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Review

Novel β -Coronavirus (SARS-CoV-2): Current and future aspects of pharmacological treatmentsNidhi Tiwari^{a,b}, Jyoti Upadhyay^c, Mohd Nazam Ansari^{d,*}, Rohit Joshi^e^a Institute of Nuclear Medicine and Allied Sciences, Defence Research and Development Organisation, Delhi 110054, India^b Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India^c School of Health Sciences, University of Petroleum and Energy Studies, Bidholi, Dehradun 248007, Uttarakhand, India^d Department of Pharmacology & Toxicology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj 11942, Saudi Arabia^e Biotechnology Division, Council of Scientific & Industrial Research-Institute of Himalayan Bioresource Technology, Palampur, Himachal Pradesh 176061, India

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ABSTRACT

The novel coronavirus outbreak has reported to be rapidly spreading across the countries and becomes a foremost community health alarm. At present, no vaccine or specific drug is on hand for the treatment of this infectious disease. This review investigates the drugs, which are being evaluated and found to be effective against nCOVID-19 infection. A thorough literature search was performed on the recently published research papers in between January 2020 to May 2020, through various databases like "Science Direct", "Google Scholar", "PubMed", "Medline", "Web of Science", and "World Health Organization (WHO)". We reviewed and documented the information related with the current and future aspects for the management and cure of COVID-19. As of 21st July 2020 a total of 14,562,550 confirmed cases of coronavirus and 607,781 deaths have been reported world-wide. The main clinical feature of COVID-19 ranges from asymptomatic disease to mild lower respiratory tract illness to severe pneumonia, acute lung injury, acute respiratory distress syndrome (ARDS), multiple organ dysfunction, and death. The drugs at present used in COVID-19 patients and ongoing clinical trials focusing on drug repurposing of various therapeutic classes of drug e.g. antiviral, anti-inflammatory and/or immunomodulatory drugs along with adjuvant/supportive care. Many drugs on clinical trials shows effective results on preliminary scale and now used currently in patients. Adjuvant/supportive care therapy are used in patients to get the best results in order to minimize the short and long-term complications. However, further studies and clinical trials are needed on large scale of population to reach any firm conclusion in terms of its efficacy and safety.

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* Corresponding author at: Department of Pharmacology & Toxicology, College of Pharmacy, PO Box 173, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

E-mail address: nazam.ansari@gmail.com (M.N. Ansari).

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1. Introduction

Novel-coronavirus (nCOVs) is spherical in shape, enveloped with single-stranded RNA, and considered as the largest viral RNA-genome (25–32 kb). Coronaviruses (CoVs) belongs to group of zoonotic viruses having enormous diversity of animal hosts i.e. birds & humans. The infection caused by CoV varies variably and greatly from asymptomatic-symptomatic to severe disease, depending on the species of virus and the host. This virus subdivided into four families: α , β , γ , δ -coronavirus. The γ , δ -CoVs are mainly infected birds, whereas α , and β -CoVs largely infected the mammals (Yin and Wunderink, 2018).

Earlier, global spread of two β -coronavirus such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), origin from Foshan (China) in November 2002 (Zhong et al., 2003) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) occurred in Saudi Arabia in June 2012 (Zaki et al., 2012). At present, a novel coronavirus (SARS-CoV-2) reported first case in China (Wuhan) on December 2019, later on February 2020, World Health Organization (WHO, 2020) given named as COVID-19 (Huids et al., 2020; WHO, 2020a). It has spread rapidly, affected many countries all over the world and declared by WHO, as COVID-19 emergency/outbreak, a pandemic (Dong et al., 2020). SARS-CoV-2 is highly infectious and transmittable diseases, highly vulnerable to entire population worldwide via a directly contact with infected person through respiratory droplets (Zheng, 2020).

According to recent evidences, this epidemic also known as zoonotic disease, a disease transmitted from animals to humans. Several genealogical analyses documented that novel CoV considerably identical to the sequence of bat SARS-like coronavirus (Benvenuto et al., 2020). The replication and transcription phase of SARS-CoV-2 starts when virus (host) enters into the cell and interacting with spike proteins (S-protein) present at the surface of target receptor. Mainly two target receptors are present within the cell to which virus binds either with angiotensin converting enzyme-2 (ACE-2) receptor or with the serine protease TMPRSS2 (Hoffmann et al., 2020). However, exact mechanism

is still unknown and need to investigate whether novel coronavirus employs ACE-2 and TMPRSS2 for the entry into the cytoplasm.

