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POTENTIAL DRUGS FOR COVID -19 TREATMENT MANAGEMENT WITH THEIR CONTRAINDICATIONS AND DRUG- DRUG INTERACTION

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Abstract:

Novel Coronavirus (2019-nCOV) causes inflammatory response with worsening symptoms. Classification of potential anti-viral and anti-inflammatory drugs in managing the symptoms of the COVID-19 and reducing morbidity is important. The objective of this study is to identify a group of drugs, best suited for COVID-19 treatment based on recent developments in clinical trials, FDA drug evaluation, directions and developments and from drug therapies globally. Online literature search was done on Medline, PubMed and google scholar databases for studies on various treatments and drug therapies for COVID-19 and relevant studies were identified and the identified drugs are described in detail as per their Pharmacological, pharmaceutical properties of the drugs, mechanism of action, current COVID-19 drug therapy, contraindications and drug-drug interactions Certain drugs can inhibit action against viral infection and protect lungs from severe inflammatory response. This article summarizes several drugs like Hydroxychloroquine, Chloroquine, Remdesivir, Favipiravir, Lopinavir, Ritonavir, Dexamethasone, Ivermectin, Baricitinib, Casirivimab / imdevimab, Bamlanivimab along with auxiliary treatment like convalescent plasma transfusion. Remdesivir is first drug approved by FDA. Hydroxychloroquine, dexamethasone and remdesivir are showing results against COVID-19 but it is important to test the efficacy and safety of such drugs though some drugs have shown remarkable results.

Keywords: COVID-19, SARS-CoV-2, Chloroquine, Hydroxychloroquine, Remdesivir, Favipiravir, Dexamethasone, Remdesivir

1. Introduction

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The novel coronavirus (2019-nCov) is also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a new strain that initially emerged from China with unknown etiology as per World Health Organisation reports. Currently, no drugs are approved by the U.S Food and Drug Administration (FDA) to treat coronavirus disease [1]. As per recent developments, some unapproved drugs like chloroquine phosphate and hydroxychloroquine sulfate re authorized through emergency use authorization (EUA) for the treatment of certain hospitalized patients [2]. It is important to classify drugs with potential efficacy for the efficient treatment of coronavirus patients. As per the U.S National Library of Medicine (NLM), National Institutes of Health (NIH) and the U.S Department of Health and Human Services (HHS), numerous studies and clinical trials are being conducted worldwide to test the efficacy of such drugs against the rapidly evolving and emerging situation of COVID-19 pandemic. Currently, there are several drugs undergoing trials as per the database maintained by NIH. The clinical outcomes of the drugs vary case to case basis [3-5]. Some of the drugs being considered against COVID-19 with antimicrobial properties are - chloroquine, hydroxychloroquine, remdesivir, lopinavir, ritonavir, favipiravir and auxiliary treatment with convalescent plasma transfusion. Pharmaceutical properties, mechanisms of action and current role in COVID-19 positive patients are discussed in this article [6-7].

2. Potential Drugs For Covid-19 Treatment

2.1 Chloroquine Phosphate

Pharmaceutical Properties

Chloroquine Phosphate is also known as chloroquine, which is approved by the U.S FDA to treat malaria and extraintestinal parasites. Chemically, it is 7-chloro-4-[[4-(diethylamino)-1-methylbutyl]amino] quinoline phosphate ($C_{18}H_{32}ClN_3O_8P_2$) with molecular weight 515.87 g/mol (Fig 1). It is a white, odourless crystalline substance consumed orally and available as 150 mg and 300 mg base dosage [8-10]. Excretion of chloroquine is slow as a small proportion of the administered dose is found in stools while the majority is absorbed in gastrointestinal tracts [11].

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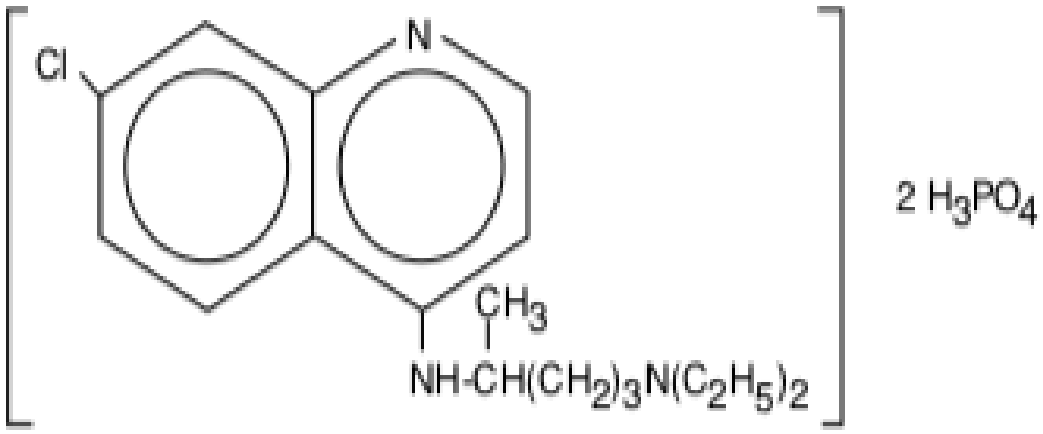

Figure 1: 2D Structure of Chloroquine Phosphate

Mechanism of Action

Chloroquine can inhibit certain enzymes and lead to the accumulation of toxic heme within the parasite. It also affects the biosynthesis of nucleic acids by inhibiting DNA and RNA polymerase. It can also affect parasite enzyme heme polymerase. . It can also cause inhibition of the fusion of the virus, which can cause acidification of the surface of the cell [12-13].

Chloroquine can inhibit certain enzymes including the parasite enzyme heme polymerase led to the accumulation of toxic heme within the parasite. It also affects the biosynthesis of nucleic acids by inhibiting DNA and RNA polymerase. It can also inhibit fusion of the virus, which cause acidification of the surface of the cell [12-13].

Drug Therapy for COVID-19 and Contraindications

Regarding treatment for coronavirus disease, chloroquine phosphate remains an unapproved emergency use drug for certain hospitalized patients suffering from COVID-19. It is an experimental drug with limited information known for safety and efficacy. Currently, the FDA has issued emergency use authorization (EUA) for Chloroquine phosphate for hospitalized COVID-19 positive cases weighing 50kgs or more [14-15]. As per studies shown, chloroquine phosphate has shown remarkable benefits for patients with pneumonia due to SARS-CoV-2 infection. It is contraindicated for patients with kidney or liver disease, diabetes, G6PD deficiency, porphyria, allergies to chloroquine phosphate, chloroquine hydrochloride, hydroxychloroquine sulfate, and pregnancy or breastfeeding [16-17].

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Drug-Drug Interactions, Side Effects & Risks

There are several drugs interact with chloroquine phosphate. People need to be concerned if they are concomitantly taking non-steroidal anti-inflammatory drugs (NSAID), antacids, azithromycin, insulin, amiodarone, moxifloxacin, drugs for epilepsy or seizure, vitamins, methotrexate, digoxin, tamoxifen, vitamins, or herbal products with chloroquine. [18]. The side effects of chloroquine phosphate are fainting due to low blood sugar, irregular heartbeats, blurred vision, difficulty hearing, muscle weakness, convulsions, yellowing of eyes, difficulty breathing, ringing in the ears etc. Chloroquine phosphate can cause QT prolongation for patients with serious comorbidities. It can also cause arrhythmias and retinal damage [19-20].

2.2. Hydroxychloroquine Sulfate

Pharmaceutical Properties

Hydroxychloroquine Sulfate is also known as hydroxychloroquine. It is a white crystalline powder soluble in water. Its chemical name is 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethyl amino]ethanol sulfate (Fig 2) and the molecular formula C18H26ClN3O.H2SO4. The molecular weight of Hydroxychloroquine Sulfate is 433.95 g/mol. It is approved to treat diseases like malaria, rheumatoid arthritis and lupus erythematosus by the FDA [21-23].

