 patients, found no significant benefit for decreasing COVID-19 associated hospitalization or any secondary outcomes.³⁷ A multicentre, prospective, open-label phase 2 study enrolling 127 patients with positive nasopharyngeal swabs, assessed a triple combination of IFN- β -1b, lopinavir-ritonavir, and ribavirin, compared to lopinavir-ritonavir alone. The study yielded a superior result from the combination group compared to the monotherapy-control group. However, as the paper authors stated, the study had several limitations such as no placebo group, and confounding factor of a subgroup omitting IFN- β -1b, which the author suggested appear to be a key component of the combination.³⁸ A rather large RCT, the RECOVERY trial, randomized 1616 patients for the lopinavir-ritonavir group and 3424 patients to receive usual care. Yet it was concluded that lopinavir-ritonavir was not associated with a reduction in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death, and therefore the findings did not support the use of lopinavir-ritonavir for COVID-19 patients.³⁹

The use of lopinavir-ritonavir was addressed since the 3rd WHO living guideline, and no change was made until the 6th version, that is, WHO recommended against the administration of lopinavir-ritonavir for treatment of COVID-19 of any severity. Within the evidence of a linked systematic review and NMA of 7 RCTs, with 7429 COVID-19 patients, the WHO GDG panel found a lack of evidence for some key outcomes was found. The evidence for mortality

and need for mechanical ventilation was moderate certainty, whereas the evidence for other outcomes such as time for clinical improvement and others. Lopinavir-ritonavir might increase the risk of diarrhea and nausea-vomiting, even though the evidence was of low certainty. The effects of viral clearance and acute kidney injury were uncertain. No effect modification of illness severity was found in subgroup analysis. Even though Lopinavir-ritonavir is not very costly compared to other drugs and is generally available in health care settings, WHO reminds the importance of not drawing attention and resources away from the best supportive care of the use of corticosteroid in severe COVID-19.^{17,18}

Hydroxychloroquine

Hydroxychloroquine is an antimalarial medication that is commonly used for the treatment and prophylaxis of malaria. This drug receives attention in the pharmacological treatment of COVID-19 because of the anti-inflammatory effect on the immune systems. Several of the anti-inflammatory mechanisms include interference with lysosomal acidification and antigen presentation, inhibition of toll-like receptor signals, inhibition of T and B cell receptors, and especially, decreasing cytokine production by macrophages such as IL-1 and IL-6.^{40,41}

WHO Solidarity trial results show that hydroxychloroquine had little or no effect on hospitalized patients with COVID-19. Death occurred in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (RR 1.19; 95% CI 0.89 to 1.59; $p = 0.23$). The main outcomes of mortality were not reduced by this medication. A systematic review and network meta-analysis found that hydroxychloroquine do not appear to have any important impact on patient-important outcomes such as mortality, the chance of mechanical ventilation, viral clearance in seven days, admission to hospital, duration of

hospital stay, ventilator-free days, time to symptom resolution, and time to viral clearance.⁴²

The third version of the WHO living guideline addressed the use of hydroxychloroquine in patients with COVID-19. WHO made a strong recommendation against using hydroxychloroquine or chloroquine for the treatment of COVID-19. This recommendation applies to patients with any disease severity and any duration of symptoms.

Ivermectin

Ivermectin is an anti-parasitic drug mainly used in onchocerciasis and strongyloidiasis.⁴³ Interest in Ivermectin as a possible COVID-19 therapy first arose in early 2020 when a study reported that the drug showed an inhibitory effect of SARS-CoV-2 *in vitro*. The authors claimed a 5000-fold reduction in the viral RNA at 48 hours in the cell culture model.⁴⁴ Since then, many studies have aimed to prove the effectiveness of Ivermectin for COVID-19 therapy.

