

**A LITERATURE REVIEW OF CLINICAL MANAGEMENT OF SARS CoV-2 AND  
FUTURE PROSPECTS****Anjali Singh\***

JJM Medical College, Davangere.

**\*Corresponding Author: Anjali Singh**  
JJM Medical College, Davangere.

Article Received on 29/10/2021

Article Revised on 19/11/2021

Article Accepted on 10/12/2021

**ABSTRACT**

This paper focuses on creating a brief literature review on drugs prescribed for clinical management of SARS CoV-2. The paper studies each medication for its origin, mechanism of action, advantages and side-effects. Several drugs have been recommended by WHO and ICMR since December 2019 for the treatment of Covid-19. The paper studies the introduction of the respective drug in Covid-19 treatment protocol by WHO and ICMR and justification for introduction of respective drug in Covid-19 treatment. Over the period of past one and half years the use of some of the drugs discontinued in the Covid-19 treatment, this review studies the trials conducted on each medication and the efficacy of the respective medication in treatment of COVID-19 based on the available data. The study also studies the drugs in combination and current Covid-19 treatment protocol.

**INTRODUCTION**

SARS-CoV-2 was initially recognized and designated as COVID-19 infection.<sup>[1]</sup> First confirmed by National Health Commission in pneumonia patients in the city of Wuhan, China in December 2019. Initially the patients reported normal respiratory infection which promptly transformed into an acute respiratory distress syndrome.<sup>[2]</sup> As of June, 2021 over 177 million cases have been reported worldwide, with over 3.8 million reported deaths.<sup>[3]</sup> The case count in India as of June, 2021 is over 29.8 million, with over 724 thousand reported deaths.<sup>[4]</sup>

Coronaviruses were first identified in the 1930s when there was evidence of an acute respiratory infection in domesticated newborn chickens caused by Infectious Bronchitis Virus (IBV).<sup>[5]</sup> Corona viruses are the member of the family Coronaviridae, which infect human and diverse species of animals.<sup>[6]</sup> Seven human coronaviruses (HCoV) have been identified, these include HCoV-NL63 and HCoV-229E alpha-CoV and HCoV-OC43 beta-CoV, HCoV-HKU1, extreme acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome-CoV (MERS-CoV), and latest being SARS-CoV-2.<sup>[7]</sup>

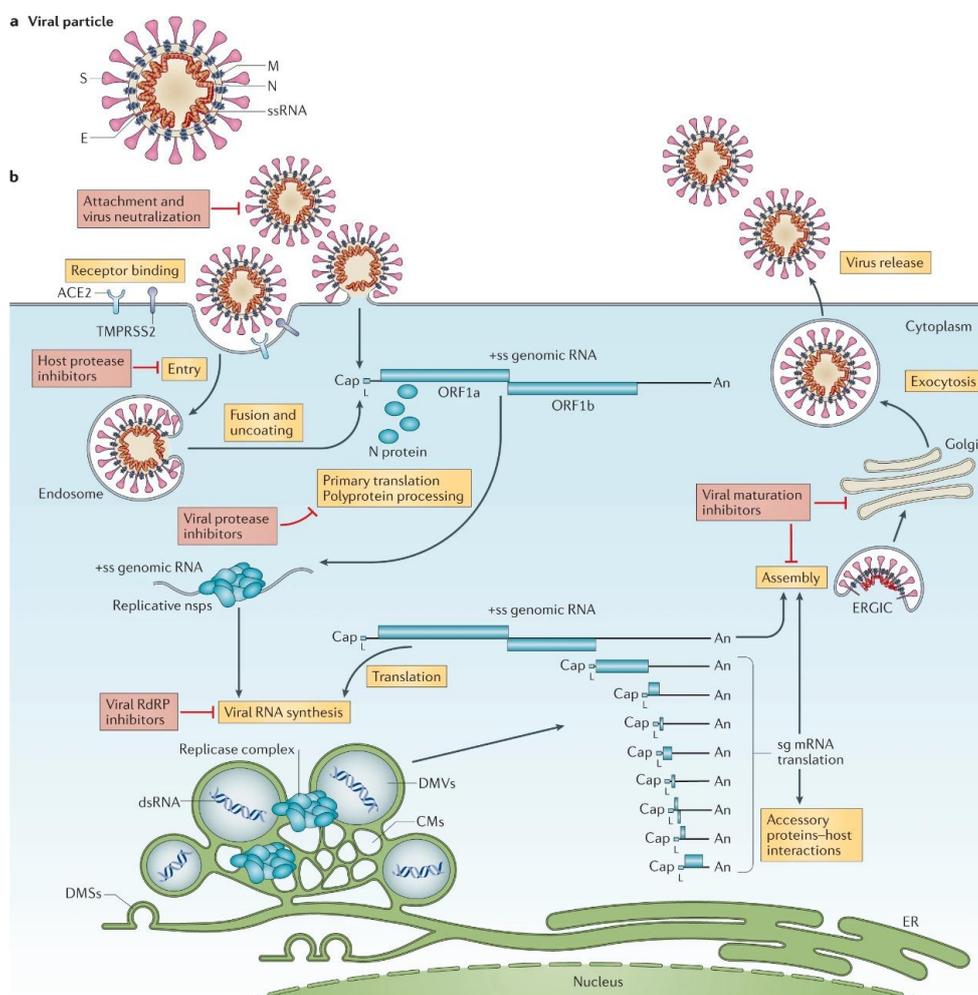
Three of the identified human coronaviruses have resulted in rapid spread diseases leading to global health crisis worldwide. the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emerged in 2002 in the province of Guangdong, China, which was subsequently associated with 8,096 cases and 774 deaths; the Middle East Respiratory Syndrome Coronavirus

