COVID-19: Current Pharmacological Therapeutic Approaches

Abstract

By the end of 2019, SARS-CoV-2, a new virus from Coronaviruses family, has been detected in China and was responsible for COVID-19 disease. This disease has been suddenly and vigorously disseminated among individuals all over the world. Based on genetic vicinity, this novel virus is similar to SARS-CoV and MERS-CoV; it can spread from an unknown animal host to individuals. Till now, there is no specific therapy or vaccine for the treatment of COVID-19 patients. However, published clinical data and *in vitro* studies may offer treatment strategies of some effective antiviral and repurposed drugs, including remdesivir, favipiravir, lopinavir/ritonavir, corticosteroids, etc. This narrative review describes current pharmacological proposed treatments for COVID-19 patients and available experimental and clinical studies for these drugs. Eventually, these data may help to explain the most preferable way to treat COVID-19 and lessen symptoms and complications accompanied with it.

Key words: SARS-COV-2, Pathophysiology, Remdesivir, Monoclonal antibodies, Favipiravir

Introduction

COVID-19, a viral respiratory disease, caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was emerged in Wuhan in 2019 [1]. It is known that coronaviruses are composed of single-stranded RNA viruses which are described by a spherical structure. These viruses are classified into α, β, γ, and δ-coronaviruses [2]. In the past two decades, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), type of β-coronaviruses, were found in China in 2002 and Saudi Arabia in 2012, respectively. However, COVID-19, a novel type of β-coronaviruses, is a highly contagious virus and has spread throughout the world [3]. The World Health Organization (WHO) has declared that COVID-19 is a global pandemic disease as its deaths surpass 500,000 with 10 million infected patients. The transmission of this epidemic disease began from animal to human [4] and then transmitted among individuals *via* respiratory droplets [5]. The clinical features of COVID-19 patients involve flu-like symptoms including, fever, dry cough, fatigue, and developed in severe cases into pneumonia and kidney failure [6]. Noteworthy, COVID-19 patients usually accompanied by a profound lymphopenia, and a storm of proinflammatory cytokines and chemokine [7]. Accordingly, this storm of cytokines may lead to acute respiratory distress syndrome (ARDS), sepsis, and finally patient's death [8]. In case of severe cases, pharmacological therapies and antivirals drugs should be provided to decrease the severity of symptoms. Currently, there is no specific vaccine to treat patients with COVID-19. Hence, this review aims to summarize the available treatments administered in COVID-19 patients focusing on the pharmacological mechanisms, safety, and experimental and clinical trials.

Pathophysiology of the virus

SARS-CoV-2, a single-stranded viral RNA, has four structural proteins, which are "S" for a spike, "E" for an envelope, "M" for membrane, and "N" for nucleocapsid[9] and its sequence is similar to bat SARS-like coronavirus [4]. The viral spike (S) protein can bind to angiotensin-converting enzyme-2 receptor (ACE2) and transmembrane serine protease (TMPRSS2) facilitates cell entry. S protein is

divided into S1 and S2 by proteases, S1 binds to ACE2. The S2 is divided by TMPRSS2, with a consequent fusion of the membrane. After binding, and fusion, the virus enters the host cells and then replication and transcription commence [10]. The nonstructural proteins produced from autoproteolytic cleavage are responsible for anchoring the coronavirus replication/transcription complex through recruitment of intracellular endoplasmic reticulumto form double-membrane vesicles (DMV). RNA-dependent RNA polymerase (RdRp) and helicase localize to DMV and drive the production of subgenomic RNAs from which the structural and accessory proteins are produced in the next phase of translation [11].

Available pharmacological treatments for COVID-19

Antiviral agents

Several numbers of antiviral drugs are used to treat some of human virus diseases including, hepatitis C, influenza virus, human immunodeficiency virus (HIV), etc. Noteworthily, certain antiviral agents are administered off-label for the treatment of COVID-19 patients. This section discusses the antiviral drugs which are currently available for the treatment of infected patients with COVID-19.