Some studies observed promising beneficial effects of Ivermectin use for COVID-19 patients. In one study, a double-blind RCT reported an improvement of clinical features of COVID-19, including dyspnoea, cough, and lymphopenia. The study also claimed that a single weight-based dose of ivermectin (0.2 mg/kg) was well-tolerated among the patients.⁴⁵ Another trial combined ivermectin with doxycycline and reported an earlier recovery compared to control, and less likely to progress to a more serious phase, and more likely to be tested negative by RT-PCR on day 14.⁴⁶ A meta-analysis assessed the association between the use of ivermectin and mortality in COVID-19 patients. The study included six RCTs with a total of 658 patients with COVID-19, in which a preliminary mortality beneficial effect with ivermectin use was observed.⁴⁷ Local use of Ivermectin was a subject of research as well. A prospective clinical trial with 114 mild COVID-19 patients assessed the therapeutic

efficacy of Ivermectin nanosuspension intranasal spray. The trial concluded that local use of the spray was safe and effective, proven by rapid viral clearance and shortening of anosmia duration in the group treated with the Ivermectin spray.⁴⁸ A prophylaxis RCT, conducted in Argentina, aimed to evaluate the protective effect of intensive short-term treatment with Ivermectin and Iota-Carrageenan combination, given as oral and nasal spray for health workers. The result was that the treatment reduced the number of health workers infected with COVID-19.⁴⁹

However, not all studies yield the beneficiary result of ivermectin used in COVID-19. A double-blind RCT aimed to determine whether Ivermectin prove to be efficacious for mild COVID-19, concluded that a 5-day course of ivermectin did not significantly improve the symptom resolution time, compared to placebo.⁵⁰ An almost similar result was observed in a double-blind RCT with single-dose ivermectin in mild and moderate COVID-19. In this study, single oral administration of Ivermectin did not significantly increase the negativity of RT-PCR or decline in day 5 viral load.⁵¹ Another double-blind RCT reported that ivermectin had no significant effect on hospitalization prevention, and the ivermectin group even required invasive mechanical ventilatory support earlier than the placebo group.⁵²

Until its latest living guideline (6th version, dated 24 September 2021), WHO recommended not to use Ivermectin in patients with COVID-19, outside of clinical trial settings. This recommendation is based on the very low certainty of the evidence of most key outcomes such as mortality, mechanical ventilation, hospital admission, duration of hospitalization, and viral clearance in many studies, and therefore, the effect of Ivermectin on these outcomes remains uncertain. The very low certainty of the evidence consists of serious imprecision for most outcomes and wide confidence intervals of the aggregate data. Risk of

bias for some outcomes also noted, such as lack of blinding or lack of trial pre-registration in some trials, and publication bias in one trial. Some low certainty evidence showed that ivermectin also might have little to no effect on clinical improvement, and even might increase the risk of adverse events. The fact that Ivermectin is widely available and at a relatively low cost does not mandate its use because any benefit remains very uncertain with ongoing concerns regarding the harms. Continuous use of Ivermectin potentially contributes to drug shortages for helminth control and elimination programs. Ivermectin, however, may still be used anyway in areas with strongyloidiasis endemic, at the discretion of the clinicians overseeing the treatment, but not for treatment of COVID-19 itself.^{18,42}

Interleukin-6 receptor blockers

COVID-19 is associated with maladaptive immune response leading to excessive inflammation and organ injury.⁵³ clinical criteria specifically to define COVID-19-associated hyperinflammatory syndrome (cHIS). One of the prominent inflammatory mediators is IL-6, a cytokine produced by macrophages that induces a proinflammatory response.⁵⁴ Elevated level of blood IL-6 were commonly seen in patients with severe COVID-19.⁵⁵