Novel-coronavirus infection is a community transmission disease, primarily affected person to person, via respiratory droplets (Li et al., 2020). Sometimes these droplets can land on objects and surfaces such as tables, doorknobs and handrail. In most of the cases, person can become infect by touching these objects and then touching their eyes, nose and mouth. The most common symptoms are fever, dry cough, tiredness, nasal congestion, sore throat and develop breathlessness. In severe cases patient symptoms can be characterized to organ failure i.e. kidney & respiratory. However, geriatrics population and person with preexisting medical condition (diabetes, hypertension, heart and lung problems) chances are higher for developing symptoms (Rawat and Sharma, 2020). Apart from these symptoms this infection can be associated with lymphopenia, interstitial pneumonia and elevated levels of pro-inflammatory cytokines like as interleukins (ILs), interferons (IFNs), Granulocyte-colony stimulating factor (G-CSF), Tumor Necrosis Factor (TNF- α), etc. This condition sometimes also called “cytokine storm” can induce patient’s death (Guo et al., 2020). Currently, only symptomatic treatments are available to minimize the symptoms like self-isolation/quarantine, supplemental oxygen, mechanical ventilation, paracetamol for fever and antibiotics only for hospitalized patients for control bacterial co-infection. Till date, there are no vaccines or drug therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of this pandemic virus COVID-19 (β -coronavirus). Due to varying nature of this virus, development of novel pharmacological treatment takes several years. Many scientist or researchers work day and night and trying to focus on drug repurposing, which already are in use in some other conditions for competently control and spread of pandemic situation all over the world (Kruse, 2020).

From this review, our aim is to provide a basic overview about currently available drugs and drugs under clinical trial for COVID-19 patients. Based on many evidences from laboratory, animal and

