



A Review On Investigation Of Therapeutics Used In Covid-19

Aishwarya sakhare¹, Shubham kaulge², Avishkar deshmukh³

Abstract:-

The global healthcare systems could be severely overwhelmed by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which could result in a high rate of morbidity and fatality. The COVID-19 pandemic has caused thousands of deaths, disruptions to worldwide health care networks, and a global economic collapse. Patients with COVID-19 are receiving a variety of medications based on in vitro and theoretical therapeutic targets. A number of these treatments have been researched, but there is little evidence to support many of them, and clinical trials to determine their effectiveness are either continuing or have not yet started. As of right now, there are no proven effective medications or vaccinations to treat COVID-19 illness. Given the current epidemic, the typical drug development progression schedule is unacceptable. Consequently, using already-approved medications for the treatment of influenza, Ebola, and malaria speeds up the development of COVID-19 medicines. The most popular COVID-19 medications were examined in this study using information from the most recent in vitro clinical trial database, internet literature, and recommendations from the US National Institute of Health (NIH) about use of these medications for COVID-19. Remdesivir and convalescent blood products are the most promising options for treating COVID-19, according to the preliminary results of clinical trials and the recommendations of the NIH and food and drug administration FDA. The evidence supporting the use of drugs under research for the treatment of COVID-19, such as remdesivir, lopinavir/ritonavir, convalescent plasma, chloroquine/hydroxychloroquine, IL-6 inhibitors is compiled in this review.

Keyword:- COVID-19, Remdesivir, National Institute of Health (NIH), clinical trials, FDA.

Introduction

Coronaviruses (CoVs), having a place to the family Coronaviridae, are positive sense wrapped RNA infections and cause contaminations in fowls, warm blooded creatures, and human creatures. The family has four genera: alpha, beta, delta, and gamma. From these genera, beta and alpha CoVs contaminate human creatures. Indeed in spite of the fact that most CoVs disease causes a gentle side effect, the contamination of the two beta CoVs, specifically Serious Intense Respiratory Disorder coronavirus (SARS-CoV) and the Middle East Respiratory Disorder coronavirus (MERS-CoV), caused more prominent than 10,000 cases with mortality rates of 37% for MERS-CoV and 10% for SARS-CoV¹⁻³. Around 54.3 million confirmed cases, 1.3 million deaths, and 37.9 million recovered patients were reported by worldometer as a result of the novel coronavirus pandemic that originated in Wuhan, China, and spread to over 200 countries and territories worldwide. The clinical presentation of patients infected by the COVID-19 ranged from asymptomatic to critically ill cases requiring intensive care^{4,5}. Due to the unexpected global pandemic of atypical pneumonia brought on by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China, there is currently a serious public health issue. The etiological agent of COVID-19 disease,

an acute pulmonary syndrome that causes fever, dyspnea, pains in the muscles, headaches, and dry cough, is SARS-CoV-2. In its most severe form, SARS-CoV-2 induces acute Respiratory Distress Syndrome, a lung inflammation that results in fluid buildup and septic shock because of low blood pressure and oxygen starvation⁶⁻⁷. Notably, the complicated COVID-19 patients showed higher serum levels of aspartate aminotransferase, creatinine, creatine kinase, and C-reactive protein, along with a number of clinical manifestations including fever, cough, dyspnea, myalgia^{8,9}. Only very sick patients have been known to have cytokine storm, which is the cause of COVID-19 problems that ultimately result in death¹⁰. Furthermore, a 15% of COVID-19 patients will experience significant lung damage as a result of an acute respiratory infection, which is often identified after 7 to 14 days. The cytokine storm-related systemic inflammatory responses define the severity of the disease¹¹. The symptoms of COVID-19 can range from a mild infection or asymptomatic illness to severe or fatal pneumonia and death. Health authorities have attempted to re-stratify risks and concentrate on the repurposing of existing drugs to develop timely and cost-effective therapeutic strategies, targeting the hospitalized and critically ill. This is due to the lack of a definitive curative treatment insight and the high mortality rate in vulnerable populations. Currently, several countries are conducting randomised controlled trials (RCTs) to assess the safety and effectiveness of immuno-modulating therapies such as tocilizumab, sarilumab, lenzilumab, eculizumab, ravulizumab, convalescent plasma, and interferon, as well as antiviral/antimalarial agents like remdesivir, ritonavir/lopinavir combination, hydroxychloroquine, and chloroquine¹². This review is intended to provide the evidence behind potential therapeutics target.

