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Evaluation of commonly used drugs in patients with COVID-19: A systematic review study

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Abstract

Introduction: COVID disease is an infectious disease caused by coronavirus 2 (SARS - CoV-2) and causes severe acute respiratory syndrome in patients. From arrival to proliferation in the deep part of the lung can be classified into three stages. Most people get only a mild form of the disease, but up to 20% of the virus may penetrate deep into the lungs and cause hypoxia and acute respiratory distress syndrome. This study provides an overview of the main treatment strategies that have been performed to date in randomized, clinical, and experimental controlled trials of COVID-19 in pubmed and Google Scholar databases. From 453 identified studies, after eliminating irrelevant and duplicate cases, 64 clinical trials were selected to extract the data. And we examined the drugs that were most effective. Due to the clinical trials of drugs with different pharmacological properties, none of them have a definite effect on the treatment of Covid 19 disease, and among them, only Ramdsavir and Barstenib are licensed for emergency use. Mulnipevirovir and Pexlovid have had good clinical trials but have not yet received final FDA approval.

Keywords: COVID-19, Drug, Clinical trial

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Introduction

COVID disease is an infectious disease caused by the coronavirus 2 (SARS - CoV-2) and causes severe acute respiratory syndrome in the patient (1). SARSCoV-2 infection can be divided into three stages: stage I, an asymptomatic incubation period; Stage II, a non-severe symptomatic period despite the virus; Stage III, severe respiratory distress is a symptomatic stage with a high viral load (2). In the first stage, the virus probably begins to multiply by attaching to the epithelial cells of the nasal cavity. ACE2 is the major SARS-CoV2 receptor. Although the virus is replicating, the innate immune response is limited. Although the viral load may be low, people are carriers and can transmit the disease. In the second stage, the virus travels to the airways and migrates to the airways, leading to a stronger innate immune response. Virus-infected epithelial cells are the main source of beta and lambda interferons. About 20% of patients reach stage 3, where the virus penetrates deep into the lungs and reaches the gas exchange area of the lungs, infecting type II alveolar cells. . Large numbers of viral particles are released and the cells undergo apoptosis and die, leading to hypoxia and ARDS. The elderly are at particular risk due to decreased immune response and reduced ability to repair damaged epithelium (3).

Currently, no treatment is very effective in treating SARS-CoV-2. However, different drug groups have been tested and used based on the different characteristics and clinical stages of COVID-19 (4). In this review study, we intend to examine the most common drugs that have been clinically studied for the treatment of COVID-19.

This study provides an overview of the main treatment strategies that have been performed so far in randomized controlled clinical, clinical, and experimental trials of COVID-19 in pubmed and Google Scholar databases.

From 453 identified studies, after eliminating irrelevant and repetitive cases, 64 clinical trials were selected to extract the data.

With the outbreak of coronavirus, different drugs with different pharmacological effects were studied in different stages of the disease. In this study, we examined their clinical effects:

1. Hydroxychloroquine

Hydroxychloroquine is a derivative of chloroquine, which is mainly used in the treatment of autoimmune diseases and has recently been identified as a possible treatment for COVID-19 disease, although recent studies have reported conflicting results regarding the efficacy of this drug (5). According to the results of new studies, the use of hydroxychloroquine in coronary patients has an effect on reducing the need for hospitalization, reducing the duration of hospitalization, reducing the number of days the patient has to use oxygen or mechanical ventilation, improving laboratory parameters on the fourth day The severity of the disease and ultimately the reduction in mortality is not general. Chloroquine also had no effect on reducing the duration of positive PCR in patients with coronary artery disease (5, 6). However, in another study, the use of hydroxychloroquine was effective in early negative PCR on the seventh day of hospitalization (7).

Also, according to another study, the use of lopinavir-ritonavir, hydroxychloroquine, or combination therapy with these drugs not only does not improve clinical outcomes in patients with severe coronary heart disease, but can have detrimental effects on patients (8). The availability of chloroquine and hydroxychloroquine around the world make these drugs an ideal option for preventing coronary heart disease, although new research proves the incidence of coronary heart disease in people in close contact with the patient. COVID-19 have not been shown to significantly reduce the incidence of coronary heart disease in patients taking hydroxychloroquine (9). The WHO has also recommended that hydroxychloroquine or chloroquine be avoided for the treatment of COVID-19 in patients with any severity of the disease and any duration of symptoms.