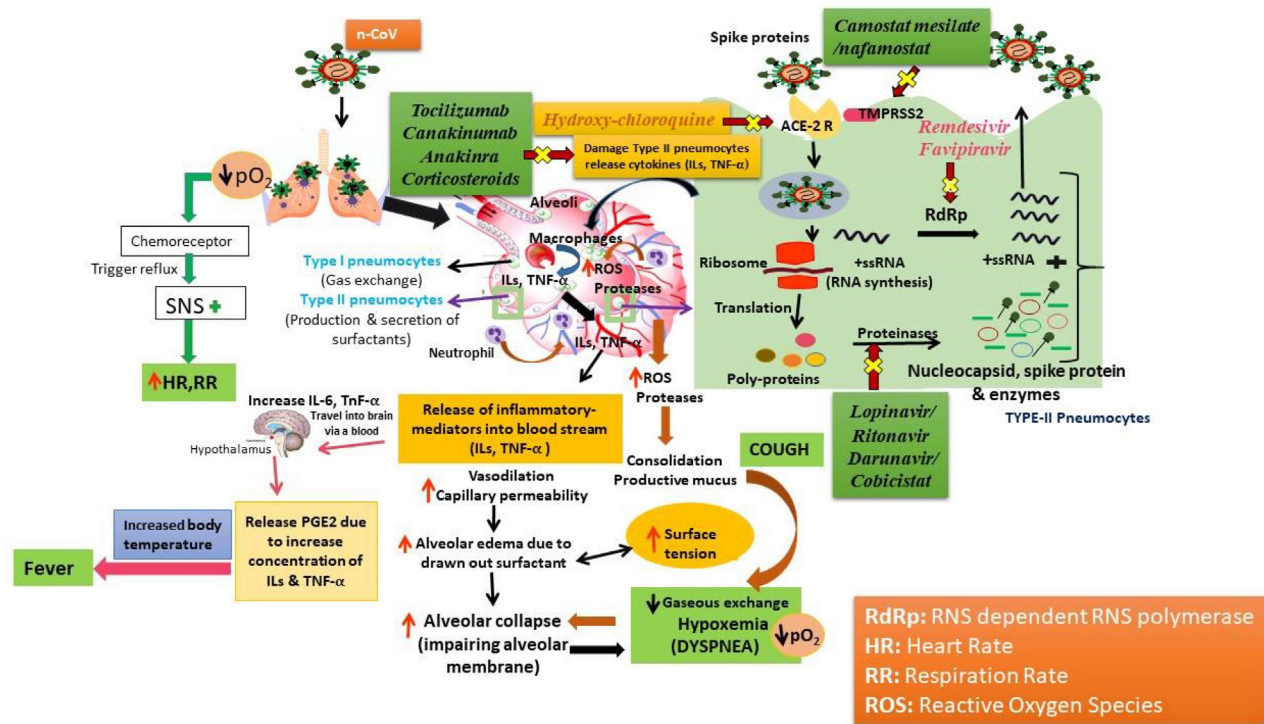


Fig. 1. Schematic diagram of targets with pathogenesis pathway for broad-spectrum antiviral agents, anti-inflammatory and immuno-modulatory agents in treatment of COVID-19.

clinical studies, all are focusing on anti-viral, anti-inflammatory and immune-modulators drugs for the treatment of the novel-coronavirus. Here, we discussed all currently used treatment, under clinical development and outlook clinical trial for the treatment of COVID-19.

2. Drug therapy for COVID-19

Patients with COVID-19 characterized by abnormal in respiration rate (Hypoxia), hear rate, fever, irregular neutrophil counts (neutropenia), and higher level of plasma cytokines i.e. interleukins (IL-1, IL-6, etc.), and TNF- α . All these symptoms are the reason to promote disease severity. SARS-CoV-2 virus detected in both Types I and II pneumocytes present in the ciliated epithelial cells of nasal, bronchial and bronchiolar mucosae of respiratory system. Type I pneumocytes is responsible for gaseous exchange whereas Type II has main role in the production and secretion of surfactants. Destruction of both types of pneumocytes, resulting in hypoxia and alveolar collapse. ACE-2 act as a target receptor for the treatment of COVID-19 infection, whereas TMPRSS2 protein, enhance the transmissibility of the virus. Increase in the production of leukocytes (neutrophil) leads to the formation of highly reactive oxygen species (ROS), and oxidative stress inside alveoli, resulting in the formation of mucus (cough) and alveolar damage. Fig. 1 describes the potential targets with pathogenesis pathway for broad-spectrum antiviral agents, anti-inflammatory and immuno-modulatory agents in treatment of COVID-19.

3. Antiviral agents

Antiviral drugs are beneficial for several infectious diseases such as herpes, hepatitis, HIV, influenza and flu like symptoms (Razonable, 2011). Researchers and scientists are endeavoring to find drugs, which are effective in the treatment of COVID-19. Drug

repurposing is widely acceptance at present, because of immediate impact of nCoVs outbreak into the society and public health emergency concern (Muralidharan et al., 2020). Many drugs that approved by USFDA for some other disease conditions are under preclinical and clinical development for the management of COVID-19. Here, we review and examine all the antiviral drug therapies and its relevance in the treatment of coronavirus as per available pharmacokinetic and pharmacodynamics data of clinical studies. Several studies has been documented that antiviral drugs delivered abruptly after beginning of symptoms and continue last up to 14 days (sputum peak around 5–6 days). These drugs minimizing the chances of infection to others by reducing release of virus from the host and replication into the respiratory secretions of infected person, and diminish risk of infection by prophylactic targeted treatment (Mitja and Clotet, 2020).

Classification, mechanism of action, adverse effects and therapeutic uses of all antiviral agents (currently used and under clinical development) against COVID-19 are shown in Table 1.

3.1. Lopinavir/Ritonavir

Lopinavir (LPV) and ritonavir (RTV) are effective agents that inhibit the protease activity of coronavirus. LPV and RTV act as an antiretroviral used for the treatment of AIDS/HIV virus (HIV-1& HIV-2). RTV enhances the plasma concentration of LPV through inhibition of cytochrome P450 (CYP3A)-mediated metabolism of LPV (Soliman et al., 2011). Previous studies reported that LPV blocks virus replication in the later stages steps of MERS-CoV cycle (de Wilde et al., 2014) and abate the activity of SARS-CoV by inhibition of proteinase activity (Hurst and Faulds, 2000). In a randomized, controlled and open-label trial involving 199 adults SARS-CoV2 positive patients, patients were divided into two groups (LPV-RTV treated & standard-care group). There is no remarkable changes were observed in both the groups in terms of improvement and mortality. Moreover, adverse effects were less

Table 1
Classification, mechanism of action, adverse effects and therapeutic uses of Antiviral agents against COVID-19.