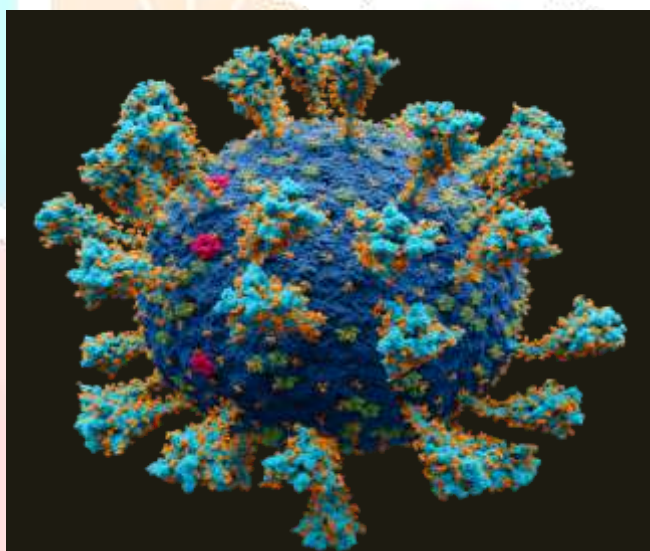


Fig.1 covid-19 corona virus disease

According to the International Clinical Trials Registry Platform of the World Health Organization, more than 590 clinical trials are presently exploring several possible COVID19 therapies¹³. These trials look into the following treatment modalities: (1) pharmaceutical interventions; (2) advanced therapy medicinal products, such as plasma, tissue extracts, cellular therapies, and vaccines; and (3) non-pharmacological interventions, such as enteral feedings, nutritional supplements, physical therapy, exercise, and psychotherapy¹⁴.

Owing to the dearth of COVID-19 treatment options and the pressing need to address the high rates of morbidity and mortality brought on by the pandemic, a number of studies were published without effective peer review. These studies included novel strategies like the transplantation of mesenchymal stem cells (MSCs), tissue plasminogen activator (tPA), convalescent plasma, and pharmaceutical intervention. In order to evaluate and analyze various COVID-19 therapeutic approaches for patients of all ages, as well as to compile data from published studies regarding the safety and effectiveness of these experimental treatments, we conducted this scoping review.

Over 50 medicines are being tested globally for their efficacy in treating COVID-19¹⁵. This study focuses on key therapies such as remdesivir, chloroquine/hydroxychloroquine, convalescent plasma, lopinavir/ritonavir, and IL-6 inhibitors.

CC(C)CCOC(=O)[C@H](C)NP(=O)(Oc1ccccc1)OP[C@H]2O[C@@H](c3ccc4nc5c(ncn5C#N)c4n3)[C@H](O)[C@@H](O)[C@H]2O

Remdesivir

Fig no.2 structure of remdesivir⁴⁴.

Adenosine analog Remdesivir, also known as GS-5734, has broad-spectrum antiviral efficacy against RNA viruses. This prodrug, GS-441524, interferes with the viral RNA-dependent RNA polymerase (RdRp) enzyme, delaying chain termination and stopping RNA synthesis and viral replication¹⁶. It must be metabolized by the host cell to reach its active form. Remdesivir has been demonstrated to prevent viral replication in MERS-CoV and SARS-CoV in vitro.