(MERS-CoV) emerged in 2012 in Saudi Arabia with the global spread of 2,494 cases and 858 deaths and now the new emerging COVID-19 (SARS-CoV-2) in 2019 in Wuhan city, Hubei province, China.<sup>[8]</sup> SARS-CoV-2 is a family of enveloped, positive-sense, single-stranded, largest known RNA viruses in the Coronaviridae family. The genome size of SARS-CoV-2 ranged from 29.8 kb to more than 30 kb, and its genome structure followed the unique gene characteristics of known CoVs.<sup>[9]</sup> CoVs are further categorised into four genera as the largest recognised RNA viruses: alpha, beta, gamma, and delta CoV ( $\alpha$ -CoV,  $\beta$ -CoV,  $\pi$ -CoV), in the subfamily Coronavirinae. Both CoVs have a highly conserved genome structure with a single large 50 open reading frame (ORF) encoding a replicase of polyprotein followed by several additional ORFs encoding structural and accessory genes scattered throughout the genome's 30 end.<sup>[7]</sup>

A number of possible animal hosts responsible for the origination SARS-CoV2 have been suggested so far by various different sources. Some sources believe the likely host for the SARS-CoV-2 is bats, pangolins. The SARS-CoV2 spreads among humans through physical contact, coughing or sneezing from an infected person to others by respiratory droplets.<sup>[10]</sup> The inhaled virus (SARS-CoV-2) possibly binds in the nasal cavity to the epithelial cells and begins replication. Its pathogenesis begins with the binding of the cellular receptor, commonly referred to as the angiotensin-converting enzyme 2 (ACE2) receptor expressed by the host cells and the virus spike proteins followed by their fusion.<sup>[11]</sup>

A protease called TMPRSS2 is used by SARS-CoV-2 to complete their infection process, the virus enters the host cell and uncoats to transcribe its genome, continuous and discontinuous RNA synthesis regulated by viral replicase encoded in a huge 20kb gene promotes genome replication in cytoplasmic membrane.<sup>[12]</sup> Immune response to SARS-CoV-2 is consistent with that of any infectious pathogens. The immune system produces antibodies that bind to the virus by selecting B cells, a store of memory B cells are extracted to counter future

infections. Each B cell produces a single species of antibody with a unique antigen binding site. Defensive mechanism is also demonstrated by T cells patrolling the body to seek and destroy infected cells and prevent replication. Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10–15 days after the onset of COVID-19 symptoms. However it is still a matter of investigation that how long the antibodies will last and if they will protect the individual from further infections.



**Fig 1: Mechanism of replication of SARS-CoV-2.**<sup>[87]</sup>

Treatment of SARS-CoV-2 is symptom based and no specific medication for treatment of SARS-CoV-2 is currently available. Recent studies have suggested the use of some wide spectrum antiviral drugs as possible path of treatment. These include nucleoside analogues, neuraminidase inhibitors, RNA-dependent polymerase and protease inhibitors. Recent studies have demonstrated that the anti-viral treatment has helped in decreasing the symptoms and reducing the period of infection by stopping the cycle of viral replication at several stages. Antiviral medications such as Remdesivir, Favipiravir, Oseltamivir, Lopinavir and Heparin have been clinically studied for treatment of SARS-CoV-2.<sup>[13]</sup> A recent study conducted trials using 19 different antiviral drugs and demonstrated that not all antiviral

drugs have direct effect on COVID-19, for example velpatasvir, ledipasvir, litonavir, lopinavir and favilavir showed negligible antiviral effect, whereas medications like Remdesivir and Chloroquine showed strong antiviral effect.<sup>[14]</sup> Key challenge is to identify the drug that interferes with viral replication without harming the host cell. Treatment of severe COVID-19 cases remains difficult. Relative to routine symptomatic treatment, the use of antiviral medications have shown little benefits.<sup>[15]</sup>

#### REMDESIVIR

Remdesivir (GS-5734) is a prodrug developed by Gilead Sciences. It was developed in collaboration with U.S. Army Medical Research Institute of Infectious Diseases and U.S. Centers for Disease Control as a drug effective

against RNA viruses with global pandemic potential like SARS, MERS and Ebola virus.<sup>[16]</sup> Remdesivir is a phosphoramidate prodrug of the C-adenosine analog GS-441524 that is metabolized within cells into the alanine metabolite (GS-704277) and further processed into the monophosphate derivative and ultimately into the active nucleoside triphosphate (NTP) derivative, which is substrate-competitive with ATP for incorporation by the viral RNA-dependent RNA polymerase, resulting in inhibition of viral RNA synthesis.<sup>[17,18]</sup> The emergency use authorization to allow the use of remdesivir for covid treatment was provided by Food and Drug Administration on 01/05/2020 on the basis of results of preliminary phase 3 trials<sup>[19]</sup>, the use was extended to hospitalized adults on 28/08/2020 and was further extended to pediatric patients above the age of 12 and weighing at least 40kgs on 22/10/2020.<sup>[21]</sup>

Several studies have been conducted to study the effectiveness of remdesivir alone or in combination for Covid-19 treatment in past few months. These include WHO SOLIDARITY trials, a four-arm trial comparing remdesivir, Lopinavir/ritonavir, lopinavir/ritonavir with interferon beta-1a, and chloroquine or hydroxychloroquine (ISRCTN83971151), the openlabel, randomized interventional DisCoVeRy trial (NCT04315948), and the multicenter retrospective REMDECO-19 trial (NCT04365725).<sup>[17]</sup> However, as of now these studies have shown conflicting results. Using CQ or HCQ with remdesivir may reduce the antiviral activity of remdesivir. Another combination of remdesivir with bericitinib, a substrate of CYP3A4, showed severe side effects despite accelerating clinical status improvement.<sup>[20]</sup> The solidarity trials conducted by WHO did not find any statistically significant difference in the mortality of remdesivir and standard care group of patients studied. There also remains uncertainty on the subject of optimal dosing to pediatrics and pregnant patients. The FDA approval and introduction of remdesivir marks an important step in development of covid-19 treatment protocol, but the uncertainties and lack of proven survival benefits demands need for further study.<sup>[22]</sup>

#### **LOPINAVIR / RITONAVIR**

FDA approved Lopinavir and ritonavir (LPV/r or Kaletra) for treatment of human immunodeficiency virus (HIV-1) infection in 2008.<sup>[23]</sup> The combination of Lopinavir and ritonavir are protease inhibitors that act against HIV. The use of this combination is being studied as an antiretroviral medication for SARS CoV 2 with studies showing mixed results.