2. Lopinavir / Ritonavir

Lopinavir is an HIV-1 protease inhibitor that, along with ritonavir, increases plasma half-lives. This combination has been suggested as a treatment for COVID-19 based on preclinical studies and observational studies. However, clinical studies were performed on 1616 patients over a period of 28 days. Ritonavir was not associated with a reduction in

mortality, length of hospital stay, or risk of progression to mechanical ventilation or death (10).

3. Remdesivir

Remdesivir is a nucleoid analogue with extensive antiviral effects that received FDA approval on May 1, 2020 for use in the treatment of patients with moderate to severe coronary heart disease (11).

In a recent study, the effect of using Remdesivir on the clinical consequences of coronary infection was investigated and the results of this study showed that the use of Remdesivir was not associated with better clinical outcomes on the 15th and 29th days of hospitalization and reduced mortality. It has not been effective in clearing the virus faster, although the injection of this drug reduces patients' need for mechanical ventilation and ECMO, and thus may delay the onset of the patient's respiratory symptoms (12). Also, a 5-day course of Remdesivir will shorten the duration of the disease and speed up the patients' recovery (13).

Recent studies have shown that injecting Remdesivir in the early days of the onset of clinical signs of coronary heart disease can improve patients' clinical status and prevent them from progressing to more severe respiratory problems. Compared to patients who received early Remdesivir injection compared to those who started Remdesivir injection later, there was a significant reduction in ICU admission and the need for mechanical ventilation. Also, this group of patients had a higher recovery rate in the first 14 days of hospitalization and a significant reduction in mortality during the 28 days of hospitalization (11, 14).

Liver and kidney damage are known to be side effects of Remdesivir treatment, although hepatic and renal failure should not be considered as a definitive contraindication to Remdesivir treatment and can be prevented by closely monitoring liver and kidney function and adjusting the dose of the drug. Also, changes in heart rhythm have been reported in patients treated with Remdesivir, which according to new studies has not shown severe cardiac toxicity in Remdesivir treatment, and even the presence of cardiac risk factors has not increased the risk of heart damage (15, 16).

4. Favipiravir

Favipiravir is a nucleic acid analogue of purine that selectively inhibits RNA production by RNA Polymerase in viruses of RNA nature and has been approved in Japan for the treatment of influenza (17, 18). It is effective against influenza A and B. It has also been shown to be effective in the treatment of zanamivir and Oseltamivir-resistant influenza, viral hepatic fever and SARS-Cov-2 in vitro (18). Favipiravir has shown hopes for efficacy in COVID-19 in the early stages of the disease (19, 20). However, to date, no effective antiviral treatment strategy has been found that is effective and validated in the Corona epidemic (21). However, studies have shown that the use of favipiravir is safe and tolerable in the short term, but more studies are needed for further investigation (20, 22). According to the WHO, the treatment protocol in Japan has been suggested for this drug as 1800 mg twice daily for loading dose on the first day and then 800 mg twice daily from the second to the tenth day of the disease, which will probably only affect the mild type of the disease. Several other studies have shown the usefulness of favipiravir in the clinical phase, including shortening the patient's hospital stay and earlier discharge from the hospital and reducing the need to use a ventilator (19, 22-24). In one A comprehensive study comparing favipiravir and lopinavir/ritonavir found that the mean viral clearance time in favipiravir users was significantly lower than in the opposite group (4 days vs. 11 days). Fourteenth CT scan in patients taking favipiravir showed more improvement in treatment (18, 25). Rapid clearance of the virus, higher recovery rate, and orality of this drug considering its safety, make favipiravir a promising drug in the treatment of COVID-19 patients (22). However, it has not had a significant effect on mortality and reduced patient mortality (19, 23, 25). There have been many studies on the side effects of this drug in COVID-19 patients taking it. Increased liver enzymes, nausea and vomiting, tachycardia, elevated blood uric acid and diarrhea have been common side effects of this drug in patients (20, 23, 25). Also, several statements point to the teratogenicity of favipiravir (20, 24). The World Health Organization (WHO) also allows the use of this drug, considering its teratogenicity, considering its risks and benefits, and only in mild cases of the disease. However, according to clinical trials

conducted in several treatment centers, the use of favipiravir in the treatment of patients with moderate COVID-19 can be beneficial because it increases the rate of recovery during the first week of treatment and effectively reduces fever and cough in patients. Its side effects are mild and manageable (21, 24).