Evidences:-

In a human airway epithelial cell line treated with remdesivir, Sheahan et al. used quantitative reverse transcriptase polymerase chain reaction to quantify intracellular genomic and subgenomic viral RNA. Both MERS-CoV and SARS-CoV showed a dose-dependent decline, which is in line with titer reduction. Similar to this, prophylactic or early administration of remdesivir decreased viral load and decreased SARS-CoV-associated pulmonary pathology, including denuding bronchiolitis, perivascular inflammatory infiltrates, and intra-alveolar edema, and prevented pulmonary function degradation in mouse models of SARS-CoV infection. It's interesting to note that despite a significant decrease in SARS-CoV lung viral titre, therapeutic remdesivir treatment did not change disease severity or mortality in patients with the virus once lung epithelial cell damage and virus replication had peaked¹⁷. These results align with research conducted on non-human primates using the Rhesus macaque paradigm. Both the therapeutic and preventive therapy groups showed a decrease in lung viral load. During the trial, the respiratory rate of animals administered remdesivir prophylactically stayed normal. On the other hand, 83% of animals treated therapeutically saw an increase in heart rate. In the group that received preventive treatment, there was no pulmonary pathology. Although 83% of the rats receiving therapeutic remdesivir treatment had gross lung lesions, the overall lung area affected was noticeably less than that of the control group¹⁸. Remdesivir was started 24 hours before to inoculation, which inhibited viral replication in lung tissue and eventually prevented histologic lung lesions and clinical illness. Remdesivir lowered clinical severity of disease, reduced viral replication in lung tissue, and fewer and less severe lung lesions when administered 12 hours after MERS-CoV inoculation. It was demonstrated in another study looking at human airway epithelial cells to suppress MERS-CoV and SARS-CoV-1 viral replication¹⁹. 53 hospitalized COVID-19 severe patients from the USA (n = 22), Europe or Canada (n = 22), and Japan (n = 9) who were treated with remdesivir were included in a recent study. Of these patients, 68% showed clinical improvement, while

23% experienced adverse effects such as diarrhea (9%), skin rash (8%), acute kidney injury (8%), and other conditions²⁰⁻²¹.

Chloroquine/hydroxychloroquine

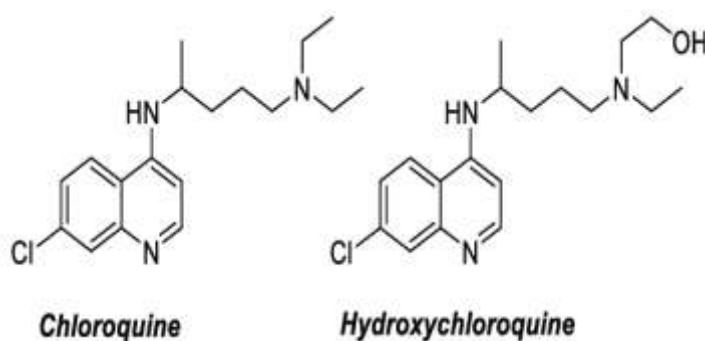


Fig no.3 structure of chloroquine and hydroxychloroquine⁴⁵.

The antiprotozoal drug chloroquine is prescribed to treat extraintestinal amebiasis, autoimmune disorders, and malaria. It disrupts the patients' nucleoprotein synthesis and affects hemoglobin digestion by raising intravascular pH in malarial parasite cells²². It is believed that chloroquine's antiviral action functions by raising the pH of the lysosomal membrane by alkalizing the phagolysosome of a virus. For many viruses to induce host cell fusion, the surrounding medium must be somewhat acidic. In turn, alkalizing the pH prevents viral replication by impeding fusion and uncoating²³.

Evidences :-

A clinical experiment with 100 Chinese patients infected with COVID-19 was carried out by Gao et al. In a scientific discussion, the authors' findings were discussed with a group of specialists from government and regulatory agencies, as well as clinical trial organizers. When compared to control groups, they observed that chloroquine had a noteworthy impact on both clinical outcome and viral clearance. It has been discovered that chloroquine can minimize the duration of pneumonia by preventing the illness from getting worse, enhancing lung imaging, and producing virus-negative results. The expert panel included chloroquine phosphate to the guidelines for the prevention, diagnosis, and treatment of COVID-19-caused pneumonia after finding that the medication has strong anti-COVID-19 activity²⁴. The authors of a case report that was released in June 2020 established the link between chloroquine and psychiatric side effects. There were two case reports of a 35-year-old female and a 46-year-old male who were given chloroquine. Anxiety symptoms included uncontrollable thoughts, frequent panic attacks, insomnia, and terror, while psychotic symptoms such visual hallucinations, aberrant conduct, and incoherent speech were noted. The symptoms subsided after the drug was stopped and proper antipsychotic and anti-anxiety medicine was administered. While the exact mechanism underlying the adverse psychiatric effects is still unknown, the authors postulated that the antagonistic activity of chloroquine on GABA, 5-HT_{3A}, and 5-HT_{3B} receptors as well as the agonistic action on NMDA receptors would be the catalyst for these psychiatric symptoms²⁵.