LPV/RTV has proven anti-SARS-CoV-2 activity in vitro by preventing the protease in Vero E6 cells.<sup>[24]</sup> In vitro studies have shown that lopinavir has antiviral activity in SARS-CoV and MERS-CoV<sup>[25]</sup>, so, the patients with SARS-CoV were treated with LPV/r. Study showed favorable results for patients that were treated with LPV/r in comparison to standard care patients. However

latest studies have revealed that LPV/r has no proven advantage over standard care patients in terms of mortality, hospitalization duration and initiation of ventilation.<sup>[26]</sup> More in-depth studies are thus needed to establish clinical benefits of this drug combination for treatment of SARS CoV-2.

#### **FAVIPIRAVIR**

Favipiravir is an oral broad spectrum RdRp inhibitor. It was discovered by Toyama Chemical Co. Ltd. through cleaning of chemical library for potential antiviral activity against influenza virus and was approved for medical use in the year 2014 in Japan for treatment of new or reemerging pandemic influenza virus. COVID-19 task force committee in India has ranked Favipiravir as one of the most promising antiviral medication for COVID-19 considering its mechanism of action, results of preclinical trials, available manufacturing base and availability of human safety data.<sup>[27]</sup>

Favipiravir (prodrug) is a purine base analog that is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation. RNA-dependent RNA polymerase (RdRp) of RNAviruses is effectively inhibited by this prodrug.<sup>[28]</sup> Favipiravir is incorporated into the nascent viral RNA by error prone viral RdRp, which leads to chain termination and viral mutagenesis.<sup>[29]</sup> Favipiravir causes cytopathic effect leading to reduction in the number of viral RNA and infectious particles by targeting RdRp complex of SARS-CoV-2. Metabolic activation of Favipiravir occurs through ribosylation and phosphorylation forming the activated metabolite favipiravir-RTP in the tissues. From February to May 2020, a study conducted in Japan studied the use of Favipiravir on 2185 patients, the study concluded that Favipiravir showed positive results on mild and moderate cases of COVID-19 and improved recovery by shortening hospitalization and ICU time.<sup>[86]</sup> In perspective of COVID-19 treatment, the recommended dosing of Favipiravir is 1800mg BID on day 1 followed by 800mg BID from day 2 to a maximum of fourteen days from first administration.<sup>[30]</sup> Better clinical recovery rate, rapid viral clearance and improvement in chest CT scans have been observed in recent studies conducted in Japan and Russia.<sup>[31]</sup>

#### **HYDROXYCHLOROQUINE**

Hydroxychloroquine is an antimalarial drug derivative of Chloroquine in the class of 4-aminoquinolones with anti-inflammatory, antiviral and anti-thrombolytic properties which has been repurposed to be used in the treatment of COVID-19. HCQ was given emergency approval by FOOD and Drug administration USA for treatment of COVID-19 and several studies are underway to establish its effectiveness. On 23<sup>rd</sup> March 2020 ICMR issued advisory to place all high risk covid-19 front line workers and their contacts under chemoprophylaxis with HCQ.<sup>[33]</sup> The ability of HCQ to interfere with the glycosylation of ACE2 and thus prevent the proper

binding of the S protein gives it its antiviral strength against COVID-19. Virus entry occurs through receptor-mediated endocytosis, which needs an acidic PH to complete the fusion and deliver the viral genome into the cell. HCQ is weak bases and thought to inhibit this process that the SARS COV-2 virus needs for replication.<sup>[32]</sup> Apart from direct antiviral properties, HCQ also seem to have immune-modulatory effects to reduce over-activation of the immune system causing cytokine storm from COVID-19.<sup>[32]</sup>

Initial reports showed promising results and suggested HCQ is effective in treating COVID-19 induced pneumonia<sup>[34]</sup> and HCQ in combination with second-generation macrolide antibiotic, Azithromycin resulted in lower mortality in COVID-19 patients.<sup>[35]</sup> However, subsequent trails have raised safety concerns with the use of HCQ in covid-19 treatment leading to adverse events and its antiviral effectiveness.<sup>[36]</sup> For example, the findings of RECOVERY trials, one of the largest study on optimum treatment of COVID-19 found no difference in mortality of standard care patients in comparison with the test group on HCQ and subsequently stopped their trial on HCQ.<sup>[37]</sup> Similarly the HCQ arm of SOLIDARITY trial was stopped by world health organization<sup>[38]</sup> citing the lack of efficacy. A recent study that examined the data collected from multiple trials using a mathematical model concluded that the use of HCQ without Azithromycin shown no benefit in reducing hospitalization time or mortality and thus suggested discontinuation of use of HCQ in COVID-19 treatment.<sup>[39]</sup>

### IVERMACTIN

Ivermectin is bio inspired macrocyclic lactone antiparasitic drug that is efficient applications against a number of viruses, parasites, bacteria and fungi.<sup>[40]</sup> Ivermectin has been approved by US Food and Drug Authority for use in treatment of head lice, lymphatic filariasis, onchocerciasis, strongyloidiasis, rosacea and scabies.<sup>[41]</sup> The drug has so far been used for the treatment of Filariasis and Onchocerciasis in Africa<sup>[42]</sup> and is seen as a mass drug for treatment of malaria in lower income group countries. The need for Ivermectin to be used in treatment of malaria comes due to increasing resistance development against chloroquine.<sup>[43]</sup>