Remdesivir is shown to be the most promising antiviral drug against wide spectrum of RNA viruses including MERS and SARS-Co*v in vitro* and *in vivo* models [12, 13]. This agent has also shown great efficacy against the Ebola virus and Marburg infection [14].It is a monophosphate prodrug that metabolized to an active C-adenosine nucleoside triphosphate analog which inhibits RNA-dependent RNA polymerase (RdRp) proteins resulting in premature termination of viral RNA transcription [12]. A preclinical study has demonstrated that a combination of remdesivir and chloroquine has effectively suppressed SARS-Cov-2 infection [15]. Besides, successful case reports in the United States on COVID-19 patients demonstrated favorable results when they treated with remdesivir[16].

Favipiravirhas been approved to be effective in the treatment of influenza viruses' subtypes and Ebola viruses It is a guanine analog prodrug and selectively inhibits RdRp, halting viral replication. Recently, a randomized multicenter clinical trial compared the safety and efficacy of favipiravir with arbidol for treatment of COVID-19 hospitalized patients has exhibited that the clinical recovery results were about 56% in the arbidol group and 70% in the favipiravir one ($P = 0.01$) [17]. Another clinical trial of hospitalized COVID-19 patients in Wuhan has indicated that the patients who received favipiravir tested negatively in 4 days only compared with the control group (11 days) and the symptoms of pneumonia were markedly diminished [18]. Lately, several clinical trials have supported the use of favipiravir in the treatment of COVID-19 patients.

Lopinavir/Ritonavir is a combination of antiretroviral protease inhibitors used with high specificity for the treatment of HIV. Ritonavir increases lopinavir half-life *via* the inhibition of cytochrome P450 [19]. This combination has promising outcomes in treatment patients with SARS infection and MERS-CoV infection and its efficacy have also been evaluated in combination with interferon-β [20]. Several small case reports and retrospective, nonrandomized cohort studies of lopinavir/ritonavir have determined the direct effect of this combination when used in the treatment of COVID-19 patients [21]. Lately, Cao et al. [22] accomplished a randomized open-label clinical trial in 199 hospitalized patients with COVID-19 to compare the efficacy of the combination versus standard care for 14 days. In terms of clinical improvement and hospital discharge, there was no difference between this

combination and standard care. Also, in viral clearance, no marked differences were observed. The most commonly used dose for this combination in the treatment of COVID-19 patients is 400mg/100mg twice daily for 14 days [22]. A contemporary study has noticed that the efficacy of Remdesivir was superior to that ofLopinavir/Ritonavir [13]. The clinical studies for the effectiveness of this combination in the treatment of COVID-19 patients is still controversial and further clinical trials are necessary to confirm its efficiency against SARS-COV2.

Umifenovir (Arbidol) is a non-nucleoside antiviral and immunomodulating agent that was commonly used for influenza treatment in Russia and China. *In vitro* data based on the activity of arbidol against SARS has suggested a great effect of it in treating COVID-19 patients [23]. Thus, for SARS-CoV-2, Umifenovir is considered as a more promising antiviral agent through targeting S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope [24]. A non-randomized clinical study showed that receiving arbidol for 9 days was associated with higher discharge rates of patients from the hospital and lower death percentage compared with the ones who did not receive the drug [25]. Moreover, according to a retrospective cohort study, arbidol could enhance the process of viral clearance and improve chest radiologic images [26]. These observational data cannot confirm the efficacy of arbidol for the treatment of COVID-19. Therefore, other clinical trials should be done for this agent to evaluate its role against COVID-19.

Camostatmesylateand**nafamostat**, two synthetic protease inhibitors, are approved for the treatment of chronic pancreatitis in Japan. As previously mentioned, ACE2 and TMPRSS2 are essential for SARS-CoV-2 binding and cell entry. Therefore, both agents can prevent viralcell entry through inhibition of the host serine protease, TMPRSS2. This novel mechanism provides an additional drug target for future research [10]. A randomized, placebo-controlled clinical study is conducted using 180 COVID-19 patients to evaluate the safety and efficacy of camostatmesylate (NCT04321096).

Other antiviral agents are considered as potential therapies for COVID-19 patients. Among these agents, **darunavir/cobicistat** combination, approved for the treatment of HIV, is an inhibitor of the dimerization and has a catalytic activity of the HIV-1 protease. Cobicistat is used to inhibit cytochromes P450 and enhance darunavir plasma concentration [27]. A plethora of preclinical trials have indicated that this combination has an inhibitory effect on this novel coronavirus [28]. Furthermore, **tenofovir, sofosbuvir**, and **galidesivir** may show promising results against SARS-COV-2 [29]. However, there should be clinical trials to confirm the use of these agents for the management of COVID-19.