Convalescent plasma

"Convalescent" or "immune" plasma is plasma that has been extracted from a patient after their infection has cleared up and their antibodies have grown. Convalescent plasma transfusions used in passive antibody treatment have the potential to reduce clinical severity or avoid clinical infection in those who have recently been exposed to pathogens. Additionally, patients who are already exhibiting symptoms of varied degrees might be treated with antibody treatment. However, preventive administration or using passive antibody treatment soon after symptom onset yields the best results^{26,27}.



fig no.3 :- convalescent plasma in covid-19 treatment⁴⁶

Evidences :-

The immunological (or "convalescent") plasma's antibodies work through a number of different methods to mediate their therapeutic effects. A pathogen, such as a virus, can be bound by an antibody, which immediately neutralizes its infectivity. Additionally, the antibody may have a therapeutic impact through additional antibody-mediated pathways, such as complement activation, antibody-dependent cellular cytotoxicity, and/or phagocytosis. Prophylaxis and/or improved recovery may also be aided by non-neutralizing antibodies that attach to the pathogen but do not prevent it from replicating in in vitro settings²⁸⁻²⁹. Neutralizing antibody titers at or above a 1:640 dilution were obtained from convalescent plasma in a pilot trial including ten patients with severe COVID-19³⁰. The participants of convalescent plasma transfusion did not experience any significant side effects. Within one to three days following the transfusion, all ten patients showed improvement in their symptoms, including fever, cough, shortness of breath, and chest pain. They also showed improvement in their pulmonary lesions on radiological examination. Transfusion of convalescent plasma was temporarily linked with undetectable viral loads are able. Additionally, screening revealed that 39 out of 40 (97.5%) of the COVID-19 patients who had recovered had neutralizing antibody titers of 160 or above. Weaning off mechanical ventilation, a decrease in viral loads, better oxygenation, and clinical stabilization were among the clinical status improvements following transfusion with convalescent plasma (SARS-CoV-2 IgG titers >1000) that were documented in a case series of five critically ill patents in China³¹. Serious adverse events were not documented in any of the studies examined in the 2015 systematic review, despite the fact that their reporting was undoubtedly incomplete. 2015 saw 99 patients participate in a convalescent plasma trial for Ebola disease, to which we contributed. Minor adverse events were noted in 8% of patients, mostly an increase in temperature (5%) and/or itching or skin rash (4%)³². No significant adverse events were reported in this experiment. Remarkably, two case reports of a patient with MERS-CoV³⁴ and an Ebola patient³³ may have involved transfusion-related acute lung injury (TRALI) after convalescent plasma.

lopinavir/ritonavir

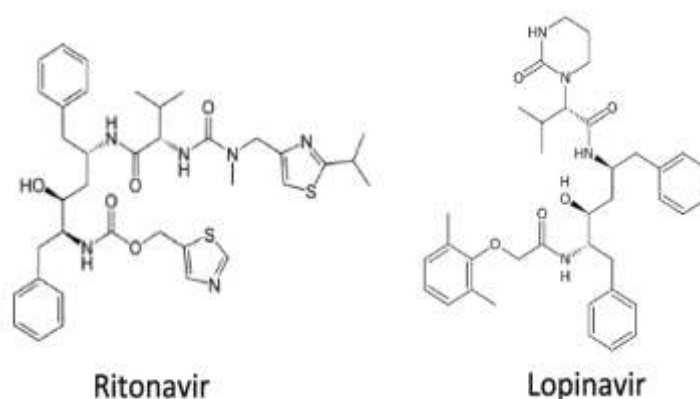


Fig no.4 :- structure of lopinavir and ritonavir⁴⁷.