Ivermectin is a promising drug against a variety of human and animal diseases, its antiviral action has made it a promising candidate for treatment of COVID-19. Recent study observed Ivermectin docked in the region of leucine 91 of the SARS-CoV-2 spike protein and histidine 378 of the host cell ACE-2 receptor blocking its entry into the host cell<sup>[44]</sup>, another mode of antiviral action is inhibition of importin a/b1 heterodimer, which is essential for nuclear trafficking viral protein, thus important for viral replication.<sup>[45]</sup> However, multiple trials have shown the effect of Ivermectin over COVID-19 to be inconclusive, with no proven benefits over

standard care patients. A WHO advisory issued on 31/03/2021 recommended Ivermectin to be used only in clinical trials and not as a standard treatment of COVID-19 until further information is available.<sup>[46]</sup>

### AZITHROMYCIN

Azithromycin is an economical, widely available and generally safe orally active synthetic macrolide antibiotic that has wide range antibacterial, antiviral and anti-inflammatory properties.<sup>[47]</sup> It has previously been used to treat viral infections like MERS-CoV.<sup>[48]</sup> The antiviral properties of Azithromycin have suggested its potential use as a repurposed drug for the treatment of COVID-19. In-vitro studies have suggested that Azithromycin may interfere with intracellular SARS-CoV-2 activity and replication by increasing the pH of Golgi network and recycling endosome.<sup>[49]</sup> Azithromycin can also prevent initiation of cytokine storm by reducing levels of proinflammatory cytokines such as IL-6.<sup>[50]</sup>

Initial clinical trials reported better viral clearance when using the combination of HCQ and Azithromycin then in patients using HCQ alone.<sup>[51]</sup> Several clinical trials have been conducted or are underway since then to study the benefits of Azithromycin in treatment of COVID-19 and several of these trials have found Azithromycin to be ineffective in treatment of COVID-19. For example in a randomized clinical trial conducted in UK 2582 patients were randomly assigned to Azithromycin on a 500 mg per day dose for 10 days or until discharge. The study reported no improvement in the mortality or hospitalization period when compared to standard care patients.<sup>[52]</sup> Concerns have also been raised towards patients developing antibacterial resistance when using Azithromycin for COVID-19 treatment. More in-depth study and trials are needed to ascertain benefits of Azithromycin in COVID-19 treatment and formulate appropriate dosing regimen for patients of different age group.

### DOXYCYCLINE

Doxycycline (DOX) is a broad-spectrum synthetic derivative of tetracycline, a bacteriostatic antibiotic drug.<sup>[53]</sup> Doxycycline has been a drug of choice in treatment of Mycoplasma Pneumonia, it also demonstrates immunomodulation and antiviral effects which make it a potential drug for treatment of COVID-19.<sup>[54]</sup> DOX inhibits protein synthesis by reversibly binding to 30 s subunit at A site blocking the binding of aminoacyl t-RNA to mRNA, thus inhibiting addition of new amino acids to growing peptide chain, stopping the translation process.<sup>[55]</sup> DOX has been studied in antiviral role to control the chikungunya virus infection (CHIKV) by inhibiting the protease cysteine in Vero cells and showed a significant decrease in the CHIKV blood titer in mice.<sup>[55]</sup>

Doxycycline is an inexpensive widely available drug with a well-studied safety profile. COVID-19 has severely affected patient's lungs leading to coagulation,

extracellular matrix destruction, leading to damage to the endothelial basal plate and increased vascular permeability.<sup>[56]</sup> DOX acts as an inhibitor of metalloproteinases in virus induced lungs infection, this helps attenuate viral-mediated acute respiratory distress syndrome.<sup>[57]</sup> DOX is also suggested to act as an ionophore, this suppresses viral replication by, increasing Zinc intracellular concentrations.<sup>[58]</sup> DOX has shown promising qualities to be a potent drug for treatment of COVID-19 and needs careful investigation to be used as a clinical medication.

### PLASMA THERAPY

The application of plasma therapy can be dated back to 20<sup>th</sup> century when plasma of animals stimulated with infectious agents was used to for immediate short-term antibody based immunization for the prevention and treatment of diseases.<sup>[59]</sup> The development of antibiotics lead to suppression of use of plasma therapy in bacterial infections but is still considered useful against viral infections when treatment is not available.<sup>[60]</sup> Plasma therapy was found to be effective and used in mass scale during the Spanish flu pandemic in 1918.<sup>[61]</sup> Plasma therapy uses donated blood from a recover patient who has developed humoral immunity against a particular disease-causing pathogen, apheresis generates plasma containing specific neutralizing antibodies and the plasma is then transfused to patient after matching ABO compatibility.<sup>[62]</sup>

Plasma therapy is being considered as an antiviral and anti-inflammatory agent against COVID-19. Multiple trials have been conducted so far to study the efficacy of plasma therapy, for example a study was conducted on 80 patients at Prince of Wales Hospital in Hong Kong that were not showing improvement to standard medical care, the patients were administered convalescent plasma and the outcome of the study positive improvement.<sup>[63]</sup> The study also observed that the patients who received plasma within 14 days of infection showed more improvement as compared to patients who received plasma after 14 days of infection.<sup>[63]</sup> PLACID trials conducted by ICMR across 39 private and public hospitals in India reported that convalescent plasma therapy showed no reduction in mortality and prevention of progressive severity of COVID-19.<sup>[64]</sup> Similar trials conducted China and Netherlands also reported no significant benefits of convalescent plasma therapy in treatment of COVID-19.<sup>[65,66]</sup>