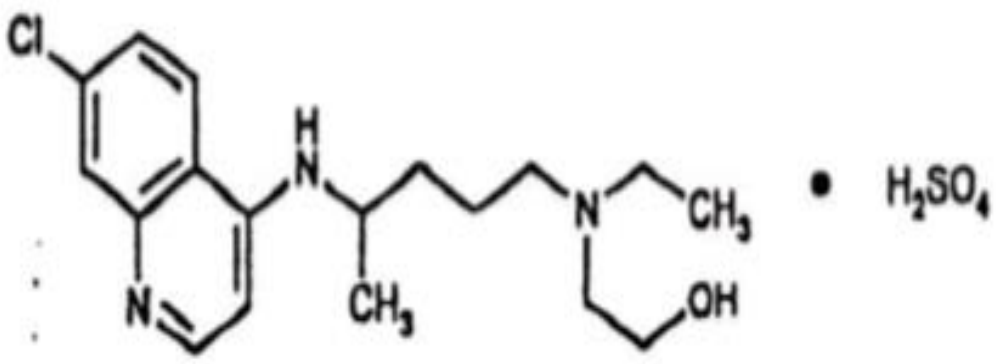

Figure 2: 2D Structure of Hydroxychloroquine Sulfate

Mechanism of Action

Hydroxychloroquine Sulfate can inhibit certain enzymes through its interaction with DNA. It can inhibit processes like virus release, virus particle transport, viral protein glycosylation and DNA & RNA polymerase. It can cause inhibition of the fusion of the virus through acidification of the surface of cell membranes. It also inhibits polymerization of heme [24-26].

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Drug Therapy for COVID-19 and Contraindications

FDA issued EUA for Hydroxychloroquine Sulfate in 2020 for treating patients suffering from COVID-19 and weighing 50 kgs or more. Based on certain parameters, FDA states that there is an optimal dosage for patients who tested positive for COVID-19. But, it recommends 800 mg of hydroxychloroquine sulfate base on the first day for COVID-19 positive patients and then 400 mg base dosage for the next 4-7 days, respectively [27-28]. The suggested dose can vary as per the results of ongoing clinical trials. It is also recommended that patients should be observed and monitored for QT interval prolongation along with renal and hepatic functions. Hydroxychloroquine sulfate is contraindicated for cardiac disease patients, specifically with bradycardia, ventricular arrhythmias, potassium or magnesium imbalances, etc. As per studies, it can have activity against SARS-CoV-2 and is more potent than chloroquine phosphate [29].

Drug-Drug Interactions, Side Effects & Risks

QT interval prolongation remains as a viable risk factor for patients undertaking drugs like azithromycin and other antibacterial drugs. Electrocardiograms of such patients should be monitored. Retinopathy or retinal damage due to abnormal blood flow is also noted among patients receiving long term hydroxychloroquine sulfate. Hydroxychloroquine can also increase the risk of arrhythmia and cause myocarditis, pericarditis and cardiomyopathy. It can also cause severe hypoglycemia with decreased insulin clearance. Loss of consciousness is also reported among patients taking anti-diabetic medication [30]. Drugs like cimetidine which can inhibit the metabolism of hydroxychloroquine sulfate thereby it increase the level of hydroxychloroquine in the blood plasma. Hence, both drugs should not be consumed together. Similarly, serum digoxin levels can increase with hydroxychloroquine and its level should be monitored closely during combined dose intake. Antacids can also reduce the absorption of hydroxychloroquine. It is recommended by the FDA that a gap interval of at least 4 hours should be observed between both the drugs [31-32].

2.3. Remdesivir

Pharmaceutical Properties

Remdesivir is approved by the FDA for emergency use, and clinical studies are yet to be conclusive. It has demonstrated activity against viral pathogens in animal models *in-vitro* and *in-vivo*, which causes middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

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The chemical formula of Remdesivir is $C_{27}H_{35}N_6O_8P$(Fig 3) and themolecular weight is 602.6 g/mol [33-34].

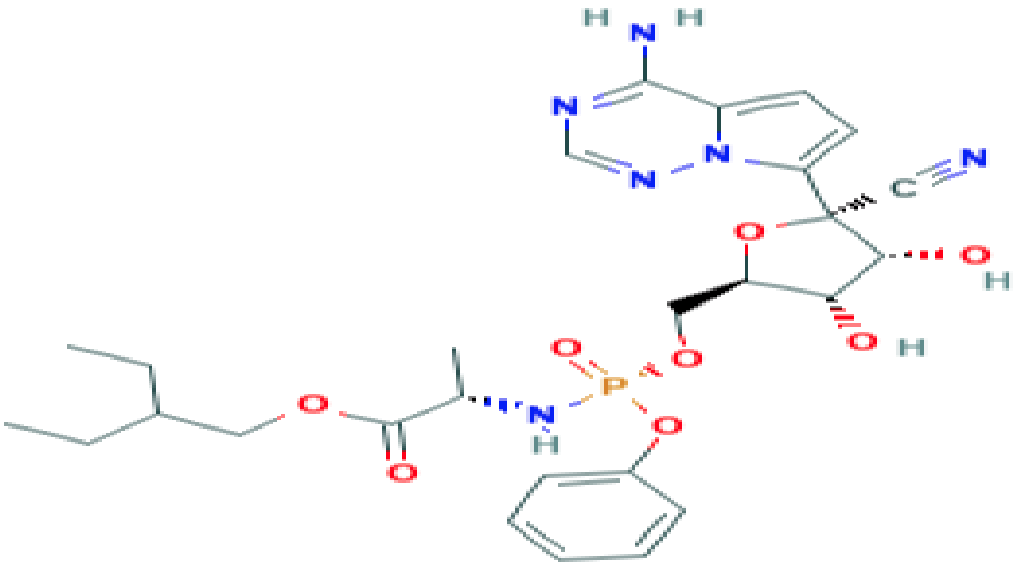

Figure 3: 2D Structure of Remdesivir

Mechanism of Action

Remdesivir is an inhibitor of RNA dependent RNA polymerase (RdRp). It competes with adenosine triphosphate and assimilates into viral RNA chains. Remdesivir triphosphate (RDV-TP) does not cause immediate chain termination. Remdesivir is a prodrug of remdesivir triphosphate (RDV-TP) [35].

Drug Therapy for COVID-19 and Contraindications

FDA has conducted a rapid review of Gilead's investigational new drug (IND) - Remdesivir. It has initiated phase 3 clinical trials to evaluate the safety and efficacy of the drug. This randomized, open-label study conducted globally in multiple centers allowing patients from high-risk COVID-19 countries to participate [36]. The studies are evaluating Remdesivir's role in COVID-19 positive patients with severe manifestation like oxygen requirement and also in patients with with no severe manifestation. Remdesivir is also being used in an independent study by the United States National Institute of Allergy and Infectious Diseases (NIAID) for the potential treatment of COVID-19 positive patients. Some of the contraindications of Remdesivir could be renal or hepatic dysfunction [37].

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Drug-Drug Interactions, Side Effects & Risks

Certain analgesics like metamizole can potentially decrease the exposure of Remdesivir. Antibacterials like rifabutin, rifampin and rifapentine can significantly decrease the exposure of Remdesivir. Similarly, anticonvulsants like carbamazepine, phenobarbital, phenytoin, oxcarbazepine, primidone, rufinamide etc. can reduce the potential exposure of Remdesivir. Anti-hypertensive medication like Bosentan can also reduce the potential of Remdesivir substantially. The side effects and potential risk of Remdesivir are currently being evaluated through clinical studies in patients infected with SARS-CoV-2 [38-39].

2.4 Lopinavir and Ritonavir

Pharmaceutical Properties

Lopinavir and Ritonavir are antiretroviral drugs classified as HIV-1 Protease inhibitors for adults and pediatric patients older than 14 days. The combination of these two drugs - Lopinavir and Ritonavir is also known as Kaletra. The molecular formula of Lopinavir is $C_{37}H_{48}N_4O_5$, (Fig 4) and the molecular weight is 628.8 g/mol. The molecular formula for Ritonavir is $C_{37}H_{48}N_6O_5S_2$(Fig 5) and the molecular weight is 720.95 g/mol [40]. The tablet is recommended to be swallowed as a whole instead of chewing, breaking or crushing it. It can be taken with or without food. The recommended dose varies for adults 800/200mg once or twice daily, and children 100/25mg as recommended by physician. It contains 15.3% propylene glycol and 42.4% alcohol volume per volume, respectively [41].