5. Ivermectin

Ivermectin is a US Food and Drug Administration-approved antiparasitic agent that has been shown to inhibit SARS-CoV-2 in vitro (26, 27).

A study of 72 hospitalized patients with the aim of using ivermectin to reduce the duration of hospitalization showed that using 12 mg of ivermectin alone for 5 days reduced virus clearance compared to control groups (27). Studies have shown that ivermectin does not significantly reduce the need for mechanical ventilation and mortality (26, 28). However, studies show that it reduces the length of hospital stay (27, 29).

One study also showed that ivermectin had no significant effect on preventing hospitalization of patients with COVID-19 (30). However, another study has shown that ivermectin can increase clinical improvement, improve laboratory parameters, and reduce mortality, even in patients with severe COVID-19 (31). However, for final conclusions, we need more studies on a larger scale (26, 30, 31).

The FDA has not yet approved or approved ivermectin for the treatment or prevention of COVID-19. Because it has not yet been proven to be safe, and there is a lot of misinformation around, and you may have heard that taking large doses of ivermectin is not a problem, which is not true.

6. Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) with a high affinity for S1R. Previous studies have shown that it can reduce the destructive aspects of the inflammatory response during sepsis via the S1R-IRE1 pathway. Therefore, a study was conducted to investigate whether Fluvoxamine could help prevent the disease from getting worse in outpatients with COVID-19 syndrome. The results showed that of the 152 patients in this study, patients treated with Fluvoxamine were less likely to have clinical deterioration over 15 days compared with placebo (32).

In another study of 9020 patients, it was found that treatment with Fluvoxamine (100 mg twice daily for 10 days) in high-risk outpatients with early diagnosis of COVID-19 required long-term emergency observation or hospitalization. Our reductions had no significant relative effect between the Fluvoxamine and placebo groups on virus clearance and mortality (33).

7. Baricitinib

Barsitinib is a selective and reversible inhibitor of Gallus kinase 1 and 2. It has recently been recognized as a new hope for the treatment of COVID-19 pneumonia. On November 19, 2020, its use in a dose of 4 mg in COVID-19 as an emergency use permit (EUA) was obtained from the FDA. In one study, a high dose of Baricitinib(8 mg) was compared with the usual dose of 4 mg, in which blood oxygen saturation was stabilized earlier in the HD group than in the UD group. [P <0.05] As well as the support needs of intensive care, the reduction in readmission rate decreased with the mortality rate compared to the usual daily dose (34).

The aim of this study was to evaluate the efficacy of Baricitinib with Remdesivir for patients admitted to the hospital with COVID-19. 1033 patients were randomly selected (515 patients were treated with Baricitinib + Remdesivir and 518 patients were treated with Remdesivir + placebo). In which combination therapy was superior to Remdesivir in reducing recovery time and accelerating the improvement of clinical status in patients with COVID-19, especially among those receiving high-flow oxygen or non-invasive ventilation (35).

8. Tofacitinib

Tofacitinib is a Janus kinase inhibitor, a group of intracellular enzymes involved in signaling pathways that affect hematopoiesis and immune cell function. In the EC study, two patients received tofacitinib (TOF group) and 30 patients who had not received any anti-cytokine drugs (control group [CON]) were studied. The results showed that tofacitinib was effective and safe for the management of cytokine release syndrome in COVID-19 patients and the mortality and incidence

of intensive care units in the TOF group were lower than the CON group. There was also a significant reduction in the volume of the damaged part of the lungs (p = 0.022) (36).

In another study, the effect of tofacitinib in patients admitted with COVID-19 pneumonia was evaluated. The results showed that among patients admitted with COVID-19 pneumonia, tofacitinib reduced the risk of death or respiratory failure by day 28 compared to placebo (37).

9. Anakinra

Anakinra is an interleukin-1 receptor antagonist that can be effective in several inflammatory diseases. A study has shown that initial treatment with AAnakinra prevents severe respiratory failure (38).