Anti-inflammatory and immune-modulatory agents

As previously mentioned, COVID-19 disease is associated with cytokine storm and release of large number of proinflammatory cytokines and the development of cytokine storm, such as tumor necrosis factor-α (TNF-α) and interleukin-(IL)-1, -2, -6, particularly in severe cases. This augmented immune response and cytokine release may lead to sepsis, reduction in respiratory function, and significant organ damage, especially lung and kidney. Thus, several monoclonal antibodies, anti-inflammatory, and immune-modulatory agents are potential therapies for COVID-19 patients.

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor and has been approved for the treatment of rheumatoid arthritis [30].A small clinical report case in China was demonstrated that treatment with tocilizumab improved the clinical outcomes in 91% of COVID-19 patients manifested as enhanced respiratory function, reduction in lung complications, and high hospital discharge [31]. Additionally, a

single-center retrospective cohort study was the first study to compare tocilizumab and standard care in severe COVID-19 patients. According to this study, there was no significant difference between tocilizumab and standard care patients after 28 days and patients experienced reduced fever and lower need for supplemental oxygen [32].

Another monoclonal antibody, **mepolizumab**, acts through binding to CD147 glycoprotein which interacts with S protein and facilitates viral entry and increases cytokine secretion and leukocytes chemotaxis[33]. Therefore, the preliminary study conducted by Chinese scientists on this agent seems to control the viral replication and reduce the production of inflammatory cytokine and chemokine related to SARS-COV-2 infection compared to baseline (NCT04275245). Indeed, this drug may be a promising therapy against COVID-19 patients and require high-quality clinical studies.

Among other monoclonal antibodies, **sarilumab**, IL-6 receptor antagonist, is tested in a multicenter, double-blind clinical trial for severe COVID-19 patients (NCT04315298).**Eculizumab**, used for the treatment of a typical hemolytic uremic syndrome and myasthenia gravis, is tried *via* a clinical trial for the treatment of COVID-19 patients (NCT04288713). Also, other clinical studies are carried out for evaluating **bevacizumab** (NCT04275414). A randomized phase 2/3 clinical study is done to investigate the efficacy and safety of **anakinra** (IL-1 receptor blocker) for SARS-CoV-2 infected patients (NCT04324021).

On the other hand, **Corticosteroids,** as anti-inflammatory agents**,** may be used against SARS-COV-2 to decrease acute lung injury and prevent ARDS. However, their use may lead to some adverse events including, a higher risk of secondary infection and delayed clearance of the virus. Some observational and meta-analysis studies of using corticosteroids in patients with SARS and MERS confirmed an increased risk of mortality and secondary infection, and other complications [34]. On the contrary, a recent retrospective clinical study of COVID-19 patients in China stated that treatment with methylprednisolone has been associated with decreased mortality rates for ARDS patients [35]. Therefore, the use of corticosteroids should be with caution and under evaluation by physicians until confirmed clinical trials for its indication in COVID-19 patients.

Chloroquineand**hydroxychloroquine**, used in the treatment of malaria and other autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis, can block viral entry and inhibit glycosylation of host receptors. Besides, they have immune-modulatory actions through the prevention of cytokine production, which makes them effective against SARS-COV-2 [36]. These agents are off-label used for the treatment of COVID-19 patients in China and other countries [37]. A clinical study has shown that the combination of remdesivir/chloroquine or hydroxychloroquine is greatly effective against patients with SARS-Cov-2 infection [38]. Moreover, Gautret et al. [39] have reported that the addition of azithromycin to hydroxychloroquine resulted in superior virus clearance (100%) compared with hydroxychloroquine alone (57%). It is worthy to note that both agents have impaired metabolism because the elevation of liver enzymes and hepatic impairment increased markedly in COVID-19 patients, resulting in a high risk of liver injury [40].

Baricitinib, another inhibitor of cytokine-release, is a Janus kinase reversible inhibitor approved for the treatment of rheumatoid arthritis [41]. Furthermore, it seems to have antiviral impacts by blocking AP2-associated protein (AAK1), which may decrease SARS-CoV-2 endocytosis [42]. This seems to inhibit the cytokine storm associated with COVID-19 and reduce the progression of the disease. Richardson et al. [43] have suggested thatbaricitinib may be a potentially promising drug for COVID-19 patients. Moreover,

a small non-randomized clinical pilot study has revealed a significant improvement in respiratory function, clinical features, and reduction in CRP value compared to baseline [44].