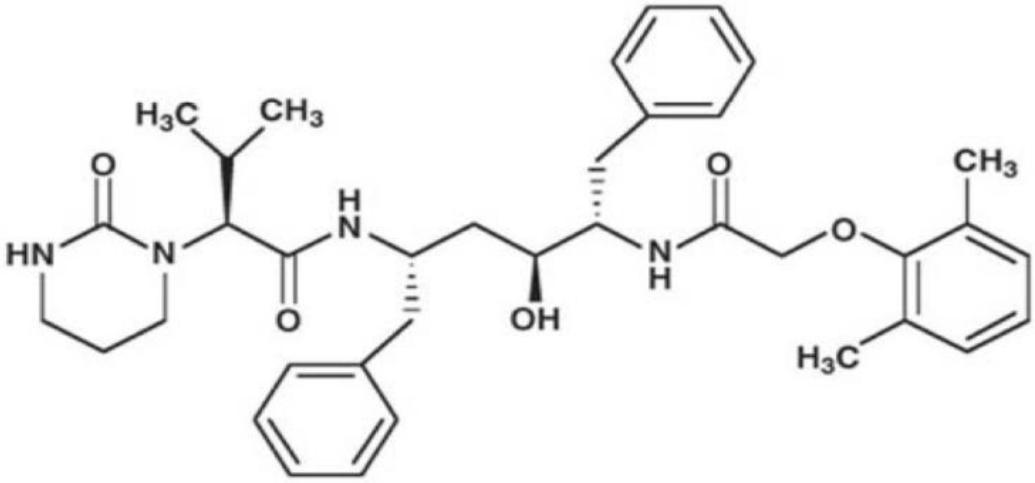

Figure 4: 2D Structure of Lopinavir

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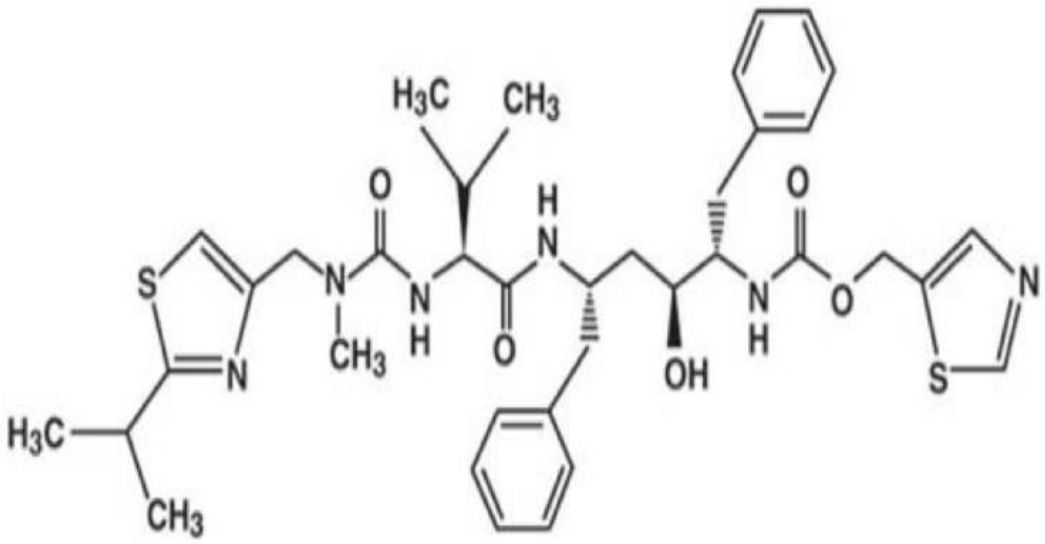

Figure 5: 2D Structure of Ritonavir

Mechanism of Action

As per clinical studies shown, Kaletra - Lopinavir; Ritonavir may suppress coronavirus activity by binding to one of the critical enzymes M^{pro}. The plasma level of lopinavir is increased through ritonavir induced inhibition of CYP3A mediated metabolism of lopinavir [42].

Drug Therapy for COVID-19 and Contraindications

This combination shown potent activity against SARS-CoV and MERS-CoV coronaviruses as per animal and *in-vitro* studies. Currently, randomized, controlled, open-label trials are being conducted on COVID-19 infected patients. Pre-clinical studies show activity with Kaletra for coronaviruses, while certain cohort retrospective studies on COVID-19 positive hospitalized patients show no difference in the duration of viral shedding [43]. Kaletra is contraindicated for patients with hypersensitivity like Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, erythema multiforme etc. Patients with high serum cholesterol and triglyceride levels are contraindicated from taking Kaletra along with patients who have diabetes, Torsades de pointes (TdP), cardiomyopathy and low oxygen content in blood [44].

Drug-Drug Interactions, Side Effects & Risks

The potential plasma concentration of Kaletra can be reduced due to certain drugs which are potential CYP3A inducers, specifically lopinavir and reduce virologic response. Moreover, drugs that are

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dependent on CYP3A clearance can lead to high levels of Kaletra in plasma concentration and lead to serious health consequences. Some of the drugs which are contraindicated are - alfuzosin (alpha1 - adrenoceptor antagonist), which can lead to hypotension with Kaletra due to increased concentration of alfuzosin [45]. Drugs like dronedarone, antiarrhythmic drugs can lead to cardiac arrhythmias. Similarly, certain muscle relaxants like propofol, sevoflurane can cause QT prolongation and TdP. The concentration of analgesics can increase with Kaletra. Serious life-threatening reactions can be caused due to antipsychotics like pimozide and lurasidone with life-threatening manifestations. Similarly, hepatic and renal impairment can be caused by anti-gout drugs like colchicine [46-48].

2.5. Favipiravir

Pharmaceutical Properties

Favipiravir is an investigational drug against SARS CoV-2 viruses. It is known for its activity against RNA viruses. It is a derivative of pyrazine carboxamide, and it inhibits influenza viral RNA-dependent-RNA-polymerase through conversion to ribofuranosyl triphosphate derivate through host enzyme. The molecular formula of Favipiravir is $C_5H_4FN_3O_2$(Fig 6) and molecular weight is 157.1 g/mol. Investigational studies show Favipiravir's role in the treatment of influenza. It prevents the reproduction of viruses through a unique RNA polymerase inhibitor, which prevents the copying of the viral genome [49-50].

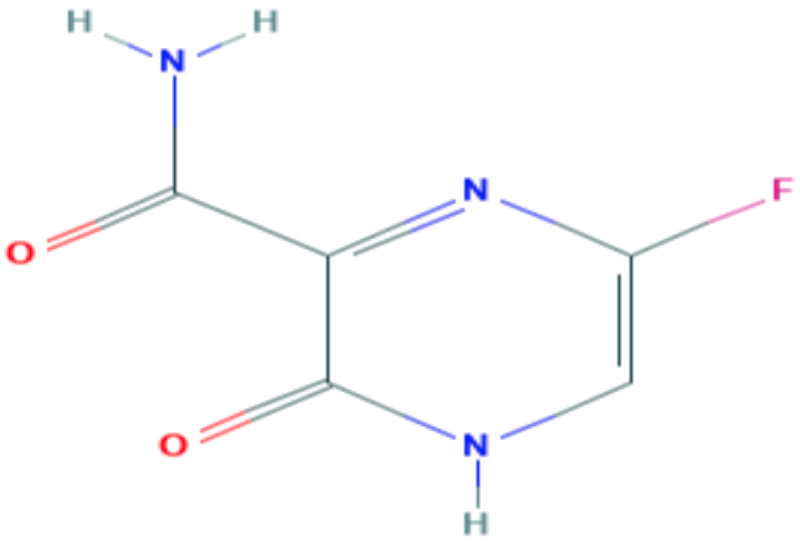

Figure 6: 2D Structure of Favipiravir

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Mechanism of Action

Favipiravir inhibits viral RNA synthesis through RNA dependent RNA polymerase inhibition. It targets influenza viral polymerase without affecting host cellular RNA or DNA synthesis as host cell enzymes convert Favipiravir into Favipiravir ribofuranosyl phosphate [51-52].

Drug Therapy for COVID-19 and Contraindications

The clinical efficacy of Favipiravir against COVID-19 is being investigated through numerous studies worldwide. It is a broad-spectrum antiviral drug with *in-vitro* activity against RNA viruses as per research studies conducted. It is contraindicated in pregnant and lactating women [53].

Drug-Drug Interactions, Side Effects & Risks

Favipiravir is an investigational drug with ongoing clinical studies. The analgesic activity of paracetamol will increase with Favipiravir. It can also increase the potential of anti-diabetic medications like pioglitazone, rosiglitazone and repaglinide [54]. It can increase the anti-hypertensive potential of Treprostinil for pulmonary hypertension. Also, it can increase the antiviral potential of oseltamivir, ombitasvir/paritaprevir + dasabuvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir. Favipiravir can also increase the concentration of certain bronchodilators like aminophylline, montelukast and theophylline [55-56]. It produces side effect like diarrhoea, increases AST, ALT, γ-GTP, blood uric acid and triglyceride levels. It can decreases neutrophil count, WBC count and blood potassium. Moreover, asthma, duodenal ulcer, rhinitis blurred vision, eye pain and vertigo are less frequent adverse events.