In another study, the effect of Anakinra in patients with COVID-19 and mild to moderate pneumonia was shown to show that Anakinra did not improve outcomes in patients with mild to moderate COVID-19 pneumonia. However, further studies are needed to evaluate Anakinra in different disease conditions (39).

10. Tocilizumab

COVID-19 is associated with immunosuppression with hyper inflammation, including elevated levels of interleukin 6. The use of tocilizumab is a monoclonal antibody against the interleukin 6 receptor that, in case reports and retrospective observational cohort studies, results It has been shown to improve COVID-19 in patients with severe pneumonia (40).

In a study conducted by Carlos Salama with the aim of evaluating tocilizumab in patients admitted to COVID-19 pneumonia in which 389 patients were randomly admitted with COVID-19 pneumonia and were not mechanically ventilated, 249 patients in the group were selected. Tocilizumab and 128 patients were placed in the placebo group. The results showed that the cumulative percentage of patients who received mechanical ventilation or died by the 28th day was 12% in the Tocilizumab group and 19.3% in the placebo group. Death from any cause occurred on day 28 in 10.4% of patients in the Tocilizumab group and 8.6% of patients in the placebo group. The results showed that Tocilizumab reduced the need for mechanical ventilation or death, but did not improve survival (41).

Also in another study by John H Stone to evaluate the effectiveness of Tocilizumab in inpatients, 243 patients were randomly assigned to 141 males and 102 females. The results showed that the risk ratio for intubation or death in the Tocilizumab group was 0.83 compared to the placebo group. And the risk ratio for disease exacerbation was 1.11. At 14 days, 18% of patients in the Tocilizumab group and 14.9% of patients in the placebo group had their disease worsen. The mean oxygen withdrawal time was 5.0 days in the Tocilizumab group and 4.9 days in the placebo group. Patients receiving tocilizumab had fewer serious infections than patients receiving placebo. As a result, in this study, the efficacy of tocilizumab to prevent intubation or death in hospitalized patients with COVID-19 disease was low and was not more effective than placebo (40).

But there was also a study in which Tocilizumab, along with standard care in patients with severe or critical COVID-19, did not outperform standard caregivers alone in improving clinical outcomes and may even increase mortality (42).

Also, the independent effect of Tocilizumab from corticosteroids in patients with severe disease is still unknown, which is why several studies have been performed in this field (43, 44). One group was assigned to treatment with Tocilizumab (46 patients) and the other group to treatment with dexamethasone (63 patients). Cox regression analysis showed that, with Tocilizumab treatment compared to the dexamethasone group, the neutrophil/lymphocyte ratio was higher, PaO2 / FiO2 was lower in the two days after treatment. In this study, dexamethasone showed better survival in patients with severe COVID-19 compared to TCZ (44).

11. Corticosteroids

Corticosteroid drugs are anti-inflammatory drugs that were previously used in rheumatology, skin diseases, etc. Some recent studies indicate a reduction in the length of hospital stay of patients with COVID-19 due to the use of these drugs. However, the World Health Organization considers the use of corticosteroids necessary only in severe forms of the disease, such as pulmonary involvement and hypoxia, and the use of

corticosteroids is not recommended in the treatment of mild forms of COVID-19 disease (45).

A study was conducted in Brazil. The results of this study, which included a total of 299 patients in this study, show that there was no significant difference in inpatient mortality in the first 28 days, no hospitalization in the intensive care unit and the use of mechanical ventilation. Also, there was no significant difference between the two groups in the side effects of corticosteroids such as infections and hyperglycemia (46).

In another study of 2104 patients, the results showed that the mortality rate in the group of patients undergoing mechanical ventilation and oxygen therapy was significantly different between the two groups receiving dexamethasone and the other group of patients, while mortality was between the two The group was not significantly different in happy patients who did not use ventilatory support (47).

In another study conducted in Iran, 68 patients were studied for one month. These patients were in the early stages of pulmonary involvement (48).

Another study in China found that 86 patients admitted to COVID-19 were given methylprednisolone for 7 days and then monitored for 14 days for clinical signs. It was that between the two groups in terms of worsening clinical symptoms but the persistence of the hereditary substance of the virus in the throat of patients for 11 days was longer in those receiving methylprednisolone (49).