Ivermectin is a broad-spectrum antiparasitic agent and has antiviral activity against a wide range of viruses. *In vitro* trial has shown that ivermectin can inhibit the viral replication of SARS-COV-2 by 99% after 48 hr[45]. The researchers recommended that its early administration may decrease the viral load and inhibit disease progression. Interestingly, a recent systemic review has highlighted the safety and efficacy of using a high dose of ivermectin compared to standard low one in treating COVID-19 [46]. More importantly, experts hypothesized that a combination of hydroxychloroquine and ivermectin may have a synergistic effect for the treatment of COVID-19 depending on the pharmacological action of both drugs [68]. Consequently, ivermectin may be a promising agent against SARS-CoV-2 infection and require further clinical studies to approve its efficacy.

Interferon has shown mixed efficacy against SARS-CoV and MERS-CoV. Interferon-1, an anticancer and antiviral agent, is used in the treatment of hepatitis C, leukemia, and HIV. It inhibits SARS coronavirus in cell-based models so it may be examined against SARS-CoV-2 [47]. Its antiviral activity is considered through binding to interferon receptors type 1 and then phosphorylation of the Janus kinase 1 and tyrosine kinase 2 [48]. Further clinical trials are essential to ensure its efficacy and safety against SARS-CoV-2 infection. Additionally, interferon β1 (IFN-β1) may be a safe treatment against COVID-19 patients in the early stages of infection [49].

Other Miscellaneous therapeutic options

Depending on the immune system of the patient to treat COVID-19 disease, scientists have suggested the use of **immunoglobulin** purified from IgG antibodies [50]and **convalescent Plasma** of COVID-19 patients who are recently recovered from this infection [51]. The rationale for using this strategy is using antibodies from the recovered patients may help with immune cell clearance for the virus. A preliminary report has depicted that convalescent plasma from COVID-19 patients enhances the clinical symptoms and increases the survival rate [52]. Indeed, Shen and his colleagues have treated 5 critically COVID-19 patients with convalescent plasma from the recovered patients and have found after one day of infusion that the viral load and body temperature significantly reduced and three of them were discharged from hospital [53].

Thalidomide, an immunomodulatory and anti-inflammatory drug, is considered to be used for the treatment of interstitial pulmonary fibrosis and effective against HIV through inhibition of nuclear factor-κB, pro-inflammatory cytokines secretion, and regulate immunity [54]. Notably, Chen et al. [55] have assumed, *via* randomized controlled clinical study, that using thalidomide in combination with glucocorticoids may be effective in the treatment of COVID-19 patients. Thus, this drug is hypothesized to be an effective agent for the treatment of COVID-19 and two clinical studies are being carried out to test its efficacy against SARS-COV-2 patients (NCT04273529, NCT04273529).

Ascorbic acid (vitamin C) is a water-soluble vitamin used as an antioxidant. Recent reports have suggested that vitamin C inhibits cytokine production, decreases reactive oxygen species, and lung fibrosis. Furthermore, Vitamin C has antiviral activity at higher concentrations and the ability to decrease the load of some viruses [56]. Based on anti-inflammatory and antiviral characteristics of vitamin C,

various clinical studies are being done for treatment of SARS-CoV-2 infected pneumonia patients (NCT04323514, NCT03680274, NCT04326725, and NCT04264533,)

Azithromycin is a macrolide antibiotic and has both antibacterial and antiviral activities. It is mainly used in the treatment of skin infections, pneumonia, sinusitis, and has antiviral activity against Zika Virus [57]. As previously mentioned, experts have demonstrated that the combination of azithromycin and hydroxychloroquine has a great efficacy against COVID-19 pneumonia patients and decrease viral load [39]. Clinical trials are required for this drug to test its safety and efficacy in monotherapy and combination with other drugs (NCT04321278).