2.7. Dexamethasone

Pharmaceutical Properties

Dexamethasone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. In addition to binding to specific nuclear steroid receptors, dexamethasone also interferes with NF-kB activation and apoptotic pathways. This agent lacks the salt-retaining properties of other related adrenal hormones. It is a glucocorticoid agonist and also known as dexone or decadron, belongs to the class of organic compounds known as 21-hydroxysteroids (Fig 7). These are steroids carrying a hydroxyl group at the 21-position of the steroid backbone. [55,57]

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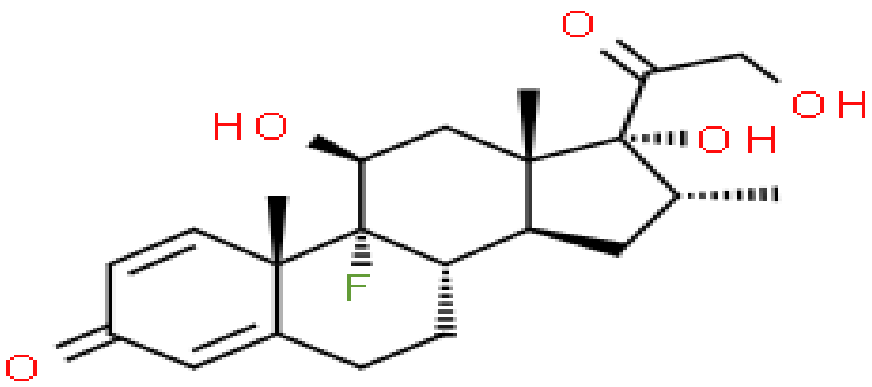

Fig 7: 2D Structure of Dexamethasone

Mechanism of Action

Dexamethasone act on the body by suppressing the migration of neutrophils and decreasing lymphocyte colony proliferation. The short term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. There are higher concentrations of vitamin A compounds in the serum, and prostaglandin and some cytokines (interleukin-1, interleukin-12, interleukin-18, tumor necrosis factor, interferon-gamma, and granulocyte-macrophage colony-stimulating factor) become inhibited. Increased levels of surfactant and improved pulmonary circulation have also been shown with dexamethasone use. [55-60]

Drug therapy for Covid-19 and contraindication

The Covid-19 patient suffer a hyper inflammatory state. The 3 C-like proteinase on SARS-CoV-2 inhibits Histone deacetylases-2 (HDAC2) transport into the nucleus, and so impairs the way in which it mediates inflammation and cytokine response, so activation of histone deacetlase by dexamethasone may directly oppose the action of SARS- CoV-2. Dexamethasone use is contraindicated if patients have systemic fungal infections, hypersensitivity to dexamethasone, or cerebral malaria. [61-64]. On the basis of the preliminary report from the recovery trial, the COVID-19 treatment guidelines Panel (the Panel) recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in

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hospitalized patients who are mechanically ventilated and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated. [65-68]

Drug-Drug Interactions, Side Effects & Risks

Some common side effects are increased appetite, irritability, difficulty sleeping (insomnia), swelling in ankles and feet (fluid retention), heartburn, muscle weakness, and impaired wound healing. Dexamethasone increases the risk of peptic ulceration and bleeding if taken with NSAIDS and of gastrointestinal ulceration with Nicorandil.[65-71]

2.8. Ivermectin

Pharmaceutical Properties:

Ivermectin is semi-synthetic derivative of the entire class of avermectins, discovered by fermentation products of the actinomycete bacterium *Streptomyces avermitilis in* 1975[72]. It is most effective broad-spectrum anti-parasite medication. Ivermectin is a macrocyclic lactone and a mixture of 22, 23-dihydroavermectin P_{1A} (80%) and 22, 23-dihydroavermectin P_{1B} (20%) (Fig. 8) [73]. It was approved for human use by US-FDA for the treatment of onchocerciasis, however it is also effective against strongyloidiasis, ascariasis, trichuriasis and enterobiasis. Due to its safety, scientist in current decade also discovered its potential in various viral disorders such as HIV , Dengue Virus 1-4 (DENV), Influenza Pseudorabies virus , Venezuelan Equine Encephalitis Virus (VEEV), West Nile Virus (WNV)and SARS-CoV-2 virus. [74-81]

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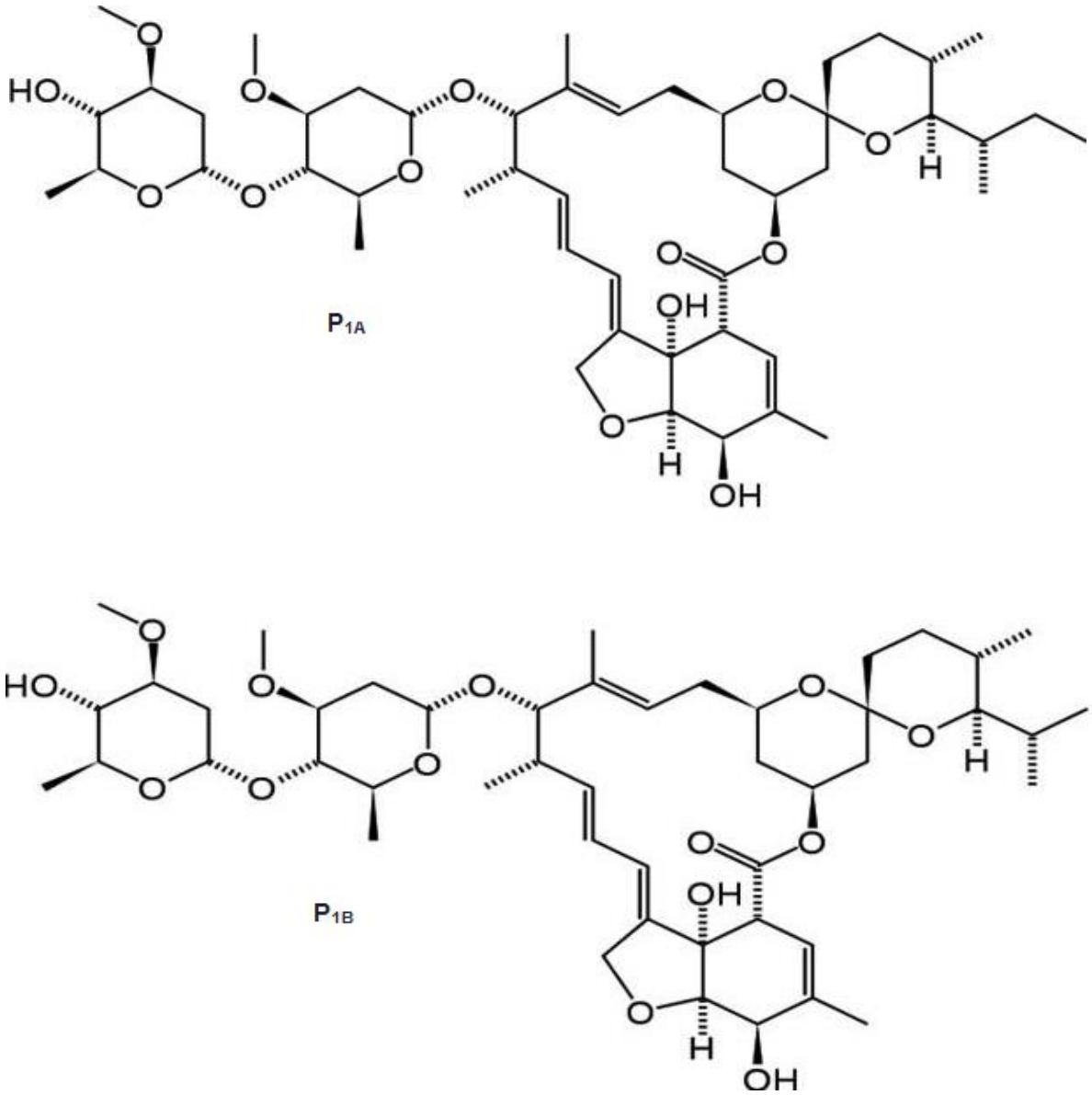

Fig 8: Structure of Ivermectin

Mechanism of action

The exact mechanism of action is still unknown, but scientist find various mechanism behind its broad-spectrum antiviral activity. The first one is, inhibition of importin α/β1-mediated nuclear import of viral proteins of RNA viruses [81]. As SARS-CoV-2 is an RNA virus, so possibility of similar action is also higher [82].

The second one is based on ionophore concept because these molecules are considered as potential antiviral drugs [83]. In case of Ivermectin, both compound present shown in figure 9 interact with each other either spontaneously or by binding some plasma transport proteins, such as albumin. Further, the oxygen atoms (shown in green), work as Lewis bases and could therefore coordinate a series of cations (Lewis acids). In addition, –OH groups are highlighted in pink and they could have

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a decisive role in the stabilization of the new structure. By this way an internal cavity and stabilized structure of Ionophore is formed [84].