Name of Drug(s)	Classification	Mechanism of action	Adverse effects	Therapeutic Uses	Safety Concern
Lopinavir/Ritonavir	HIV Protease inhibitor	Lopinavir inhibit key enzyme (Protease) of coronavirus life-cycle replication Ritonavir inhibits CYP3A4 enzyme	Diarrhea, abdominal pain, nausea, dyslipidemias	HIV-1 & HIV-2 (anti-retroviral)	Cautiously used in cardiac arrhythmias (QT-prolongation), hepatic disease
Remdesivir (GS-5734)	Investigational Nucleoside analogue	Inhibit RNA dependent RNA polymerase (RdRp) enzyme	Nausea, vomiting, liver damage	Ebola, Marburg, SARS, MERS viral infections	Caution for renal and hepatic impairment patients
Ribavirin	Purine nucleoside analogue	Inhibit GTP & viral RNA synthesis	Anemia, bone marrow depression, hemolysis, GIT & CNS symptoms	Chronic hepatitis C, Influenza A & B, respiratory syncytial virus bronchiolitis	Contraindicated in pregnancy due to teratogenicity
Favipiravir (T-705)/ Umifenovir	Investigational RNA-Dependent RNA Polymerase Inhibitor	Inhibits viral RNA-synthesis	GIT and CNS symptoms, abnormal liver enzyme, elevations in serum uric acid	Influenza, arenavirus, bunyavirus filovirus, Ebola & Lassa virus	Contraindicated in pregnancy due to teratogenicity
Darunavir/cobicistat	Protease inhibitor	Inhibit key enzyme of coronavirus life-cycle replication Protease (M ^{Pr}) / inhibition of human CYP3A4 protein	Nausea, diarrhea, vomiting, muscle ache headache, joint pain,	HIV/AIDS (used in HIV-1 type virus)	Cautiously used in liver (hepatitis B & C), kidney, hemophilia, diabetes and heart patients
Camostatmesilate/ nafamostat	Serine protease inhibitor	Inhibits enzyme activity TMPRSS2 receptor	Oedema, urticaria, GIT-intolerance, abnormal liver enzyme	Acute Pancreatitis, postoperative reflux esophagitis	Hepatic diseases
Ivermectin	Antiparasitic	Inhibits RNA viral synthesis	pruritus, giddiness, nausea, abdominal pain, constipation and lethargy	Anthelmintic, Onchocerciasis, strongyloidiasis, scabies, pediculosis	Pregnant women and young children

common in LPV-RTV, as compared to standard-care group (Cao et al., 2020a, 2020b). Another study reported that, patients were assigned randomly in phase 2-trial and administered 14 days combination of LPV (400 mg), RTV (100 mg) and ribavirin (400 mg) in every 12 h with IFN beta-1b to improve the antiviral response. This combination seems to be better, superior and provides best output to LPV-RTV alone and also diminished the virus desquamation, reduces symptoms of patients, and often promoting discharge of patients in the mild-moderate COVID-19 (Hung et al., 2020). Another *in vitro* study reported that Ribavirin, analogue of guanine nucleotide having wide spectrum of antiviral activity, used along with LPV/RTV to treat SARS-CoV-2 viral infection in china (ChiCTR2000029387) (Lu et al., 2020). Earlier this combination was well-established for the treatment of SARS-CoV infection along with minimal risk of acute respiratory distress syndrome (ARDS) and mortality rate (Chu et al., 2004). Moreover, future clinical studies are needed to check this combination with other antiviral-combination against SARS-CoV-2.