Coagulopathy is a significant abnormality in COVID-19 patients, with prominent elevation in D-dimers and fibrinogen [58]. Based on early reports from China, coagulation parameters were raised in COVID-19 hospitalized patients with 36% elevation in D-dimer [59]. It is evidenced that pulmonary embolism and micro thrombosis found in severe COVID-19 patients have been documented from lung dissection [60]. Additionally, the hypoxia existed in COVID-19 patients can stimulate venous thromboembolism (VTE) and pulmonary embolism through increasing blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathway as well [61] For these reasons, experts have announced that confirmed or suspected COVID-19 patients should be treated with **anticoagulants** such as **heparin** or **low molecular weight heparin (LMWH)** to prevent the incidence of VTE [62]. Besides, Thachil et al. [63] have suggested that all COVID-19 patients should take prophylactic doses of LMWH to prevent VTE complications. Therefore, the routine screening of severely ill COVID-19 patients should be taken into consideration. Furthermore, a retrospective clinical study has demonstrated the use of LMWH as a therapeutic agent for treatment of COVID-19 patients as it can inhibit cytokine storm [64]. However, the efficacy of anticoagulants is required to be confirmed and further clinical trials should be conducted.

It is urgently needed to find and explore a specific and effective vaccine against SARS-COV-2. **Bacillus Calmette–Guérin** (BCG) vaccine used to prevent tuberculosis might decrease the mortality rate and progression of COVID-19 disease [65]. A recent epidemiological study has stated that BCG vaccination offers wide spectrum efficiency against SARS-CoV-2 and might prevent respiratory infections [66]. Importantly, some novel vaccines have shown effectiveness against SARS-COV-2 in preclinical trials and now they are under clinical trials to ensure their immunogenicity and efficacy against SARS-COV-2. For instance, **mRNA-1273 vaccine** is a novel lipid nanoparticle encapsulated mRNA-based vaccine that encodes the stabilized spike (S) protein of SARS-CoV-2. A phase I clinical trial is conducted to evaluate the efficacy, safety, and immunogenicity of mRNA-1273, manufactured ModernaTX, against COVID-19 patients (NCT04283461). Furthermore, **Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)**, manufactured by the Beijing Institute of Biotechnology and CanSino Biologics Inc., is being estimated for its immunogenicity using single-center, open-label, phase I clinical trial (NCT04313127).

Methodology:

The review was performed using **PubMed** to identify relevant articles published and the available data on clinical trials using **ClinicalTrials.gov.**

Conclusion

To date, there are no specific therapies or vaccines shown efficiency against SARS-COV-2 infection. At present, the repurposing drugs including, antiviral drugs, anti-inflammatory and immune-modulatory agents, convalescent plasma, and vaccines are being used for treating COVID-19 patients and decrease the severity of this pandemic. A plethora of clinical trials have been conducted to investigate the validity of drugs used for COVID-19 patients and explore other new ones. Thus, there is a vigorous need to discover and explore an effective vaccine or antiviral regimen against SARS-COV-2. Hopefully, all these efforts will corporate to produce therapies/vaccines or treatment strategies that seem to be effective against COVID-19.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323(11):1061-1069.

2. Yin Y, Wunderink RG. (2018) MERS, SARS and other coronaviruses as causes of pneumonia. Respirology 23(2):130-137.

3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497-506.

4. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. (2020) The 2019-new coronavirus epidemic: Evidence for virus evolution. J Med Virol 92(4):455-459.

5. Xu J, Zhao S, Teng T, Abdalla AE, Zhu W, Xie L, Wang Y, Guo X. (2020) Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses 12(2):244.

6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395(10223):507-513.

7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054-1062.

8. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 7(1):11.

9. Yuki K, Fujiogi M, Koutsogiannaki S. (2020) COVID-19 pathophysiology: A review. Clin Immunol 215:108427.

10. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 181(2):271-280.

11. Chen Y, Liu Q, Guo D. (2020) Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 92(4):418-423.

12. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. (2020) Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis 34:101615.

13. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO. (2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11(1):222.

14. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, Neville S, Carra E, Lew W, Ross B, Wang Q, Wolfe L, Jordan R, Soloveva V, Knox J, Perry J, Perron M, Stray KM, Barauskas O, Feng JY, Xu Y, Lee G, Rheingold AL, Ray AS, Bannister R, Strickley R, Swaminathan S, Lee WA, Bavari S, Cihlar T, Lo MK, Warren TK, Mackman RL. (2017) Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. J Med Chem 60(5):1648-1661.

15. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30(3):269-271.

16. Kujawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, Abedi GR, Ahmed NS, Almendares O, Alvarez FN. (2020) First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. MedRxiv:doi: 10.1101/2020.1103.1109.20032896.

17. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Zhang J. (2020) Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv:https://doi.org/10.1101/2020.1103.1117.20037432.

18. Watanabe S, Chan M, Suzuki W. China says Japan-developed drug Avigan works against coronavirus. 2020. Available from: https://asia.nikkei.com/Business/Pharmaceuticals/China-says-Japan-developed-drug-Avigan-works-against-coronavirus2. [Accessed on: March 18th, 2020].

19. Soliman EZ, Lundgren JD, Roediger MP, Duprez DA, Temesgen Z, Bickel M, Shlay JC, Somboonwit C, Reiss P, Stein JH, Neaton JD. (2011) Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. Aids 25(3):367-377.

20. Dayer MR, Taleb-Gassabi S, Dayer MS. (2017) Lopinavir; a potent drug against coronavirus infection: insight from molecular docking study. Arch Clin Infect Dis 12(4):e13823.

21. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. (2020) A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol 92(6):556-563.

22. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. (2020) A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 382(19):1787-1799.

23. Khamitov RA, Loginova S, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. (2008) [Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]. Vopr Virusol 53(4):9-13.

24. Kadam RU, Wilson IA. (2017) Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci U S A 114(2):206-214.

25. Wang Z, Yang B, Li Q, Wen L, Zhang R. (2020) Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis:doi: 10.1093/cid/ciaa1272.

26. Xu K, Chen Y, Yuan J, Yi P, Ding C, wu W, Li Y, Ni Q, Zhou R, Li X, Xu M, Zhang Y, Zhao H, Zhang X, Yu L, Su J, Lang G, Liu J, Wu X, Li L. (2020) Clinical efficacy of arbidol in patients with 2019 novel coronavirus-infected pneumonia: A retrospective cohort study. Lancet:doi: 10.2139/ssrn.3542148.

27. Deeks ED. (2018) Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection. Drugs 78(10):1013-1024.

28. Lin S, Shen R, He J, Li X, Guo X. (2020) Molecular Modeling Evaluation of the Binding Effect of Ritonavir, Lopinavir and Darunavir to Severe Acute Respiratory Syndrome Coronavirus 2 Proteases. bioRxiv:https://doi.org/10.1101/2020.1101.1131.929695.

29. Elfiky AA. (2020) Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life Sci 253:117592.

30. June RR, Olsen NJ. (2016) Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis. Expert Opin Biol Ther 16(10):1303-1309.

31. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. (2020) Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 117(20):10970-10975.

32. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, Tomelleri A, Baldissera E, Rovere-Querini P, Ruggeri A, Monti G, De Cobelli F, Zangrillo A, Tresoldi M, Castagna A, Dagna L. (2020) Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med 76:43-49.

33. Bian H, Zheng Z-H, Wei D, Zhang Z, Kang W-Z, Hao C-Q, Dong K, Kang W, Xia J-L, Miao J-L, Xie R-H, Wang B, Sun X-X, Yang X-M, Lin P, Geng J-J, Wang K, Cui H-Y, Zhang K, Chen X-C, Tang H, Du H, Yao N, Liu S-S, Liu L-N, Zhang Z, Gao Z-W, Nan G, Wang Q-Y, Lian J-Q, Chen Z-N, Zhu P. (2020) Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. MedRxiv:https://doi.org/10.1101/2020.1103.1121.20040691.

34. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. (2019) The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 23(1):99.

35. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. (2020) Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 180(7):1-11.

36. Zhou D, Dai S-M, Tong Q. (2020) COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 75:1667–1670.

37. Dong L, Hu S, Gao J. (2020) Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 14(1):58-60.

38. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. (2020) Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents 55(4):105932.

39. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, Mailhe M, Doudier B, Aubry C, Amrane S, Seng P, Hocquart M, Eldin C, Finance J, Vieira VE, Tissot-Dupont HT, Honoré S, Stein A, Million M, Colson P, La Scola B, Veit V, Jacquier A, Deharo JC, Drancourt M, Fournier PE, Rolain JM, Brouqui P, Raoult D. (2020) Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis 34:101663.

40. Rismanbaf A, Zarei S. (2020) Liver and kidney injuries in COVID-19 and Their effects on drug therapy; a letter to editor. Arch Acad Emerg Med 8(1):e17.