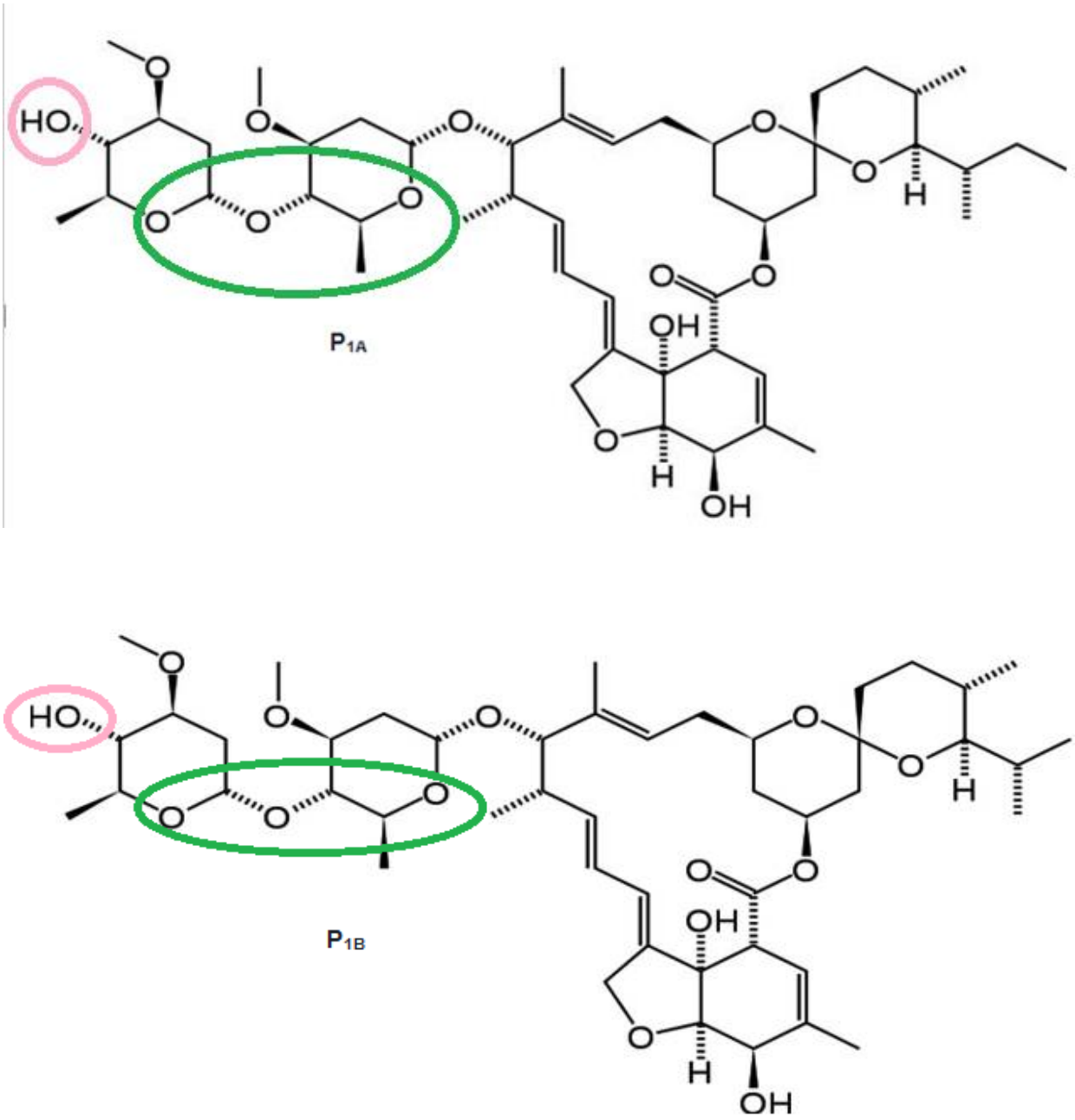

Fig 9: Possible interaction mechanism between two Ivermectin molecules for formation of Ionophore

Drug Therapy for COVID-19 and Contraindications

Even in the absence of solid evidence, some countries in Latin America have authorized Ivermectin use for the management of patients with COVID-19. An externally controlled pilot trial performed to check the effectiveness of Ivermectin as add-on therapy in COVID-19 management. In this trial 16

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patients were included and a dose of 0.2 mg/kg (single dose at once =2 tablets of 6mg/weekly) given to mild and moderate symptom with a comorbidity of hypertension, diabetes, and asthma. All the patient treated successfully in 4-week time frame. Moreover, In a retrospective study performed at hospital clinic in Barcelona, Spain between March 10th and 30th 2020. In this study a single dose of 200 μg/kg of Ivermectin did not improve clinical and microbiological outcomes of patients with severe COVID-19, compared to a similar group of patients not receiving Ivermectin . In patient with significant hepatic disease, Ivermectin should be administered with caution due to its extensive hepatic metabolism. In addition, patient of severe asthma should take Ivermectin cautiously because systemic Ivermectin has been reported to worsen bronchial asthma [85-87].

Drug-Drug Interactions, Side Effects & Risks

If alcohol is taken with Ivermectin, it increases the plasma concentrations of ivermectin. Orange juice decreases the AUC and C_{max} of Ivermectin due to potent inhibitors property of certain drug transporters [88]. Some side effects of this drug are pruritus, giddiness, nausea, abdominal pain, constipation, lethargy, transient ECG changes, fever, urticaria, myalgia, edema of lymph nodes. Safety of ivermectin in pregnant women is not established [87-88].

2.9. Baricitinib

Pharmaceutical Properties

Baricitinib is a small molecule and selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor. The chemical formula of Baricitinib is $C_{16}H_{17}N_7O_2S$ and molecular weight is 371.42. The 3D structure of Baricitinib is shown in figure 10. In 2017, the European Union approved Baricitinib as a second-line orally administered treatment for moderate to severe active rheumatoid arthritis in adults [89].

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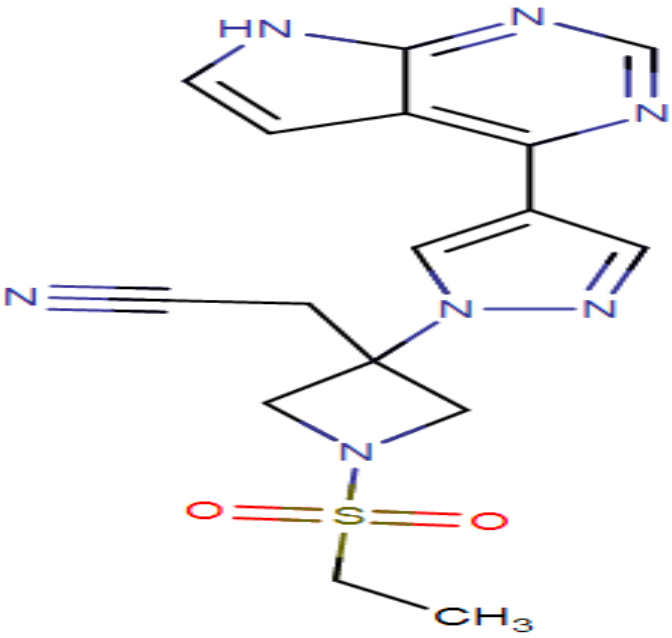

Figure 10: 3D Structure of Baricitinib

Mechanism of action

SARS-CoV-2 virus when bind to angiotensin-converting enzyme 2 (ACE2), it activates 2 host-derived kinases, AP2-associated protein kinase 1 (AAK1) and cyclin G associated kinase (GAK). AAK1 and GAK undergoes many intermediate any intermediate steps and helps in various stages of the SARS-CoV-2 lifecycle [90-91]. Baricitinib has been shown to inhibit AAK1 and, GAK to a lesser degree, thus impede viral cell entry and internal transport . Another mechanism proposed by scientist is JAK–STAT signal blocking by baricitinib (a selective JAK1 and JAK2 inhibitor) produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection [92-94].

Drug Therapy for COVID-19 and Contraindications

On 19 November 2020, Baricitinib in combination with remdesivir was granted an FDA EUA for the treatment of COVID-19. It is approved for hospitalized adults and pediatric (two years of age or older) confirmed COVID-19 patients requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Baricitinib is being tested in clinical trials for both 2 mg/day and 4 mg/day. However, every country has different recommendation. Recently the European Medicines Agency (EMA) recommends a 50% dose reduction in the patients of age ≥ 75 years, a history of chronic or recurrent infections, creatinine clearance (CrCl) between 30mL/min and 60 mL/min, and concomitant use of a strong organic anion transporter-3 (OAT3) inhibitor . Baricitinib is contraindicated in patients with CrCl < 30 491 mL/min [95].