3.2. Remdesivir (RDV, GS-5734)

The drug was developed in 2017, for the treatment of Ebola and Marburg virus infections. RDV is a prodrug of nucleotide (adenosine) analogue and having a broad-spectrum antiviral activity. In body, it is metabolized into active metabolite GS-441524. The antiviral mechanism of RDV is to inhibit RNA-dependent RNA polymerase (RdRp) enzyme, necessary for virus replication (Al-Tawfiq et al., 2020). Earlier *in vitro* studies reported that RDV inhibits single stranded RNA virus replication such as SARS-CoV and MERS-CoV (Agostini et al., 2018). Another mouse model study reported that combination of RDV and IFN-beta is better than LPV & RTV for the treatment of MERS-CoV (Sheahan et al., 2020). Currently preclinical study reported that association of RDV & chloroquine is greatly efficient for preventing SARS-Cov-2 infection (Wang et al., 2020). In addition, phase 3 clinical trials conducted in 237 participants to

check efficacy and safety of the RDV (loading dose, 200 mg on day 1 only followed by 100 mg maintenance dose, OD for 9 days) in COVID-19 patients (Cao, 2020). RDV shows promising output in some of the US patients with COVID-19 (Holshue et al., 2020). Furthermore, Beigel et al. (2020) reported remdesivir shows possible efficacy better as compared to placebo group in hospitalized patients for the treatment of SARS-CoV-2 virus. A randomized, double-blind and placebo-controlled clinical trial has been conducted and the patients received remdesivir i.v. (day1 loading dose (200 mg) + daily maintenance dose (100 mg) up to 9 additional days). Patients are assigned randomly and total of, 1063 infected patients are enrolled and divided into two groups, remdesivir group: 541 patients and placebo group: 522 patients. The overall time to recovery rate is better in remdesivir and also lowers infection in respiratory system as compared to placebo. In addition, various evidences suggested serious adverse event i.e acute respiratory failure and sudden death in few patients and strict monitoring is required to manage dose at the time of treatment. From this report, we can conclude antiviral treatment always need supportive care or supplemental oxygen to prevent other negative outcomes. Recently, Hetero pharma company launched COVIFOR vials, brand name of remdesivir, a game-changer drug for treatment of COVID-19. This drug is restricted used in patients who already have kidney problems, pregnant and lactating women (<https://www.pharmaceutical-technology.com/news/cipla-hetero-remdesivir-covid-19/>). Hence, further research is requisite to evaluate its pharmacological and pharmacodynamics characteristics against SARS-CoV-2 virus.

3.3. Favipiravir (FPV) & Umifenovir

Favipiravir (Avigan) is an antiviral drug, firstly developed by Japan in the year 2014, for treatment of influenza virus infections (Furuta et al., 2017). It is a nucleotide (guanine) analogue, & converted into active metabolite by phosphorylation, then inhibits

the synthesis of RNA (RdRp) and virus mutagenicity (Vanderlinden et al., 2016). It has been documented by *in vitro* study that FPV inhibits SARS-CoV-2 in Vero E6 cell ($EC_{50} = 61.88 \mu\text{M}$) (Du and Chen, 2020). An open & controlled study designed to determine the efficacy of FPV (1600 mg BD, on day 1 followed by 600 mg BD on 2–14 days) Vs LPV/RTV (400 mg/100 mg BD) along with IFN- α 1b, BD) for the treatment of COVID-19. Preliminary results showed that there is significant difference between viral clearance & chest improvement rate (Cai et al., 2020). In India, Glenmark is the first company to initiate the Phase 3 trials on FPV by enrolled 150 participants, duration of treatment maximum of 14 days and total study duration of an individual maximum upto 28 days, with mild to moderate COVID-19 under restricted emergency used. Recently, on June 22, 2020 glenmark permitted FPV, under brand name of Fabiflu tablets (1800 mg BD on first day followed by 800 mg BD from day 2 to day 14) into the market for treatment of mild to moderate cases of COVID-19 patients (Baravkar et al., 2020).

Umifenovir (Arbidol) is a dual-acting direct antiviral/host-targeting agent used as a prophylaxis in the influenza and respiratory infections. A cohort study enrolled 102 adult patients characterized by lymphopenia showed no significant difference in the results obtained between the survival and non-survival groups by receiving treatment with antiviral, antibiotic and glucocorticoid therapy. However, there is a significant data and less mortality rate for those patients who receive arbidol (Cao et al., 2020a, 2020b).