### DEXAMETHASONE

Dexamethasone is a corticosteroid used for treatment of reduction of inflammation in various disorders like rheumatoid arthritis, systemic lupus erythematosus, asthma, and certain cancers by mimicking anti-inflammatory hormones produced by the body.<sup>[67]</sup> COVID-19 infection leads to severe lung infection, respiratory failure and cytokine storm. Dexamethasone acts as an immunosuppressant, thus helping prevent cytokine storm, however the use of Dexamethasone in

early stage of COVID-19 is not advised as the suppressed immunity will encourage viral replication.<sup>[68]</sup> ARDS Dexamethasone is being considered as a promising medication for management of severe COVID-19 cases. The drug dampers down immune system and helps treat inflammation in airway and lungs of allergic and asthmatic patients.<sup>[69]</sup> Based on the results of RECOVERY trials, WHO issued a guideline in September 2020 titled 'Corticosteroids for COVID-19'.<sup>[70]</sup> The guideline recommends use of corticosteroid for severe cases of COVID-19 and advises to avoid the use in non-severe patients. The RECOVERY trials tested low dose Dexamethasone at the rate of 6mg/day and concluded that the use of Dexamethasone reduced mortality by one third in patients on ventilator support and by one fifth in patients on oxygen support when compared to standard care patients.<sup>[71]</sup> However the use of Dexamethasone needs to be carefully monitored in order to prevent side effects like increased risk of other infections in the body due to compromised immunity when the person is on corticosteroid. Prolonged use of corticosteroid is not recommended and the use must be strictly limited to severe cases as the use in case of early infection can lead to late viral clearance and increased viral load.

### MOLNUPIRAVIR

Molnupiravir (MK448/EIDD-2801) is a prodrug of synthetic nucleoside derivative N4-hydroxy-cytidine, a broad spectrum antiviral drug designed for treatment of Alphavirus infections.<sup>[72]</sup> Before the COVID-19 pandemic Molnupiravir was under trial for treatment of seasonal flu, but later the focus was shifted to treatment of COVID-19 infection. Merck, known as MSD, developed Molnupiravir in collaboration with Ridgeback Biotherapeutics. Molnupiravir is currently undergoing phase 3 clinical trials for treatment of non-severe and asymptomatic cases of laboratory confirmed cases of COVID-19. In November 2020 Merck has also started trials on hospitalized patients. Molnupiravir inhibits the replication of viral DNA by introducing copying error during viral replication.<sup>[72]</sup> It is phosphorylated in tissue to the active 5'-triphosphate form, which is incorporated into the genome of new virions, resulting in the accumulation of inactivating mutations, known as viral error catastrophe.<sup>[73]</sup>

Initial trials of Molnupiravir have been promising and it can very well become an oral pill available for treatment of COVID-19. The results of phase 3 trials are awaited and more targeted clinical studies will be helpful if determining the efficacy of Molnupiravir.

### TOCILIZUMAB

Tocilizumab is a recombinant monoclonal antibody developed by Osaka University and Chugai, and was licensed in 2003 by Hoffmann-La Roche for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis.<sup>[74]</sup> It was granted an emergency use authorization by FDA in June 2021 for the treatment of

COVID-19.<sup>[75]</sup> Tocilizumab blocks assembling of the activated complex with the transmembrane protein by interfering with IL-6 soluble and membrane binding site of the receptor (IL-6R). Tocilizumab is also able to block IL-6 trans-signaling which is related to the pro-inflammatory effects of IL-6.<sup>[76]</sup>

Several observational studies have been conducted to study the efficacy of Tocilizumab on COVID-19 patients. For example a study conducted in China on 24 patients receiving Tocilizumab reported improvement in fever resolution and oxygen saturation within 24 hours of drug administration as compared to standard care patients.<sup>[77]</sup> Another open, single-arm, multicenter study conducted on 63 patients receiving Tocilizumab reported improvements in respiratory and laboratory parameters, the study also reported improved survival rate when Tocilizumab was administered within six days of admission.<sup>[78]</sup> On the other hand several studies found no significant improvement in patients administered with Tocilizumab when compared to standard care group. For example, study conducted on 21 patients in Italy found no improvement in mortality or ICU admission in Tocilizumab group as compared to standard care patients.<sup>[79]</sup>

Very limited data is available on clinical trials conducted on Tocilizumab and thus it is early to draw a conclusion on its effectiveness in clinical management of COVID-19. The trials that have been conducted so far have very small sample size and very limited parameters have been studied.<sup>[77,78,79]</sup> Given the scale of the pandemic, the availability of Tocilizumab and the cost of drug is a major challenge in itself for considering it as a potential drug for clinical management of COVID-19.

#### **CASIRIVIMAB WITH IMDEVIMAB**

Casirivimab with Imdevimab, is a monoclonal antibody cocktail under investigation and authorized for the treatment of COVID-19. The drug combination is recommended for patients above 12 years of age and with mild or moderate COVID-19 infection who are at high risk of developing severe infection.<sup>[80]</sup> The drug combination received emergency use authorization from FDA in November 2020 for treatment of COVID-19. The drug was given emergency use authorization by India's Central Drugs Standards Control Organization (CDSCO) in May 2021. Developed using recombinant DNA technology, Casirivimab and imdevimab are human immunoglobulin G-1 (IgG1) monoclonal antibodies with ability to attack and attach to different parts of spike proteins of SARS CoV-2, thus blocking the entry and attachment of virus in human cells.<sup>[81]</sup>

#### **LOW-MOLECULAR WEIGHT HEPARIN (LMWH)**

Venous Thromboembolism is a major risk associated with the patients infected with COVID-19 and hence WHO has recommended the use of antithrombotic prophylaxis with Low Molecular Weight Heparin.<sup>[82]</sup>

Multiple trials have so far been conducted on use of LMWH with conflicting results being published. A trial conducted on 2574 patients in Italy reported 40% reduction in fatality with the use of LMWH when compared to standard care patients, the study also reported prophylactic doses to be more effective when compared to therapeutic doses.<sup>[83]</sup> In another systematic review the results of eight different studies with a total of 2946 patients were studied and the meta-analysis did not find any significant reduction in mortality with the use of LMWH.<sup>[84]</sup> Another study conducted on mild cases of COVID-19 that do not require ventilation reported that mild cases do benefit from use of LMWH and it is useful in reducing severity of COVID-19 infection.<sup>[85]</sup> The conflicting results presented by above mentioned and many more published trials indicate uncertainty in the benefits of use of LMWH for clinical management of COVID-19, detailed trial with a bigger sample size is needed to ascertain the efficacy.