In HIV infection treatment and prevention, lopinavir (LPV), an antiretroviral protease inhibitor, is used in conjunction with ritonavir (booster). As an inhibitor of HIV type 1 aspartate protease, peptidomimetic LPV binds to the enzyme's catalytic site to stop viral polyprotein precursors from being cleaved into mature, functional proteins that are required for viral replication. Typically, low booster doses of ritonavir are used with LPV to enhance its pharmacokinetics by inhibiting the cytochrome P450 3A4 enzyme, which slows down LPV's hepatic metabolism³⁵.

Evidences :-

The effectiveness of lopinavir/ritonavir versus conventional therapy in adult COVID-19 patients was examined in a study by Cao et al. The outcomes included a shorter ICU stay and a lower 28-day death rate, indicating clinical improvement comparable to standard treatment. Additionally, compared to the usual therapy arm, the lopinavir/ritonavir arm demonstrated a higher rate of clinical improvement. Nonetheless, over 50% of the patients experienced adverse events, with gastrointestinal side effects being more common in the lopinavir/ritonavir group³⁶. The mortality of patients on lopinavir/ritonavir was assessed by Pan et al. In addition, 1399 patients were treated with lopinavir/ritonavir, whereas 1372 patients served as controls and had normal treatment. The findings revealed that 148 patients in the group receiving lopinavir/ritonavir died, while 145 patients in the control group died (rate ratio 1.00; 95% CI 0.79–1.25; P = 0.97). Additionally, 126 patients in the group treated with lopinavir and ritonavir and 121 patients in the control group underwent ventilation. Accordingly, this study's findings indicate that lopinavir/ritonavir medication had no effect on COVID-19 patients' death or the start of ventilation³⁷. In a randomized controlled experiment, it was discovered that 14.3% of adult hospitalized patients with mild or moderate SARS-CoV-2 infection had diarrhea, elevated ALT levels, and lack of appetite, accounting for 23.8% of gastrointestinal side effects³⁸.

IL-6 inhibitors

COVID-19 Interleukins and other cytokines, which are pro-inflammatory chemicals, appear to be released in response to 19 illnesses. A subgroup of individuals experience the ensuing "cytokine storm," which is thought to cause a more serious sickness. More harm to the lungs may result from the immune reaction than from actual virus illness.

Evidences:-

Prior studies on these pro-inflammatory cytokines during the initial SARS CoV outbreak identified IL-6 as a molecule of interest that fuels the cytokine storm and inflammatory state³⁹. TCZ, SAR, or IL-6 inhibitors were examined in 255 individuals with severe COVID-19 in the study by Sinha et al. Patients were split into two groups: those in stage IIB (fiO₂ ≤ 45%) and those in stage III (fiO₂ > 45%). Patients in stage IIB

had greater rates of recovery and decreased rates of death⁴⁰. In the last several years, rheumatoid arthritis and cancer have been identified as two more disease processes that target IL-6 and have strong inflammatory responses. There is growing anecdotal evidence supporting its use in COVID-19 patients. Tocilizumab, an anti-IL-6 monoclonal antibody, was used to treat 20 patients with critical COVID-19 in a short retrospective study from China during the first outbreak⁴¹. On CT imaging, the authors observed a drop in the burden of lung disease, a reduction in fever, oxygen needs, and pro-inflammatory markers. Sarilumab, an additional IL-6 monoclonal antibody, was the subject of a randomized controlled trial that was announced for COVID-19 patients in the US and elsewhere⁴². Somers et al.'s study compared the effectiveness of TCZ in COVID-19 patients requiring mechanical ventilation. Results showed a significant reduction in mortality risk, with TCZ-treated patients having a higher number of hospital discharges and fewer mechanical ventilation patients. However, TCZ-treated patients also had a higher risk of superinfection, mainly ventilator-associated pneumonia, associated with *Staphylococcus aureus*⁴³.