41. Bechman K, Subesinghe S, Norton S, Atzeni F, Galli M, Cope AP, Winthrop KL, Galloway JB. (2019) A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatology (Oxford) 58(10):1755-1766.

42. Marotto D, Sarzi-Puttini P. (2020) What is the role of rheumatologists in the era of COVID-19? Autoimmun Rev 19(6):102539.

43. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Rawling M, Savory E, Stebbing J. (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 395(10223):e30-e31.

44. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. (2020) Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect:doi: 10.1016/j.jinf.2020.1004.1017.

45. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 178:104787.

46. Navarro M, Camprubí D, Requena-Méndez A, Buonfrate D, Giorli G, Kamgno J, Gardon J, Boussinesq M, Muñoz J, Krolewiecki A. (2020) Safety of high-dose ivermectin: a systematic review and meta-analysis. J Antimicrob Chemother 75(4):827-834.

47. Paragas J, Blatt LM, Hartmann C, Huggins JW, Endy TP. (2005) Interferon alfacon1 is an inhibitor of SARS-corona virus in cell-based models. Antiviral Res 66(2-3):99-102.

48. Zorzitto J, Galligan CL, Ueng JJ, Fish EN. (2006) Characterization of the antiviral effects of interferon-alpha against a SARS-like coronoavirus infection in vitro. Cell Res 16(2):220-229.

49. Sallard E, Lescure F, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. (2020) Type 1 interferons as a potential treatment against COVID-19. Antivir Res 178:104791.

50. Jawhara S. (2020) Could Intravenous Immunoglobulin Collected from Recovered Coronavirus Patients Protect against COVID-19 and Strengthen the Immune System of New Patients? Int J Mol Sci 21(7).

51. Hopkins JS. (2020) Drugmaker Takeda is working on coronavirus drug. Wall Street Journal:Available from: https://www.wsj.com/articles/drugmaker-takeda-is-working-on-coronavirus-drug-11583301660.

52. Cantore I, Valente P. (2020) Convalescent plasma from COVID 19 patients enhances intensive care unit survival rate. A preliminary report. Transfusion and Apheresis Science:102848.

53. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. (2020) Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA 323(16):1582-1589.

54. Kwon HY, Han YJ, Im JH, Baek JH, Lee JS. (2019) Two cases of immune reconstitution inflammatory syndrome in HIV patients treated with thalidomide. Int J STD AIDS 30(11):1131-1135.

55. Chen C, Qi F, Shi K, Li Y, Li J, Chen Y, Pan J, Zhou T, Lin X, Zhang J. (2020) Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 pneumonia. Preprints:2020020395.

56. Biancatelli RM, Berrill M, Marik PE. (2020) The antiviral properties of vitamin C. Expert Rev Anti Infect Ther 18(2):99-101.

57. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. (2014) Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther 143(2):225-245.

58. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18(5):1094-1099.

59. Cui S, Chen S, Li X, Liu S, Wang F. (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 18(6):1421-1424.

60. Luo W, Yu H, Gou J, Li X, Sun Y, Li J, Liu L. (2020) Clinical Pathology of Critical Patient with Novel Coronavirus Pneumonia (COVID-19). Preprints:2020020407.

61. Gupta N, Zhao YY, Evans CE. (2019) The stimulation of thrombosis by hypoxia. Thromb Res 181:77-83.

62. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 18(7):1743-1746.

63. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 18(5):1023-1026.

64. Shi C, Wang C, Wang H, Yang C, Cai FEI, Zeng F, Cheng F, Liu Y, Zhou T, Deng BIN, Vlodavsky I, Li J, Zhang YU. (2020) The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective clinical study. MedRxiv:20046144.

65. Phillips RO, Phanzu DM, Beissner M, Badziklou K, Luzolo EK, Sarfo FS, Halatoko WA, Amoako Y, Frimpong M, Kabiru AM, Piten E, Maman I, Bidjada B, Koba A, Awoussi KS, Kobara B, Nitschke J, Wiedemann FX, Kere AB, Adjei O, Löscher T, Fleischer B, Bretzel G, Herbinger KH. (2015) Effectiveness of routine BCG vaccination on buruli ulcer disease: a case-control study in the Democratic Republic of Congo, Ghana and Togo. PLoS Negl Trop Dis 9(1):e3457.

66. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. (2020) Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. MedRxiv:https://doi.org/10.1101/2020.1103.1124.20042937.