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

Debjyoti Talukdar ¹†, Vivek Jain², Vishal M Balaramnavar³, Swayam Prakash Srivastava⁴, Palanisamy Sivanandy⁵, Madan Mohan Gupta ⁶*, †

¹ Teerthankar Mahaveer College of Pharmacy, Moradabad, Uttar Pradesh, India
² Department of Pharmaceutical Sciences, Mohan Lal Sukhadia University, Udaipur, Rajasthan, India
³ School of Pharmacy, Sanskriti University, Mathura, UP, India
⁴ Department of Paediatrics, Yale University, CT, New Haven CT, USA
⁵ Department of Pharmacy Practice, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia
⁶ School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad & Tobago, WI

*Correspondence: mmningupta@gmail.com, (MMG)
† These authors contributed equally to this work
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
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_{3}O_{8}P_{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].
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].

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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].
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]penty] 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](image)

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

![Figure 3: 2D Structure of Remdesivir](image)

**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 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].
**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_{4}O_{5}, (Fig 4) and the molecular weight is 628.8 g/mol. The molecular formula for Ritonavir is C_{37}H_{48}N_{6}O_{5}S_{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](image-url)
Mechanism of Action

As per clinical studies shown, Kaletra - Lopinavir; Ritonavir may suppress coronavirus activity by binding to one of the critical enzymes M\textsuperscript{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
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 $\text{C}_5\text{H}_4\text{FN}_3\text{O}_2$ (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].

![2D Structure of Favipiravir](image)
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]
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
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

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

![Diagram of Ivermectin molecules](image)

**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
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 $C_{\text{max}}$ 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].
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 Contraindication

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

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