Therapeutics	Mechanism	Adverse reaction	drug	Evidences
Remdesivir	Nucleoside analog inhibiting RdRp	Diarrhea, skin rash, kidney injury	rash	prevent viral replication in MERS-CoV and SARS-CoV in vitro
Chloroquine / hydroxychloroquine	Inhibits viral enzymes or processes, ACE2 receptors acidifies the cell membrane surfaces and involves the immunomodulation of cytokine release	Panic attack, insomnia, psychotic symptoms	attack, ,psychotic	Active against SARS-CoV-2 inhibits the exacerbation of pneumonia; shortened disease course and faster viral clearance
Convalescent plasma	Passive immunotherapy	transfusion-related acute lung injury (TRALI)		Improvement in pulmonary region; better oxygenation
Tocilizumab, sarilumab	IL-6 inhibitors	risk of superinfection, mainly ventilator-associated pneumonia		Reduction in mortality risk; decreased O ₂ demand

Table no.1 :- Therapeutic approaches applied to COVID-19 patients

Discussion:-

Many of these treatments are unpublished and have not undergone peer review, despite the fact that many of them appear promising. The authors agree with the World Health Organization that, whenever possible, COVID-19 treatments should be used in randomized, controlled studies that have been ethically authorized⁴⁸.

References

1. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM. SARS-CoV-2 and coronavirus disease 2019: what we know so far. *Pathogens*. 2020;9(3):231. doi:10.3390/pathogens9030231
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (covid-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924. doi:10.1016/J.Ijantimicag.2020.105924
3. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. COVID-19 spike-host cell receptor grp78 binding site prediction. *J Infect*. 2020;80(5):554–562. doi:10.1016/j.jinf.2020.02.026
- 4 Wang Z, Yang B, Li Q, et al. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):769–777
- 5 Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J*. 2020;133(9):1025–1031
6. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype of SARS-CoV-2-specific t-cells in covid-19 patients with acute respiratory distress syndrome. *Medrxiv*. 2020.
7. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. 2020;395(10235):1517–1520. doi:10.1016/S0140-6736(20)30920-X
8. Harapan H, Itoh N, Yufika A, Winardi W, Kean S, et al. Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health*. 2020;13(5):667–73.
9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19
10. Papadopoulos C, Patoulas D, Teperikidis E, et al
11. Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*. 2020;395(10223):497–506
12. Saha A, Sharma AR, Bhattacharya, et al. Probable Molecular mechanism of remdesivir for the treatment of COVID-19: need to know more. *Arch Med research*. 2020;S0188–4409(20):30699
13. WHO welcome to the WHO ICTRP; 2020. Available from: <https://www.who.int/clinical-trialsregistry-platform2020>.
14. Aronson JK, Ferner RE, DeVito N, et al. COVID-19 registered trials – and analysis – CEBM;2020.
15. Zimmer C. Hundreds of Scientists Scramble to Find a Coronavirus Treatment. *The New York Times*. <https://www.nytimes.com/2020/03/17/science/coronavirus-treatment.html>. Published March 17, 2020. Accessed March 24, 2020.
16. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exonuclease. *MBio*. 2018. <https://doi.org/10.1128/mbio.00221-18>.
17. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Trans Med*. 2017. <https://doi.org/10.1126/scitranslmed.aal3653>
18. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci USA*. 2020;117(12):6771–6.