12. Anticoagulants

The class of anticoagulants, due to the changes in homeostasis and coagulation that occur due to COVID-19 disease, which is effective on the prognosis of these patients (50) in some studies has been effective in reducing mortality due to pneumonia following coronavirus.

A group of researchers simultaneously studied patients in COVID-19 who needed intensive care and those who did not. In this study, the therapeutic dose of enoxaparin was more effective than the prophylactic dose of heparin. In terms of improving the general condition of patients and reducing the need for intensive care. In contrast, in patients under intensive care, it was observed that the therapeutic dose of heparin was not able to prevent the formation of coagulation and inflammatory cascades (51).

In critically ill patients at the time of enrollment, no significant difference was observed in the prognosis of patients between the two groups treated with the therapeutic dose and the prophylactic dose of thrombosis (51).

In a retrospective study, a decrease in mortality was observed among patients with 19 low molecular weight heparin-receiving COVID-19 (52).

New drugs in the study phase

A number of drugs showed good results in laboratory studies and entered clinical phases. This drug is as follows:

1. Hesperidin

Hesperidin is an ancient herbal medicine rich in flavonoids derived from citrus and is known for its antioxidant and anti-inflammatory properties (53) and heart protection (54). Cov-2 has been shown to be effective in the prevention and adjuvant therapy of COVID-19 (53, 55). Or a specific substance that can prevent the disease has not been obtained (55). Increasing cellular immunity of host cells, minimizing the release of inflammatory factors and preventing cytokine storms, as well as its effectiveness in combination with heparin and providing protection against venous thrombosis in COVID-19 patients, can prevent disease progression and its onset (54). Accordingly, hesperidin may be a suitable option for clinical trial studies (53, 54). Recently, two clinical studies have been started to investigate the effects of this compound on the symptoms of COVID-19, one of which, which has successfully passed the second phase, has shown positive results and to conclude studies (ClinicalTrials.gov Identifier: NCT04715932) Safety, short half-life in the body, no cytotoxicity at high doses (54), low-cost extraction and mass production capability and worldwide availability are some of the advantages. This combination is no longer effective.

2. Probenecid

Probenecid belongs to a group of medicines known as uricosuric. This works by accelerating the elimination

of uric acid by the kidneys. This lowers uric acid in the blood. In vitro studies, probenecid has been shown to strongly inhibit SARS-CoV-2 proliferation in mammalian cells and virus replication in a hamster model. Also showed no cytotoxicity at high concentrations. Therefore, this drug can be a good option for entering clinical studies for the treatment of COVID-19.

3. Molnupiravir

Molnupiravir is a new antiviral drug that has been shown to be effective against coronaviruses (56). The disease progresses to severe forms. According to an article published in January 2021, the use of this drug is in its second phase and has not yet been approved by the Food and Drug Administration. According to a study, the use of Molnupiravir was effective in killing viruses within 5 days and was the first oral antiviral drug to reduce the burden of the disease with high tolerability. No serious side effects have been reported following the use of Molnupiravir (57). Another study in non-hospital COVID-19 patients found that using 200 mg for 5 days was negative in testing and reducing the burden of the virus in patients (58).

4. Paxlovid

Pfizer's oral antiviral drug, Paxlovid, significantly reduces hospitalization and mortality of COVID-19 patients at high risk for severe disease compared with placebo, according to Pfizer. The drug will be approved for emergency use. The UK Health Organization also found the approval to be an effective weapon in combating COVID-19 with vaccines and other drugs such as Molnupiravir (59).

Conclusion

Due to the clinical trials of drugs with different pharmacological properties, none of them have a definite effect on the treatment of COVID-19 disease. Among these drugs, Remdesivir received FDA approval on May 1, 2020 for use in the treatment of patients with moderate to severe coronary heart disease. Barsitenib was then authorized by the FDA for emergency use (EUA). A number of new drugs were also included in the study, including a new molecule, Paxloid, developed by Pfizer but not yet approved by the FDA. Another new drug is Molnupiravir, which has had good clinical trials and has been approved for use in the UK but has not yet been finally approved by the FDA.