#### **DISCUSSION**

Several vaccines are under development and have been approved for prevention and protection against COVID-19. However, the availability and administration of vaccines remains a challenge especially in developing and Under-developed countries. Vaccines do not guarantee protection against infection and mortality and several cases of infection have been reported in vaccinated patients. Mutations and emergence of new strains of COVID-19 has also presented challenge to effectiveness of vaccines and concept of herd immunity. Given the high communicability and chances of infections after vaccination, vaccination alone cannot be considered a dependent solution to COVID-19 pandemic, therefore development of clinical treatment is a must.

As mentioned in this review, several drugs have been studied for treatment of COVID-19 based on in-vitro studies and clinical trials have been conducted over past one and a half year. Broad spectrum antiviral drugs like Remdesivir, Favipiravir, Lopinavir etc have been tested over last one year as a potential drug to check viral replication in Covid-19, initial results for Remdesivir were satisfactory but multiple trials have contradicted any significant improvement in hospitalization or mortality in patients administered Remdesivir. Hydroxychloroquine was seen as a potential drug for clinical management of COVID-19, however severe side effects and no significant benefits indicated in RECOVERY trials resulted in discontinuation of its use. Antibiotics like Doxycycline and Azithromycin were also clinically tested based on in-vitro studies but again conflicting results and no conclusive clinical benefits were observed. A number of clinical trials reported Doxycycline to have benefits in COVID-19 treatment, but limited data is available and focused trials are needed to draw a conclusion. Corticosteroids like Dexamethasone have shown benefits in controlling inflammation and lung clearance when used carefully for short interval. Recombinant monoclonal antibody like

Tocilizumab and Casirivimab are promising, but the cost, availability and very limited clinical data is a challenge in its use for clinical management of COVID-19.

## CONCLUSION

Search for effective clinical management of COVID-19 is still an ongoing process. Several independent studies have been conducted over past one and a half year on a variety of promising drugs. It is the conflicting results of these trials that have pointed to a need of more centralized approach to test and identify potential drugs for COVID-19 treatment. Independent clinical trials with a large enough sample size that cover patients of different age groups, pre-existing medical conditions, dosing regime, drug-drug interaction and other vital parameters must be identified and data collected to ascertain efficacy of drugs being studied. Given the scale of the pandemic, the availability and cost of drugs being proposed must also be considered a critical factor.

## REFERENCES

1. Y.A. Helmy, M. Fawzy, A. Elasad, A. Sobieh, S.P. Kenney, A.A. Shehata, The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control, *J. Clin. Med.*, 2020; 9(4).
2. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet*, 2020; 395(10223): 497–506.
3. World Health Organization. (n.d.). Who coronavirus (COVID-19) dashboard. World Health Organization. Retrieved October 18, 2021, from <https://covid19.who.int/>.
4. Delhi, I. N. Indian Council of Medical Research, New Delhi, 2021. ICMR. <https://www.icmr.gov.in/>
5. Estola, T., Coronaviruses, a new group of animal RNA viruses. *Avian Dis.*, 1970; 14(2): 330–336.
6. Channappanavar, R., Perlman, S., Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopathol*, 2017; 39(5): 529–539.
7. Yin, Y., Wunderink, R.G., MERS, SARS and other coronaviruses as the cause of pneumonia. *Respirology*, 2018; 23(2): 130–137.
8. Current updates on adaptive immune response by B cell and T cell stimulation and therapeutic strategies for novel coronavirus disease 2019 (COVID-19) treatment, Neeraj Pal a, Anil Kumar Mavi b, Sundip Kumar a, Umesh Kumar c,\*\*, Maya Datt Joshi d, Rohit Saluja e,\*
9. Livingston, E., Bucher, K., 2020. Coronavirus disease (COVID-19) in Italy, *Jama*, 2019; 323(14): 1335.
10. Rothan, H.A., Byrareddy, S.N., The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun*, 2020; 102433.
11. Wan, Y., et al., Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J. Virol.*, 2020; 94(7): 127-20.
12. Current updates on adaptive immune response by B cell and T cell stimulation and therapeutic strategies for novel coronavirus disease 2019 (COVID-19) treatment
13. Shah, B., Modi, P., Sagar, S.R., In silico studies on therapeutic agents for COVID-19: drug repurposing approach. *Life Sci.*, 2020; 252: 117652.
14. Xia, S., Liu, M., Wang, C., Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. *Cell Res.*, 2020; 30: 343–355.
15. Cao, B., et al., A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N. Engl. J. Med.*, 2020; 382: 1787–1799.
16. T. Warren, R. Jordan, M.K. Lo, et al., Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys, *Nature*, 2016; 531: 381e385.
17. R.T. Eastman, J.S. Roth, K.R. Brimacombe, et al., Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19, *ACS Cent. Sci.*, 2020; 6: 672e683.
18. R.N. Kirchoerfer, Halting coronavirus polymerase, *J. Biol. Chem.*, 2020; 295: 4780e4781.
19. Center for Drug Evaluation and Research. Emergency use authorization (EUA) for remdesivir. May 1, 2020.
20. FDA, FDA EUA Remdesivir Fact Sheet for Health Care Providers. <https://www.fda.gov/media/137566/download> , 2020.
21. Center for Drug Evaluation and Research. Combined cross-discipline team leader, division director, and ODE director summary review for NDA 214787. October 21, 2020.
22. FDA Approval of Remdesivir — A Step in the Right Direction List of authors. Daniel Rubin, Ph.D., Kirk Chan-Tack, M.D., John Farley, M.D., M.P.H., and Adam Sherwat, M.D. J.L. Morris, D.M. Kraus, New antiretroviral therapies for pediatric HIV infection, *J. Pediatr. Pharmacol. Ther.*, 2005; 10(4): 215–247.
23. T.T. Yao, J.D. Qian, W.Y. Zhu, Y. Wang, G.Q. Wang, A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option, *J. Med. Virol.*, 2020; 92(6): 556–563.
24. C.M. Chu, Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings, *Thorax*, 2004; 59(3): 252–256.