3.4. Darunavir/cobicistat

This combination of drug used as an antiretroviral in the treatment of HIV/AIDS. Darunavir is a HIV protease inhibitor and cobicistat enhances the plasma concentrations of darunavir by blocking its metabolism by CYP 450 enzyme (Deeks, 2018). Preclinical studies documented that this combination showed beneficial effects in the SARS-CoV-2 virus infections (Lin et al., 2020; Omotuyi et al., 2020). The effectiveness and safety concern of darunavir/cobicistat combination is being evaluated under development of clinical trials phase 3 by enrolling 30 COVID-19 patients and estimated completion of study on December 31, 2020. Lastly, the primary outcomes measures shows the clearance rate of virological salivation, less throat infections and decreases respiratory secretion at day 7 (Time frame: 7 day after first randomization) (Lu, 2020).

3.5. Camostatmesilate/nafamostat

Initially, Camostatmesilate and Nafamostat are used in postoperative reflux esophagitis and in chronic pancreatitis (Uno, 2020). Camostatmesilate and Nafamostat, both drugs act on attractive target TMPRSS2, a serine protease inhibitor and block the entry of the virus into the lung alveolar cells (Hoffmann et al., 2020). Recently, Camostat mesilate enters into the phase 2 trials by taking 114 participants (administered dose approx. 200 mg for 7 days, TID). The outcomes obtained like changes in COVID-19 symptoms (frequency and severity), body temperature and changes entry in SARS-CoV-2 viral load.

3.6. Ivermectin

Ivermectin is a FDA approved drug, used as an anti-parasitic and in the treatment of many types of virus infections such as HIV, dengue, influenza and Zika (Caly et al., 2020). Recent study showed that Ivermectin, inhibits the growing of virus in cell culture approximately for 48 hrs. Till date, test is only carried out *in vitro*, for confirmation, strong clinical trials are needed to evaluate its safety and efficacy in the treatment of COVID-19 patients (Scavone et al., 2020). Clinical studies of Ivermectin in COVID-19

patients are underway by enrolling 50 confirmed cases of COVID-19, as per hospital protocol. This study is in progress and might be getting its primary outcomes about its safety and clinical efficacy by the end of July 2020 (Budhiraj and Mishra, 2020).

4. Anti-inflammatory and immunomodulatory agents

Earlier data about coronavirus (SARS & MERS) showed, cell infiltration and cytokine storm (CS) leads to acute cell lung injury, ADRS and death of many patients (Channappanavar and Perlman, 2017; Chousterman et al., 2017). Recently, COVID-19 infection, which is due to SARS-CoV-2 virus, accompanied by rapid replication of virus and a massive release of cytokine profile as same in other two reported coronavirus SARS and MERS (Teijaro, 2017). Currently, study documented that cytokines like interleukins (IL-1B, IL-6, IL-7, IL-9 & IL-10); G-CSF; IFNs; interferon- γ -inducible protein (IP10); monocyte chemoattractant protein (MCP1), tumor necrosis factor (TNF α), vascular endothelial growth factor (VEGF), platelet derived growth factors (PDGF) and other pro-inflammatory mediators are increase in COVID-19 patients (Huang et al., 2020). Another studies reported extensively elevation in the level of IL-6 in critically severe poorly in COVID-19 infected patients (Ruan et al., 2020; Zhou et al., 2020). Classification, mechanism of action, adverse effects and therapeutic uses of all anti-inflammatory and immunomodulatory drugs (currently used and under clinical development) against COVID-19 are listed in Table 2.

4.1. Chloroquine/Hydroxychloroquine (HCQs)

It is an anti-malarial and over the counter (OTC) drug, activity similar to chloroquine. Recently, it was reported that HCQs shortened the time to clinical recovery on the SARS-CoV-2 patients. Due to its interferon blocking property, it has diminished the immune response to a viral infection. This immunomodulatory property makes its useful in autoimmune disorder such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The safety profile of HCQ is superior as compared to chloroquine during long term used in COVID-19 patients and little concern about drug-drug interactions (Yao et al., 2020). Several *in vitro* studies reported CQs/HCQs are used as an effective treatment in SARS-CoV-2 virus. As they are weak bases and enhance pH of endosomal in host cell organelles, inhibit fusion of autophagosome-lysosome and inactivates enzyme require for replication of virus. They also have a potential to deactivate ACE-2 glycosylation, for which coronavirus may enters into the cell (Ferner and Aronson, 2020). Currently studies showed that HCQ administered for 3–6 days, effective in clearing viral nasopharyngeal carriage of SARS-CoV-2 in most of the COVID-19 patients and strengthen its effects along with azithromycin (Gautret et al., 2020). Azithromycin, a macrolide antibacterial drug was shown to be successful in the treatment of Zika and Ebola viruses by *in vitro* studies (Madrid et al., 2015; Bosseboeuf et al., 2018). Previous studies reported that combination of HCQ and azithromycin showed synergistic effect and prevent respiratory tract infections when administered by viral infection patients (Bacharier et al., 2015).