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Drug-Drug Interactions, Side Effects & Risks

Baricitinib is not an inhibitor or inducer of CYP450 enzymes or drug transporters at clinically relevant concentrations. Due to this, ketoconazole and rifampin did not have a clinically significant drug-drug interaction on baricitinib [95]. The commonest side effects with baricitinib are headache (11-24%), upper respiratory tract infection (14-22%), and nasopharyngitis (11-18%) [96].

2.10. Casirivimab / Imdevimab

Pharmaceutical Properties

This combination of drugs is discovered by Regeneron Pharmaceuticals Inc, USA. These Casirivimab is a monoclonal antibody combined with Imdevimab, an artificial antibody cocktail known as REGN-COV2 for the treatment of COVID-19. Recently in 2020, US-FDA issued EUA for this combination [97-98]. However, no information is available on pharmaceutical properties like formula and molecular weight.

Mechanism of Action:

Spike protein of SARS-CoV-2 is playing a quite important role in virus attachment, fusion and entry into the host cell. Casirivimab and imdevimab both are recombinant human IgG1 monoclonal antibody which binds to nonoverlapping epitopes of the spike protein of SARS-CoV-2. Together with casirivimab and imdevimab, neutralizes the spike protein of SARS-CoV-2 [98-99].

Drug Therapy for COVID-19 and Contraindications

Casirivimab and Imdevimab can be utilized for the treatment of confirmed SARS-CoV-2 infection who are adults and children aged 12 years of age and older, weighing at least 40 kg with mild to moderate COVID-19 symptoms. Along with that the patients who are at high risk for progressing to require hospitalization or severe COVID-19, this combination is reserved for them. This combination is allowed in single intravenous infusion with authorized dosage of 1,200 mg each drug in healthcare settings with immediate access to treat any hypersensitive reactions. However, the combination has some limitation as Casirivimab and Imdevimab is not for use in covid-19 patients who currently hospitalized, patients requiring oxygen therapy, patients requiring increases in baseline oxygen flow rate, or patients on oxygen therapy for non-COVID-19 related morbidity [99]. Still no contraindication found with this combination [99].

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Drug-Drug Interactions, Side Effects & Risks

Both monoclonal antibodies (mAbs) are not excreted by renal route. The said combination is metabolized by cytochrome P450 enzymes; consequently, the interactions with associated medications that are excreted through kidney or that are inhibitors or inducers, substrates, of cytochrome P450 enzymes are improbable. Casirivimab and imdevimab at a dose of 2,400 mg reported adverse events in phase-1 clinical trials, that are hyperglycemia, nausea, vomiting, intestinal obstruction, dyspnea, urticaria, pruritus, flushing, pyrexia, shortness of breath, and chest tightness. However, all events resolved after discontinuation of the infusion [99]. On the other hand, scientist associated with this research are awaiting the clinical trial results to confirm the high risk category patient.

2.11. Bamlanivimab

Pharmaceutical Properties

Bamlanivimab (LY-CoV555) is well known as LY3819253. AbCellera Biologics, National Institute of Allergy, and Infectious Diseases (NIAID), and Eli Lilly developed Bamlanivimab, a monoclonal antibody which got EUA by US-FDA on November 09, 2020; based on phase2 clinical trial (BLAZE-1) interim results. It is a synthetic monoclonal antibody (mAb) derived from one of the first blood samples of patient who recovered from COVID-19 in the United States [100-101]. Bamlanivimab contain two identical heavy chains of 455 amino acids and two identical light chains of 214 amino acids. It also contains the unmodified region of Fc present on light and heavy chain [102]. The molecular weight of Bamlanivimab is 146000.0 Da and chemical formula is $C_{6498}H_{10068}N_{1732}O_{2032}S_{46}$.

Mechanism of Action

Bamlanivimab binds the receptor-binding domain (RBD) of the S protein at a position overlapping the ACE2 binding site and which is accessible in both the up and down conformations of the RBD [100]. This binding of Bamlanivimab to RBD is confirmed by X-ray crystallography and cryo-EM. Specifically, bamlanivimab binds to the S protein with a K_D of 0.071 nM and blocks S protein-ACE2 interactions with an IC_{50} value of 0.025 μg/m

Drug Therapy for COVID-19 and Contraindications

Bamlanivimab can be utilized for the treatment of confirmed SARS-CoV-2 infection who are adults and children aged 12 years of age and older, weighing at least 40 kg with mild to moderate COVID-

19 symptoms. Along with that the drug can be used in patients who are at high risk for progressing to require hospitalization or severe COVID-19. However, Bamlanivimab cannot be used for patients who are hospitalized due to COVID-19, who require oxygen due to COVID-19. As well as it also restricted for use in patients who are on oxygen therapy for a non-COVID-19-related comorbidity who require an increased oxygen flow rate due to COVID-19 [102]. Bamlanivimab (700 mg) must be diluted and administered as a single IV infusion over at least 60 minutes. At the time of writing this article no contraindication was found [102].

Drug-Drug Interactions, Side Effects & Risks

Bamlanivimab not excreted by renal route. The said combination is metabolized by cytochrome P450 enzymes; consequently, the interactions with associated medications that are excreted through kidney or that are inhibitors or inducers, substrates, of cytochrome P450 enzymes are dubious. At 700 mg dose, Bamlanivimab produces side effect like nausea, vomiting, diarrhea, dizziness, headache, pruritis, flushing and hypersensitivity reactions [102]. Nevertheless, scientist associated with this research are awaiting the phase-3 results to confirm the high-risk category patient.

2.12. Convalescent Plasma

Pharmaceutical Properties

Convalescent Plasma denotes the plasma donated by patients who recovered from COVID-19 virus disease. It is the liquid part of the blood which contains certain proteins to help fight against infection. Convalescent Plasma contains antibodies to help fight patients recover from COVID-19 [57-58].

Drug Therapy for COVID-19 and Contraindications

Further investigations are ongoing to test the role of Convalescent Plasma in terms of reducing mortality, morbidity, and duration of illness among COVID-19 patients. Currently, it is not conclusive whether Convalescent Plasma is effective against COVID-19. FDA has given EUA for Convalescent Plasma among hospitalized COVID-19 positive patients [59]. It can be a potential risk factor for those who suffer from adverse transfusion reactions etc.

Drug-Drug Interactions, Side Effects & Risks

Convalescent Plasma is generally considered safe in terms of transfusion and tolerated well among the patients. A licensed physician can request the use of Convalescent Plasma for a single patient

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through emergency investigational new drugs (eIND). It also denotes that the probable risk factor of Convalescent Plasma is not greater than the disease or condition [60-62]

3. DISCUSSION

Battling the COVID-19 virus is a humanitarian challenge as thousands of health professionals worldwide are engaged in addressing the crisis globally. This review shows the importance of drugs for treating patients and reducing morbidity and mortality. Several studies has shown the importance of chloroquine phosphate in treating COVID-19 positive patients with pneumonia manifestation. The National Health Council of the People's Republic of China has considered adding chloroquine phosphate in its guidelines for treating pneumonia caused by the SARS CoV-2 virus [63-67]. Similarly, studies by Yao X, et al. shows hydroxychloroquine's role in treating severe acute respiratory syndrome caused by the SARS CoV-2 virus [14,68]. According to Agostini ML, et. al., a study on corona virus susceptibility with remdesivir shows the importance of inhibiting human and zoonotic coronavirus in-vitro and severe acute respiratory syndrome in mice models [69]. Similarly, a study by Yao et al. signifies that lopinavir can inhibit the protease of activity of coronavirus and its role in SARS and theMERS epidemics [69]. Auxiliary treatment like convalescent plasma transfusion in critically ill patients suffering from COVID-19 virus and acute respiratory distress syndrome (ARDS) has improved clinical status, as per a study conducted by Shen C, et al [71]. Moreover, investigational favipiravir drug treatment is being studied as a potential combination treatment against COVID-19 [68-71].

4. CONCLUSION

It is important to establish potential drug therapies against SARS CoV-2 based upon ongoing clinical trials, emergency use authorization and compassionate use protocols. As per studies conducted globally, certain antimicrobials have shown potent activity against SARS CoV-2 such as Hydroxychloroquine, Chloroquine, Remdesivir, Favipiravir, Lopinavir, Ritonavir, Dexamethasone, Ivermectin, Baricitinib, Casirivimab / imdevimab, Bamlanivimab. Investigational use of convalescent plasma from COVID-19 recovered patients is also being studied and these drug therapies have shown remarkable progress among COVID-19 patients in alleviating their symptoms, reducing morbidity and underlying comorbid conditions.