Author contributions

ShD, **PM**, **FB**, **HM** and **KD** wrote and compiled this article. **ShD** wrote and edited the manuscript comprehensively. All authors confirmed the final version of the paper.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Yuliana Y. Corona virus diseases (Covid-19): Sebuah tinjauan literatur. Wellness And Healthy Magazine. 2020;2(1):187-92.
2. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020;27(5):1451-4.
3. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55(4):2000607.
4. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: An overview. Eur J Pharmacol. 2020;889:173644.
5. Dubée V, Roy P-M, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. Clin Microbiol Infect. 2021;27(8):1124-30.
6. Gupta S, Dixit PK, Ghana P, Abhisheka K, Khurana H, Jha VK, et al. Open-label randomized control trial of hydroxychloroquine in patients with moderate to severe coronavirus disease 2019 infection. Med J Armed Forces India. 2021;77:S305-S11.
7. Kamran SM, Moeed HA, Mirza Z-EH, Naseem A, Azam R, Ullah N, et al. Clearing the Fog: Is Hydroxychloroquine Effective in Reducing Coronavirus Disease-2019 Progression? A Randomized Controlled Trial. Cureus. 2021;13(3):e14186-e.
8. Arabi YM, Gordon AC, Derde LP, Nichol AD, Murthy S, Beidh FA, et al. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with

COVID-19: REMAP-CAP randomized controlled trial. Intensive Care Med. 2021;47(8):867-86.
9. Barnabas RV, Brown ER, Bershteyn A, Stankiewicz Karita HC, Johnston C, Thorpe LE, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. Ann Intern Med. 2021;174(3):344-52.
10. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020;396(10259):1345-52.
11. Mehta RM, Bansal S, Bysani S, Kalpakam H. A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis. Int J Infect Dis. 2021;106:71-7.
12. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis. 2021.
13. Garibaldi BT, Wang K, Robinson ML, Zeger SL, Bandeen-Roche K, Wang M-C, et al. Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19. JAMA Netw Open. 2021;4(3):e213071-e.
14. Hussain Alsayed HA, Saheb Sharif-Askari F, Saheb Sharif-Askari N, Hussain AAS, Hamid Q, Halwani R. Early administration of remdesivir to COVID-19 patients associates with higher recovery rate and lower need for ICU admission: A retrospective cohort study. PLoS One. 2021;16(10):e0258643.
15. van Laar SA, de Boer MG, Gombert-Handoko KB, Guchelaar HJ, Zwaveling J, group LCr. Liver and kidney function in patients with Covid-19 treated with remdesivir. Br J Clin Pharmacol. 2021;87(11):4450-4.
16. Brunetti ND, Poliseno M, Bottalico IF, Centola A, Montemurro L, Sica S, et al. Safety and heart rate changes in Covid-19 patients treated with Remdesivir. Int J Infect Dis. 2021;112:254-7.
17. Esposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. Infez Med. 2020;28(2):198-211.
18. Coomes EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother. 2020;75(7):2013-4.
19. Dabbous HM, Abd-Elsalam S, El-Sayed MH, Sherief AF, Ebeid FF, Abd El Ghafar MS, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Arch Virol. 2021;166(3):949-54.
20. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir–a potential treatment in the COVID-19 pandemic? J Virus Erad. 2020;6(2):45-51.
21. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020.
22. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8.
23. Alamer A, Alrashed AA, Alfaifi M, Alosaimi B, AlHassar F, Almutairi M, et al. Effectiveness and safety of favipiravir compared to supportive care in moderately to critically ill COVID-19 patients: a retrospective study with propensity score matching sensitivity analysis. Curr Med Res Opin. 2021:1-13.
24. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: a simplified summary. Drug Res. 2021;71(03):166-70.
25. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: A systematic review and meta-analysis of clinical trials. Sci Rep. 2021;11(1):1-11.
26. Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, et al. Clinical Study Evaluating the Efficacy of Ivermectin in COVID-19 Treatment: A Randomized Controlled Study. J Med Virol. 2021;93(10):5833–8.
27. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021;103:214-6.
28. Galan LEB, Santos NMd, Asato MS, Araújo JV, de Lima Moreira A, Araújo AMM, et al. Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathog Glob Health. 2021;115(4):235-42.