Recently, World Health Organisation (WHO) updated information on 17 June 2020, about safety and efficacy of chloroquine (CQs)/Hydroxychloroquine (HCQs) and compared it with standard care treatment for COVID-19 patients. The overall outcomes showed that there is no significant difference in case of mortality when compared with standard care treatment. In addition, some reports evaluated HCQs cause's serious adverse effects like prolongation of QT interval, ventricular fibrillation, arrhythmia and some-

Table 2
Classification, Mechanism of action, adverse effects and therapeutic uses of Anti-inflammatory & Immunomodulatory agents against COVID-19.

Name of Drug(s)	Classification	Mechanism of action	Adverse effects	Therapeutic Uses	Safety Concern
Chloroquine/ Hydroxy- chloroquine (HCQ)	4-aminoquinolones	Inhibit viral DNA & RNA polymerase enzyme, viral protein glycosylation, ACE2 receptor, also inhibit cytokine release immune-modulation	Cardiovascular symptoms (prolongation of QT interval)	Antimalarial, Immuno-modulator	Cautiously used in liver & heart damage, GIT, retinal, neurological & hematological diseases
Anakinra	Biological agents	Recombinant human IL-1 receptor antagonist	Fever, chills, sweating, cough, sore throat, nausea, vomiting, diarrhea, stomach pain	Refractory rheumatoid arthritis	Caution in patients with thrombocytopenia & neutropenia, infusion related reactions
Canakinumab (ACZ885)	Human monoclonal antibody	IL-1 β receptor antagonist	CNS (headache, vertigo), GI symptoms, musculoskeletal pain, rhinitis, bronchitis	Periodic fever syndromes, Sudden Juvenile Idiopathic Arthritis (SJIA)	Caution in patients with thrombocytopenia & neutropenia
Tocilizumab/ Itozilumab	Humanized monoclonal antibody	IL-6 receptor antagonist	Allergic reactions, headache, hypertension, mouth ulcers, increase in hepatic enzymes	Autoimmune disorder/ immunosuppressive effects (rheumatoid arthritis, giant cell arteritis)	Contraindicated in hepatic diseases, GIT perforation patients, infusion related reactions
Aviptadil	Vasoactive intestinal polypeptide (VIP) analogue	Inhibits production of IL-6 and TNF- α	Alterations in blood pressure, Heart rate	Erectile dysfunction, sarcoidosis, acute lung damage	Cautiously used in cardiovascular patients
Eculizumab	Protein Based Therapies Monoclonal antibody (mAb)	Inhibitor of the terminal portion of complement cascade	Allergic reactions, anemia, GIT & flu like symptoms, headache & leukopenia	Atypical hemolytic uremic syndrome, generalized myasthenia gravis	Contraindicated in patients with unresolved serious Neisseria meningitides infection
Baricitinib	Tyrosine protein kinase family	Janus-kinase (JAK1 & JAK 2) inhibitors	Allergic reactions, increased LDL cholesterol, nausea, trouble in breathing	Autoimmune disease (rheumatoid arthritis)	Contraindicated in kidney and liver diseases (hepatic B&C), bone-marrow depression and cancer

times leads to abrupt death. The safety and efficacy assurance for CQs/HCQs, there is necessitate that other clinical studies are needed to be performed and exemplify with safety concern (Cochrane, 2020). Further, US FDA summarized details on July 1 with safety concern, and permitted used of CQs/HCQs is now accessible to take care of patients with COVID-19 but some strict monitoring are required while treatment as it shows various heart related problems, blood and lymph disorders, renal injury and hepatic failure (US FDA, 2020).