25. R. Zhang, E. Mylonakis, In inpatients with COVID-19, none of remdesivir, hydroxychloroquine, lopinavir, or interferon beta-1a differed from standard care for in-hospital mortality, *Ann. Intern. Med.*, 2021; 174(2): JC17.
26. Arshad U, Pertinez H, Box H, Tatham L, Rajoli RKR, Curley P, et al. Prioritization of anti-SARS-Cov-2 drug repurposing opportunities based on plasma and target site concentrations derived from their established human pharmacokinetics. *Clin Pharmacol Ther.*, 2020, doi:<http://dx.doi.org/10.1002/cpt.1909> 10.1002/cpt.1909. [Online ahead of print].
27. Role of favipiravir in the treatment of COVID-19 Shashank Joshia, Jalil Parkarb, Abdul Ansaric, Agam Vorad, Deepak Talware, Mangesh Tiwaskarf, Saiprasad Patilg, \*, Hanmant Barkateh.
28. Baranovich T, Wong SS, Armstrong J, Marjuki H, Webby RJ, Webster RG, et al. T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. *J Virol*, 2013; 87: 3741–51.
29. Favipiravir: A new and emerging antiviral option in COVID-19 Umang Agrawal, Reyma Raju, Zarir F. Udawadia. *Med J Armed Forces India*, Oct, 2020; 76(4): 370–376. Published online 2020 Sep 2. doi: 10.1016/j.mjafi.2020.08.004 PMID: PMC7467067
30. Doi Y, Kondo M, Matsuyama A, et al. Preliminary report of the favipiravir observational study in Japan (2020/5/15). 2020. [Accessed on 6 July 2020] [http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19\\_casereport\\_en\\_200529.pdf](http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf).
31. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*, 2020; 75(7): 1667–70.
32. <https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf>
33. Gao J, Tian Z, Breakthrough Yang X. Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*, 2020; 14(1): 72–3. infection and progression. *J Antimicrob Chemother*, 2020; 75(7): 1667–70.
34. <https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf>
35. Gao J, Tian Z, Breakthrough Yang X. Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*, 2020; 14(1): 72–3.
36. Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France.
37. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. *Heart Rhythm*, 2020; 17(9): 1472–9.
38. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. *medRxiv*, 2020. 2020.07.15.20151852.
39. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. *Heart Rhythm*, 2020; 17(9): 1472–9.
40. Efficacy of chloroquine and hydroxychloroquine in treating COVID-19 infection: A meta-review of systematic reviews and an updated meta-analysis Tawanda Chivese a, Omran A.H. Musa a
41. Q. Dou, H.N. Chen, K. Wang, K. Yuan, Y. Lei, K. Li, J. Lan, Y. Chen, Z. Huang, N. Xie, L. Zhang, R. Xiang, E.C. Nice, Y. Wei, C. Huang, Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt axis in breast cancer, *Cancer Res.*, 2020; 76(15): 4457–4469. doi:10.1158/0008-5472..
42. Merck\_&\_Co. Stromectrol. FDA approved package insert 2009. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/050742s026lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s026lbl.pdf) Accessed Dec 2020.
43. A. Crump, S. Omura, Ivermectin, 'wonder drug' from Japan: the human use perspective, *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.*, 2020; 87(2): 13–28, doi:10.2183/pjab.87.13.
44. C. Chaccour, N.R. Rabinovich, Advancing the repurposing of ivermectin for malaria, *Lancet*, 2020; 393(10180): 1480–1481. doi:10.1016/S0140-6736(18)32613-8.
45. Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. *Vivo*, 2020; 34: 30236. <https://doi.org/10.21873/invivo.12134>. PMID: 32871846; PMID: PMC7652439
46. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin a/b1 heterodimer. *Antivir Res.*, 2020; 177. <https://doi.org/10.1016/j.antiviral.2020.104760>
47. WHO advises that ivermectin only be used to treat COVID-19 within clinical trials [Internet]. [cited 2021 May 13]. Available from: <https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-beused-to-treat-covid-19-within-clinical-trials>
48. 1 Oliver ME, Hinks TSC. Azithromycin in viral infections. *Rev Med Virol*, 2021; 31: e2163.
49. 3 Arabi YM, Deeb AM, Al-Hameed F, et al. Macrolides in critically ill patients with Middle East respiratory syndrome. *Int J Infect Dis.*, 2019; 81: 184–90.