29. Samaha AA, Mouawia H, Fawaz M, Hassan H, Salami A, Bazzal AA, et al. Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon. Viruses. 2021;13(6):989.
30. Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis. 2021;21(1):1-11.
31. Okumuş N, Demirtürk N, Çetinkaya RA, Güner R, Avcı İY, Orhan S, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infect Dis. 2021;21(1):1-11.
32. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020;324(22):2292-300.
33. Reis G, dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2022;10(1):e42-e51.
34. Hasan MJ, Rabbani R, Anam AM, Huq SMR, Polash MMI, Nessa SST, et al. Impact of high dose of baricitinib in severe COVID-19 pneumonia: a prospective cohort study in Bangladesh. BMC Infect Dis. 2021;21(1):1-9.
35. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795-807.
36. Maslennikov R, Ivashkin V, Vasilieva E, Chipurik M, Semikova P, Semenets V, et al. Tofacitinib reduces mortality in coronavirus disease 2019 Tofacitinib in COVID-19. Pulm Pharmacol Ther. 2021;69:102039.
37. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-15.
38. Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N, et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. Elife. 2021;10:e66125.
39.mTharaux P-L, Pialoux G, Pavot A, Mariette X, Hermine O, Resche-Rigon M, et al. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med. 2021;9(3):295-304.
40. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333-44.
41. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;384(1):20-30.
42. Veiga VC, Prats JA, Farias DL, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021;372.
43. Mehta M, Purpura LJ, McConville TH, Neidell MJ, Anderson MR, Bernstein EJ, et al. What about tocilizumab? A retrospective study from a NYC Hospital during the COVID-19 outbreak. PLoS One. 2021;16(4):e0249349.
44. Rashad A, Mousa S, Nafady-Hego H, Nafady A, Elgendy H. Short term survival of critically ill COVID-19 Egyptian patients on assisted ventilation treated by either Dexamethasone or Tocilizumab. Sci Rep. 2021;11(1):1-7.
45. Organization WH. Coronavirus disease (COVID-19): Dexamethasone. WHO; 2020.
46. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA. 2020;324(13):1307-16.
47. Group RC. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
48. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J. 2020;56(6).
49. Tang X, Feng Y-M, Ni J-X, Zhang J-Y, Liu L-M, Hu K, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit

patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. Respiration. 2021;100(2):116-26.
50. Luo H-c, You C-y, Lu S-w, Fu Y-q. Characteristics of coagulation alteration in patients with COVID-19. Ann Hematol. 2021;100(1):45-52.
51. REMAP-CAP A-a, Investigators A. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021;385(9):777-89.
52. Di Castelnuovo A, Costanzo S, Antinori A, Berselli N, Blandi L, Bonaccio M, et al. Heparin in COVID-19 patients is associated with reduced in-hospital mortality: The Multicenter Italian CORIST Study. Thromb Haemost. 2021.
53. Meneguzzo F, Ciriminna R, Zabini F, Pagliaro M. Review of evidence available on hesperidin-rich products as potential tools against COVID-19 and hydrodynamic cavitation-based extraction as a method of increasing their production. Processes. 2020;8(5):549.
54. Haggag YA, El-Ashmawy NE, Okasha KM. Is hesperidin essential for prophylaxis and treatment of COVID-19 Infection? Med Hypotheses. 2020;144:109957.
55. Cheng F-J, Huynh T-K, Yang C-S, Hu D-W, Shen Y-C, Tu C-Y, et al. Hesperidin is a potential inhibitor against SARS-CoV-2 infection. Nutrients. 2021;13(8):2800.
56. Holman W, Holman W, McIntosh S, Painter W, Painter G, Bush J, et al. Accelerated first-in-human clinical trial of EIDD-2801/MK-4482 (molnupiravir), a ribonucleoside analog with potent antiviral activity against SARS-CoV-2. Trials. 2021;22(1):1-7.
57. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NC, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother. 2021;65(5):e02428-20.
58. Painter W, Sheahan T, Baric R, Holman W, Donovan J, Fang L, et al. Reduction in infectious SARS-CoV-2 in treatment study of COVID-19 with molnupiravir. Top Antivir Med. 2021:304-5.
59. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ. 2021;375:n2713.