19. Ko WC, Rolain JM, Lee NY, et al. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. *Int J Antimicrob Agents*. 2020;105933. <https://doi.org/10.1016/j.ijantimicag.2020.105933>
20. Administration, U.S.F.a.D. Fact sheet for health care providers: emergency use authorization (EUA) of remdesivir (GS-5734). 2020; Available from: <https://www.fda.gov/media/137566/download>.
21. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327–36.
22. Fox R. Anti-malarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. *Lupus*. 1996;5(1_suppl):4–10.
23. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55(3):105923
24. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14: 72-73.
25. Benjelloun R, Otheman Y, Kettani CE (2020) Psychiatric side effects of chloroquine in COVID-19 patients: two case reports. *Pan Afr Med J*. 35(Suppl 2):83. <https://doi.org/10.11604/pamj.suppl.2020.35.24064>
26. Casadevall A, Pirofski LA. Antibody mediated regulation of cellular immunity and the inflammatory response. *trends immunol*, 2003;24(9):474-478.
27. Casadevall A, Schraff MD. Serum therapy revisited: animal model of infections and development of passive immunotherapy. *antimicrobe agent chemotherp*. 1994;38(8):1695-1702.
28. van Erp EA, Luytjes W, Ferwerda G, van Kasteren PB. Fc-mediated antibody effector functions during respiratory syncytial virus infection and disease. *Front Immunol*. 2019;10:548.
29. Gunn BM, et al. A role for Fc function in therapeutic monoclonal antibody-mediated protection against Ebola virus. *Cell Host Microbe*. 2018;24(2):221–233.e5.
30. Shen C, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma [published online March 27, 2020]. *JAMA*. <https://doi.org/10.1001/jama.2020.4783>.
31. Duan K, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. <http://doi.org/10.1101/2020.03.16.20036145>. Posted on medRxiv March 23, 2020
32. Van Griensven J, Edwards T, de Lam-ballerie X, et al.: Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N Engl J Med* 2016;374:33–42
33. Mora-Rillo M, Arsuaga M, Ramirez-Olivencia G, et al.: Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. *Lancet Respir Med* 2015; 3:554–62
34. Chun S, Chung CR, Ha YE, et al.: Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. *Ann Lab Med* 2016; 36:393–5
35. . LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Available online: <https://pubmed.ncbi.nlm.nih.gov/31643176> (accessed on 21 May 2020)
36. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787–1799. doi:10.1056/NEJMoa2001282

37. an H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19 — interim WHO solidarity trial results. *N Engl J Med*. 2021;384(6):497–511.
38. Li Y, Xie Z, Lin W et al (2020) An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). MedRxiv. <https://doi.org/10.1101/2020.03.19.20038984>
39. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial 26881152, 2020, 3,OA articles 237 cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2008;83(7):3039-3048.
40. P. Sinha, A. Mostaghim, C.G. Bielick, et al., Early administration of Interleukin-6 inhibitors for patients with severe Covid-19 disease is associated with decreased intubation, reduced mortality, and increased discharge [published online ahead of print, 2020 Jul 25], *Int J Infect Dis*. (2020), <https://doi.org/10.1016/j.ijid.2020.07.023>. S1201-9712(20)30568-3
- 41.. Xu, X.Effective Treatment of Severe COVID 19 Patients with Tocilizumab. ChinaXiv 1–12. www.chinaxiv.org. Accessed March 23, 2020.
42. Sanofi and Regeneron begin global KevzaraR (sarilumab) clinical trial program in patients with severe COVID-19 - Mar 16, 2020. <http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-withsevere-COVID-19>. Accessed March 24, 2020
43. E.C. Somers, G.A. Eschenauer, J.P. Troost, et al., Tocilizumab for treatment of mechanically ventilated patients with COVID-19 [published online ahead of print, 2020 Jul 11], *Clin Infect Dis*. (2020), <https://doi.org/10.1093/cid/ciaa954>.
44. Recent Advances Made in the Synthesis of Small Drug Molecules for Clinical Applications: An Insight - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Structure-of-remdesivir_fig2_351031801 [accessed 24 Aug 2024]
45. Ultrasonic Synthesis and Preliminary Evaluation of Anticoronaviral Activity of 6,7-Dimethoxy-4-(4-(4-methoxyphenyl)piperazin-1-yl)-1-methylquinolin-1-ium Iodide - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Chemical-structures-of-chloroquine-and-hydroxychloroquine_fig1_361745065 [accessed 24 Aug 2024]
46. <https://www.medpagetoday.com/infectiousdisease/covid19/96430>.
47. Amorphous Solid Dispersion Formation via Solvent Granulation – A Case Study with Ritonavir and Lopinavir - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Molecular-structures-of-ritonavir-and-lopinavir_fig1_337194465 [accessed 24 Aug 2024].
48. Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (nCoV) Infection Is Suspected. World Health Organization. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected). Accessed March 21, 2020.