Clinical trials of two IL-6 receptor blockers found promising results. Tocilizumab and sarilumab improve organ support-free days in patients with COVID-19 who were admitted to the intensive care unit and receive respiratory or cardiovascular organ support. The median number of organ support-free days was 10 (interquartile range [IQR] -1 to 16) in the tocilizumab group, 11 (IQR, 0 to 16) in the sarilumab group, and 0 (IQR -1 to 15) in the control group.⁵⁶ The RECOVERY Trial found that treatment with tocilizumab reduces mortality. The primary outcomes of all-cause mortality were assessed at 28 days after randomization to tocilizumab

versus usual care. Mortality occurred in 621 (31%) of the 2022 patients allocated with tocilizumab and 729 (35%) of the 2094 allocated to usual care (RR 0.85; 95% CI 0.76–0.94; $p = 0.0028$). Treatment with tocilizumab also increases the chances of hospital discharge within 28 days (RR 1.2; 95% CI 1.12–1.33; $p = <0.0001$), and reduces the chances of requiring invasive mechanical ventilation (RR 0.84; 95% CI 0.77–0.92; $p = <0.0001$).⁵⁷ Report from EMPACTA trial informs us about the safety and efficacy of tocilizumab in hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% CI 8.5-16.9) in the tocilizumab group and 19.3% (95% CI 13.3- 27.4) in the placebo group (hazard ratio for mechanical ventilation or death, 0.56; 95% CI 0.33 to 0.97; $p = 0.04$ by the log-rank test). Tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death.⁵⁸

Another multinational trial with sarilumab reaches a different conclusion. The trial did not show the efficacy of sarilumab in patients admitted to the hospital with COVID-19 and receiving supplemental oxygen. The primary endpoint is time to improvement of two or more points on a seven-point clinical assessment scale. No significant difference was observed between sarilumab doses and placebo up to day 29. A potential reason as to why sarilumab was not effective in this trial might be because targeting IL-6 alone is inadequate to suppress the hyperinflammation phase of COVID-19. IL-6 antagonists and cytokine inhibition, in general, have not been effective in other forms of sepsis where levels of IL-6 are comparable with COVID-19.⁵⁹ A retrospective study from New York City Hospital found similar results with tocilizumab. There was no evidence to support an improvement in hypoxemia or ventilator-free survival with the use

of tocilizumab 400 mg in the absence of corticosteroids.⁶⁰ COVACTA, a phase 3, international, randomized, double-blind, placebo-controlled trial, to assess the efficacy and safety of tocilizumab in hospitalized patients with severe COVID-19 also found no significant difference in clinical status between the tocilizumab group and the placebo group at day 28.⁶¹

The WHO living guideline recommends treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or

critical COVID-19. Compared with other treatment recommendations for COVID-19, IL-6 receptor blockers are expensive. WHO recommendation does not take into account cost-effectiveness. The trials of IL-6 receptor blockers were mostly performed in high-income countries. Lower-middle countries might be facing challenges to access this medication. However, this strong recommendation should provide a stimulus to improve equity and global access to these treatments.^{17,18}

TABLE 1. Summary of WHO recommendations

Pharmacological Treatments (Drug Classes/Name)	COVID-19 disease severity		
	Non-Severe	Severe	Critical
Systemic corticosteroids	Weak recommendation against	Strong recommendation in favor	
Remdesivir	Weak recommendation against		
Lopinavir-ritonavir	Strong recommendation against		
Hydroxychloroquine	Strong recommendation against		
Ivermectin	Recommendation against except in clinical trials		
Interleukin-6 receptor Blockers	Strong recommendation in favor		

CONCLUSION

Specific pharmacological treatment for COVID-19 is not yet available. Several recommendations have been made by WHO for some particular drugs to be used as the pharmacological treatment of COVID-19. Hydroxychloroquine, lopinavir-ritonavir, remdesivir, and ivermectin were not recommended for COVID-19 treatments regardless of disease severity and duration of symptoms. Therefore, they were excluded from the list of drugs for the treatment of COVID-19 by WHO. WHO stated strong recommendations in favor of two drugs, namely systemic corticosteroids and tocilizumab or sarilumab. Both of them are recommended for the treatment of patients with severe and critical covid-19 so they are included in the list

of COVID-19 therapeutic drugs by WHO.

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