50. Poschet J, Perkett E, Timmins G, Deretic V. Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. *bioRxiv* 2020; published online March 31. <https://doi.org/10.1101/2020.03.29.008631> (preprint).
51. Min JY, Jang YJ. Macrolide therapy in respiratory viral infections. *Mediators Inflamm*, 2012; 2012: 649570.
52. Cardiac safety and potential efficacy: two reasons for considering minocycline in place of azithromycin in COVID-19 management G Diana, R Strollo, D Diana, M Strollo
53. Abaleke E, Abbas M, Abbasi S, et al. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*, 2021; 397: 605–12.
54. Pharmacological basis for the potential role of Azithromycin and Doxycycline in management of COVID-19 Ahmed S. Ali a,b, \*, Mai A. ASattar a.
55. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance I Chopra, M Roberts
56. Rothan, H.A., Mohamed, Z., Paydar, M., Rahman, N.A., Yusof, R., 2014. Inhibitory effect of Doxycycline against dengue virus replication in vitro. *Arch. Virol*.
57. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury LE Gralinski, A Bankhead III, S Jeng,
58. Kong, M.Y., Whitley, R.J., Peng, N., Oster, R., Schoeb, T.R., Sullender, W., Ambalavanan, N., Clancy, J.P., Gaggar, A.,
59. Griffin, M.O., Fricovsky, E., Ceballos, G., Villarreal, F., Tetracyclines: a pleiotropic family of compounds with promising therapeutic properties. Review of the literature. *Am. J. Physiol.- Cell Physiol*, 299: C539–C548.
60. Graham B.S., Ambrosino D.M. History of Passive Antibody Administration for Prevention and Treatment of Infectious Diseases. *Curr Opin HIV AIDS*, 2015; 10(3): 129–134. doi:10.1097/COH.0000000000000154
61. Wong H-K, Lee C-K. Pivotal role of convalescent plasma in managing emerging infectious diseases. *Vox Sang.*, 2020; 115(7): 545–7. <https://doi.org/10.1111/vox.12927>.
62. Redden WR. Treatment of Influenza-Pneumonia by Use of Convalescent Human Serum. *Boston Med Surg J.*, 1919; 181(24): 688–91. <https://doi.org/10.1056/NEJM191912111812406>.
63. Burnouf T, Seghatchian J. Ebola virus convalescent blood products: where we are now and where we may need to go. *Transfus Apher Sci Off J World Apher Assoc Off J Eur Soc Hae mapheresis*, 2014; 51(2): 120–5. <https://doi.org/10.1016/j.transci.2014.10.003>.
64. Cheng Y, Wong R, Soo YOY, Wong WS, Lee CK, Ng MHL, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis.*, 2005; 24(1): 44–6. <https://doi.org/10.1007/s10096-004-1271-9>.
65. Agarwal A, Mukherjee A, Kumar G et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ.*, Oct 22, 2020; 371: m3939. doi: 10.1136/bmj.m3939.
66. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA*, 2020; 324: 460-70. doi:10.1001/jama.2020.10044.
67. Gharbharan A, Jordans CCE, Geurtsvan Kessel C, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. *medRxiv*, 2020; 2020.07.01.20139857.
68. Health, N.I.O., 2017. LiverTox: clinical and research information on drug-induced liver injury. *Nih. gov.* <https://livertox.nih.gov>.
69. Isidori, A., Arnaldi, G., Boscaro, M., Falorni, A., Giordano, C., Giordano, R., Pivonello, R., Pofi, R., Hasenmajer, V., Venneri, M., COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency. *J. Endocrinol. Invest.*, 2020a; 1.
70. Jiang, K., Weaver, J.D., Li, Y., Chen, X., Liang, J., Stabler, C.L., Local release of dexamethasone from macroporous scaffolds accelerates islet transplant engraftment by promotion of anti-inflammatory M2 macrophages. *Biomaterials*, 2017; 114: 71–81.
71. 6. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. *JAMA*, 2020; 324: 1330e41
72. Rees, V., 2020. Dexamethasone could reduce COVID-19 patient death risk by one-third, study shows. *Eur. Pharm. Rev.*
73. T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S. R. Leist, A. Schafer, K.H. Dinnon 3rd, L.J. Stevens, J.D. Chappell, X. Lu, T. M. Hughes, A.S. George, C.S. Hill, S.A. Montgomery, A.J. Brown, G.R. Bluemling, M.G. Natchus, M. Saindane, A.A. Kolykhalov, G. Painter, J. Harcourt, A. Tamin, N.J. Thornburg, R. Swanstrom, M.R. Denison, R.S. Baric, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, *Sci. Transl. Med*, 2020; 12(541).
74. Hampton T: New Flu Antiviral Candidate May Thwart Drug Resistance. *JAMA*, Jan 7, 2020; 323(1): 17. doi: 10.1001/jama.2019.20225. (PubMed ID 31910262)
75. Markus Harwart (2008). "Die Entwicklung von Tocilizumab" [The development of tocilizumab] (in

- German). *Krankenpflege-Journal*. Retrieved 2016-04-30.
76. "Coronavirus (COVID-19) Update: FDA Authorizes Drug for Treatment of COVID-19". U.S. Food and Drug Administration (FDA) (Press release). 24 June 2021. Retrieved 24 June 2021.
  77. Tocilizumab (actemra) M. Sheppard, ... +3 ... , B. Dasgupta *Hum Vaccines Immunother.*, 2017; 13: 1972-1988, 10.1080/21645515.2017.1316909
  78. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A.*, 2020; 117(20): 10970-10975.
  79. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*, 2020; 38(3): 529-532.
  80. Colaneri M, Bogliolo L, Valsecchi P, et al; The Covid Irccs San Matteo Pavia Task Force. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms*, 2020; 8(5): 695.
  81. Office of the Commissioner. (2020, November 22). Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19>.
  82. Anti-SARS-CoV-2 Monoclonal Antibodies. (2021). COVID-19 Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/the-rapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies>.
  83. World Health Organization (2020) Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. World Health Organization. <https://apps.who.int/iris/handle/10665/330893>
  84. Di Castelnuovo AF, Costanzo S, Iacoviello L. Heparin in COVID-19 patients is associated with reduced in-hospital mortality: the multicentre Italian CORIST Study. *Thromb Haemost*, 2021. <https://doi.org/10.1055/a-1347-6070>
  85. Abdel-Maboud M, Menshawy A, Elgebaly A et al. Should we consider heparin prophylaxis in COVID-19 patients? A systematic review and meta-analysis. *J Thromb Thrombolysis*, 2020. <https://doi.org/10.1007/s11239-020-02253-x>
  86. Grandone, E., Tiscia, G., Pesavento, R. et al. Use of low-molecular weight heparin, transfusion and mortality in COVID-19 patients not requiring ventilation. *J Thromb Thrombolysis* (2021). <https://doi.org/10.1007/s11239-021-02429-z>
  87. James Ives M. Preliminary report of favipiravir observational study in Japan released, 2020.
  88. Fig. 1: The coronavirus virion and life cycle. | *Nature Reviews Microbiology*, (2020, October 28). [https://www.nature.com/articles/s41579-020-00468-6/figures/1?error=cookies\\_not\\_supported&code=254c518f-227c-41be-bcbb-c9d1d59cd841](https://www.nature.com/articles/s41579-020-00468-6/figures/1?error=cookies_not_supported&code=254c518f-227c-41be-bcbb-c9d1d59cd841).