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Data Availability

The authors declare that data supporting the findings of this study are available within the article

REFERENCES

1. U.S. Food and Drug Administration. 2020. Coronavirus Disease 2019 (COVID-19), https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19; 2020 [accessed 28 April 2020].
2. U.S. Food and Drug Administration. 2020. FDA Advises Patients On Use Of Nsaids For COVID-19, https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19; 2020 [accessed 28 April 2020].
3. Who.int. 2020. Clinical Management Of Severe Acute Respiratory Infection When COVID-19 Is Suspected, https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected; 2020 [accessed 28 April 2020].
4. Clinicaltrials.gov. 2020. Search Of: COVID-19 - List Results - Clinicaltrials.Gov., https://clinicaltrials.gov/ct2/results?cond=COVID-19; 2020 [accessed 28 April 2020].

5. National Institutes of Health (NIH). 2020. *Coronavirus (COVID-19)*, https://www.nih.gov/health-information/coronavirus; 2020 [accessed 28 April 2020].
6. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of critical care. 2020 Mar 10. https://doi.org/10.1016/j.jcrc.2020.03.005
7. U.S. Food and Drug Administration. 2020. Chloroquine Phosphate Tabs Accessdata.fda.gov, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/083082s050lbl.pdf; 2009 [accessed 28 April 2020].
8. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020. https://doi.org/10.5582/bst.2020.01047
9. U.S. Food and Drug Administration. 2020. Fact Sheet for Health Care Providers Emergency Use Authorization (Eua) of Chloroquine Phosphate Supplied From the Strategic National Stockpile for Treatment of Covid-19 in Certain Hospitalized Patients Fda.gov, https://www.fda.gov/media/136535/download; 2020 [accessed 28 April 2020]
10. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug discoveries & therapeutics. 2020 Feb 29;14(1):58-60. https://doi.org/10.5582/ddt.2020.01012
11. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. International journal of antimicrobial agents. 2020 Mar 12:105938. https://doi.org/10.1016/j.ijantimicag.2020.105938
12. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, Li Y, Hu Z, Zhong W, Wang M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell discovery. 2020 Mar 18;6(1):1-4. https://doi.org/10.1038/s41421-020-0156-0
13. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochemical and biophysical research communications. 2004 Oct 8;323(1):264-8. https://doi.org/10.1016/j.bbrc.2004.08.085
14. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquinefor

the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020 Mar 9. https://doi.org/10.1093/cid/ciaa237

15. Tanenbaum L, Tuffanelli DL. Antimalarial Agents: Chloroquine, Hydroxychloroquine, and Quinacrine. *Arch Dermatol.* 1980;116(5):587–591. https://doi.org/10.1001/archderm.1980.01640290097026
16. Gendrot M, Javelle E, Le Dault E, Clerc A, Savini H, Pradines B. Chloroquine as a prophylactic agent against COVID-19? Int J Antimicrob Agents. 2020 Apr 12:105980. https://doi.org/10.1016/j.ijantimicag.2020.105980
17. Covid19-druginteractions.org. 2020. *Liverpool COVID-19 Interactions*, https://www.covid19-druginteractions.org; 2020 [accessed 28 April 2020].
18. Good MI, Shader RI. Lethality and behavioral side effects of chloroquine. Journal of Clinical Psychopharmacology. 1982 Feb;2(1):40-47. https://doi.org/10.1097/00004714-198202000-00005
19. Frisk-Holmberg M, Bergkvist Y, Domeij-Nyberg B, Hellström L, Jansson F. Chloroquine serum concentration and side effects: Evidence for dose-dependent kinetics. Clinical Pharmacology & Therapeutics. 1979 Mar;25(3):345-50. https://doi.org/10.1002/cpt1979253345
20. U.S. Food and Drug Administration. 2020. PlaquenilAccessdata.fda.gov, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf; 2017 [accessed 28 April 2020].
21. Pubchem.ncbi.nlm.nih.gov. 2020. Chloroquine, https://pubchem.ncbi.nlm.nih.gov/compound/2719 [accessed 28 April 2020].
22. Pubchem.ncbi.nlm.nih.gov. 2020. *Hydroxychloroquine Sulfate*, https://pubchem.ncbi.nlm.nih.gov/compound/12947 [accessed 28 April 2020].
23. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. InSeminars in arthritis and rheumatism 1993 Oct 1 (Vol. 23, No. 2, pp. 82-91). WB Saunders. https://doi.org/10.1016/S0049-0172(10)80012-5
24. Schrezenmeier, E., Dörner, T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology.Nat Rev Rheumatol 16, 155–166 (2020). https://doi.org/10.1038/s41584-020-0372-x

25. Ben-Zvi, I., Kivity, S., Langevitz, P. *et al*.Hydroxychloroquine: From Malaria to Autoimmunity. *Clinic Rev AllergImmunol*42, 145–153 (2012). https://doi.org/10.1007/s12016-010-8243-x
26. U.S. Food and Drug Administration. 2020. Fact Sheet for Health Care Providers Emergency Use Authorization (Eua) of Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of Covid-19 in Certain Hospitalized Patients Fda.gov, https://www.fda.gov/media/136537/download; 2020 [accessed 28 April 2020]
27. Dan Zhou, Sheng-Ming Dai, Qiang Tong, COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression, *Journal of Antimicrobial Chemotherapy*, , dkaa114, https://doi.org/10.1093/jac/dkaa114
28. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. 2020 Jan 1. https://doi.org/10.1101/2020.03.22.20040758.
29. Warner AE. Early hydroxychloroquine macular toxicity. Arthritis & Rheumatism. 2001 Aug;44(8):1959-61. https://doi.org/10.1002/1529-0131(200108)44:8<1959::AID-ART334>3.0.CO;2-A
30. Tirkkonen T, Laine K. Drug interactions with the potential to prevent prodrug activation as a common source of irrational prescribing in hospital inpatients. Clinical Pharmacology & Therapeutics. 2004 Dec;76(6):639-47. https://doi.org/10.1016/j.clpt.2004.08.017
31. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. 2020 https://doi.org/10.1136/bmj.m1432
32. Pubchem.ncbi.nlm.nih.gov. 2020. *Remdesivir*, https://pubchem.ncbi.nlm.nih.gov/compound/121304016 [accessed 28 April 2020].
33. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E. Compassionate use of remdesivir for patients with severe Covid-19. New England Journal of Medicine. 2020 Apr 10. https://doi.org/10.1056/NEJMoa2007016
34. Ko WC, Rolain JM, Lee NY, Chen PL, Huang CT, Lee PI, Hsueh PR. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. Int J Antimicrob Agents. 2020 Apr;55(4):105933. https://doi.org/10.1016/j.ijantimicag.2020.105933

35. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Medicine and Infectious Disease. 2020 Apr 2:101647. https://doi.org/10.1016/j.tmaid.2020.101647

36. Ko WC, Rolain JM, Lee NY, Chen PL, Huang CT, Lee PI, Hsueh PR. Remdesivir for SARS-CoV-2 pneumonia. Int J Antimicrob Agents. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105933

37. Wang, M., Cao, R., Zhang, L. *et al.*Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 30, 269–271 (2020). https://doi.org/10.1038/s41422-020-0282-0

38. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KP, Chu DK, Chan MC, Cheung PP, Huang X, Peiris M. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Research. 2020 Apr 3:104786. https://doi.org/10.1016/j.antiviral.2020.104786

39. U.S. Food and Drug Administration. 2020. Highlights of Prescribing InformationAccessdata.fda.gov, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021226s038lbl.pdf; 2013 [accessed 28 April 2020].

40. Pubchem.ncbi.nlm.nih.gov. 2020. *Lopinavir/Ritonavir*, https://pubchem.ncbi.nlm.nih.gov/compound/11979606 [accessed 28 April 2020].

41. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020 Mar 18. https://doi.org/10.1056/NEJMoa2001282

42. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ. Case of the index patient who caused tertiary transmission of Coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. Journal of Korean Medical Science. 2020 Jan 8;35(6). https://doi.org/10.3346/jkms.2020.35.e79

43. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a

retrospective cohort study. The Lancet. 2020 Mar 11. https://doi.org/10.1016/S0140-6736(20)30566-3

44. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. 2020 https://doi.org/10.1126/science.367.6485.1412
45. Kiser JJ, Gerber JG, Predhomme JA, Wolfe P, Flynn DM, Hoody DW. Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2008 Apr 15;47(5):570-8. https://doi.org/10.1097/QAI.0b013e318160a542
46. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovirdisoproxil fumarate on coadministration with lopinavir/ritonavir. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006 Nov 1;43(3):278-83. https://doi.org/10.1097/01.qai.0000243103.03265.2b
47. Bergshoeff AS, Fraaij PL, Ndagijimana J, Verweel G, Hartwig NG, Niehues T, De Groot R, Burger DM. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2005 May 1;39(1):63-8. https://doi.org/10.1097/01.qai.0000155203.89350.85
48. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020 Mar 18. https://doi.org/10.1016/j.eng.2020.03.007
49. Pubchem.ncbi.nlm.nih.gov. 2020. *Favipiravir*, https://pubchem.ncbi.nlm.nih.gov/compound/492405 [accessed 28 April 2020].
50. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral research. 2013 Nov 1;100(2):446-54. https://doi.org/10.1016/j.antiviral.2013.09.015
51. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, Gowen BB, Julander JG, Morrey JD. T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. Antiviral research. 2009 Jun 1;82(3):95-102. https://doi.org/10.1016/j.antiviral.2009.02.198

52. Du YX, Chen XP. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clinical Pharmacology & Therapeutics. 2020 Apr 4. https://doi.org/10.1002/cpt.1844

53. Lu CC, Chen MY, Chang YL. Potential therapeutic agents against COVID-19: What we know so far. J Chin Med Assoc. 2020 Apr 1:10.1097/JCMA.0000000000000318. https://doi.org/10.1097/JCMA.0000000000000318

54. Arab-Zozani M, Hassanipour S, Ghoddoosi-Nejad D. Favipiravir for treating novcl coronavirus (COVID-19) patients: protocol for a systematic review and meta-analysis of Controlled trials. 2020 https://doi.org/10.21203/rs.3.rs-23106/v1

55. Caroline AL, Powell DS, Bethel LM, Oury TD, Reed DS, Hartman AL. Broad spectrum antiviral activity of favipiravir (T-705): protection from highly lethal inhalational Rift Valley Fever. PLoSNegl Trop Dis. 2014 Apr 10;8(4):e2790. https://doi.org/10.1371/journal.pntd.0002790

56. Ferner R E, DeVito N, Aronson JK. Centre for Evidence-Based Medicine, Nuffield Department of Primary Crae Health Sciences University of Oxford; ttps://www.cebm.net/covid-19/dexamethasone/ (assess on 10th September 2020)

57. Covid-19 treatment guidelines https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/ (assess on 5th September 2020)

58. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.

59. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32043986.

60. ohnson DB, Lopez MJ, Kelley B. Dexamethasone. [Updated 2020 Apr 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482130/

61. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. The Lancet Infectious Diseases. 2020 Apr 1;20(4):398-400. https://doi.org/10.1016/S1473-3099(20)30141-9

62. U.S. Food and Drug Administration. 2020. Investigational Covid-19 Convalescent Plasma Fda.gov, https://www.fda.gov/media/136798/download; 2020 [accessed 28 April 2020]
63. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A. Deployment of convalescent plasma for the prevention and treatment of COVID-19. The Journal of clinical investigation. 2020 Apr 7. https://doi.org/10.1172/JCI138745
64. Mora-Rillo M, Arsuaga M, Ramírez-Olivencia G, de la Calle F, Borobia AM, Sánchez-Seco P, Lago M, Figueira JC, Fernández-Puntero B, Viejo A, Negredo A. Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. The Lancet Respiratory Medicine. 2015 Jul 1;3(7):554-62. https://doi.org/10.1016/S2213-2600(15)00180-0
65. Song Z, Hu Y, Zheng S, Yang L, Zhao R. Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience. Research in Social and Administrative Pharmacy. 2020 Apr 3. https://doi.org/10.1016/j.sapharm.2020.03.027
66. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. Jama. 2020 Jan 1. https://doi.org/10.1001/jama.2020.4940
67. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020. https://doi.org/10.5582/bst.2020.01047
68. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020 Mar 9. https://doi.org/10.1093/cid/ciaa237
69. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, Smith EC, Case JB, Feng JY, Jordan R, Ray AS. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio. 2018 May 2;9(2):e00221-18. https://doi.org/10.1128/mBio.00221-18
70. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-

19 treatment option. Journal of medical virology. 2020 Feb 27. https://doi.org/10.1002/jmv.25729

71. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA.* 2020;323(16):1582–1589. https://doi.org/10.1001/jama.2020.4783
72. Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo). 2017 May;70(5):495-505. doi: 10.1038/ja.2017.11.
73. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-6. doi: 10.1208/s12248-007-9000-9.
74. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012 May 1;443(3):851-6. doi: 10.1042/BJ20120150.
75. Tay MY, Fraser JE, Chan WK, Moreland NJ, Rathore AP, Wang C, Vasudevan SG, Jans DA. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res. 2013 Sep;99(3):301-6. doi: 10.1016/j.antiviral.2013.06.002.
76. Götz, V., Magar, L., Dornfeld, D., Giese, S., Pohlmann, A., Höper, D., Kong, B. W., Jans, D. A., Beer, M., Haller, O., & Schwemmle, M. (2016). Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific reports*, *6*, 23138. https://doi.org/10.1038/srep23138
77. Lv C, Liu W, Wang B, Dang R, Qiu L, Ren J, Yan C, Yang Z, Wang X. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. Antiviral Res. 2018 Nov;159:55-62. doi: 10.1016/j.antiviral.2018.09.010.
78. Lundberg L, Pinkham C, Baer A, Amaya M, Narayanan A, Wagstaff KM, Jans DA, Kehn-Hall K. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Antiviral Res. 2013 Dec;100(3):662-72. doi: 10.1016/j.antiviral.2013.10.004.

79. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020 May;177:104760. doi: 10.1016/j.antiviral.2020.104760. Epub 2020 Mar 3. PMID: 32135219.
80. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral research*, *178*, 104787. https://doi.org/10.1016/j.antiviral.2020.104787
81. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020 May;177:104760. doi: 10.1016/j.antiviral.2020.104760.
82. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral research*, *178*, 104787. https://doi.org/10.1016/j.antiviral.2020.104787
83. Sandler ZJ, Firpo MR, Omoba OS, Vu MN, Menachery VD, Mounce BC. Novel Ionophores Active against La Crosse Virus Identified through Rapid Antiviral Screening. Antimicrob Agents Chemother. 2020 May 21;64(6):e00086-20. doi: 10.1128/AAC.00086-20.
84. Rizzo E. (2020). Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn-Schmiedeberg's archives of pharmacology*, *393*(7), 1153–1156. https://doi.org/10.1007/s00210-020-01902-5
85. Ivermectin in Adults With Severe COVID-19 Accessed on 26 Dec 2020, from https://clinicaltrials.gov/ct2/show/NCT04602507
86. Camprubí D, Almuedo-Riera A, Martí-Soler H, Soriano A, Hurtado JC, Subirà C, Grau-Pujol B, Krolewiecki A, Muñoz J. Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. PLoS One. 2020 Nov 11;15(11):e0242184. doi: 10.1371/journal.pone.0242184.
87. Ivermectin - Drug Summary. Accessed on 26 Dec., 2020 from: https://www.pdr.net/drug-summary/Sklice-ivermectin-2415
88. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-6. doi: 10.1208/s12248-007-9000-9.

89. Baricitinib. Accessed on 25 Nov 2020 from https://go.drugbank.com/drugs/DB11817

90. Inoue Y, Tanaka N, Tanaka Y, et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J Virol 602 2007;16:8722-9.

91. Wang H, Yang P, Liu K, et al. SARS coronavirus entry into host cells through a novel clathrin and caveolae-independent endocytic pathway. Cell Res 2008;2:290-301.

92. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020;10223:e30-e31.

93. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020;4:400-02

94. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell. 2020 May 28;181(5):1016-1035.e19. doi: 10.1016/j.cell.2020.04.035.

95. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020.

96. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect 2020

97. Regeneron's antibody drug added to UK Recovery trial of COVID treatments". Reuters. Retrieved 2020-09-14.

98. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19". U.S. Food and Drug Administration (FDA) (Press release). 21 November 2020. Retrieved 21 November 2020

99. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: https://www.fda.gov/media/143892/download. Accessed Dec 24, 2020.

100. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. Biorxiv:the Preprint Server for Biology. 2020 Oct. DOI: 10.1101/2020.09.30.318972.

101. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020 Oct. DOI: 10.1056/nejmoa2029849.

102. FDA Emergency Use Authorization Fact Sheet: Bamlanivimab. Available at: https://www.fda.gov/media/143603/download Accessed Dec 20, 2020.