4.2. Interferon (IFNs) β -1b

Interferons are types of cytokines effective in the management of infections & infectious diseases (Arnaud, 2002). It is a broad-spectrum antiviral, antiproliferative & immunomodulatory drug interacting with the toll-like receptors and inhibits viral replication and protein synthesis (Uematsu and Akira, 2007). There are three types of IFN (α , β , and γ). IFN- β shows high potent specificity as compared to IFN- α in reducing the replication of MERS-CoV (Hart et al., 2014; Shalhoub, 2020). Recently, *ex-vivo* studies demonstrated SARS-CoV-2 triggers lower type 1 interferon than SARS-CoV in human lung tissue (Shalhoub, 2020). Further, several future studies are being conducted to determine its efficacy & safety along with other antiviral drug in treatment of COVID-19.

4.3. Interleukin antagonist

Interleukin plays a major role in the pathogenesis of all three coronavirus SARS-CoV-1, MERS & SARS-CoV-2 infections (Lau et al., 2013). Recent study reported several pro-inflammatory mediators plays a major role in the lung damage such as interleukins (IL-2, IL-6 etc) and inflammatory markers (D-dimer, ferritin, and C-reactive protein) (Conti et al., 2020; Kuppalli and Rasmussen, 2020). Several ILs antagonist drugs are under ongoing trials to check its safety and efficacy against SARS-CoV-2 viral infections.

4.3.1. Anakinra (IL-1 Antagonist)

Anakinra is a recombinant IL-1 receptor antagonist and may be helpful in COVID-19 patients. It prevents the binding of IL-1 α and IL-1 β to interleukin-1 receptors, which is used in the treatment of autoimmune disorders (Cavalli et al., 2020). Recently, retrospective cohort study showed high dose of anakinra (5 mg/kg, BD, iv) produces beneficial and efficacious effects in 72% Covid-19 infected patients associated with ARDS (Cavalli et al., 2020). In addition, anakinra alleviated hyper-inflammation and respiratory distress in SARS-CoV-2 infected patients (Tufan et al., 2020). Another studies reported anakinra (100 mg repeated after 6 h, sc for 7 days) administered along with remdesivir (200 mg LD, followed by 100 mg after 4 h, iv for 7 days) used in the treatment of respiratory dysfunction in COVID-19 patients (Franzetti et al., 2020). However, several clinical trials in large population are required for confirmation of its efficacy.

4.3.2. Canakinumab (IL-1 β Antagonist)

A human monoclonal antibody particularly targets and neutralizes IL-1 β thus blocking its binding with IL-1 receptors (Dhimolea, 2010). A randomized, controlled and double-blind study are underway in which 450 participants are to be enrolled, to check the efficiency and safety of canakinumab in patients with COVID-19 induced pneumonia and systemic inflammatory release syndrome (SIRS). Until date, this drug has been passed from phase 2 trials and the estimation date for the completion of clinical trials study is October 16, 2020. The dose of canakinumab administered by patients according to body weight (40–60 kg, 450 mg; 60–80 kg, 600 mg; >80 kg; 750 mg) along with 5% dextrose (iv fluid) for 2 h (Novartis Pharmaceuticals, 2020).

4.4. IL-6 receptor antagonist

These classes of drugs blocks interleukin (IL-6) mediated signaling pathways by binding competitively with soluble and membrane bound IL-6 receptors (sIL-6R and mIL-6R). IL-6 involved in

various physiological process like activation of T-cells, B-cell, hematopoietic cell proliferation and differentiation, hepatic acute-phase protein synthesis initiation and also immunoglobulin secretion (Tanaka et al., 2014).

4.4.1. Tocilizumab

It is a monoclonal antibody, firstly initiates and tested by china to decrease the lung related complications in patients with COVID-19. A randomized and retrospective study showed that tocilizumab plays a beneficial role as an adjunctive therapy in COVID-19 patients. Preliminary data proved that percentage of lymphocyte, concentration of CRP, and computed-tomography clarity changes and reduces the hospitalization duration of these patients (Xu et al., 2020). At present, three clinical trials are under advancement to assess its safety and efficacy alone or in combination with some other drugs by taking 1500 participants with SARS-CoV-2 infection (Barrett, 2020; de Paris, 2020; Regeneron Pharmaceuticals, 2020). The phase 3 clinical-trial of tocilizumab approved by US-FDA in severe COVID-19 pneumonia patients. Moreover, other IL-6 inhibitors such as *clazakizumab* and *sarilumab* are underway in the clinical trials (phase 2& 3) to evaluate its efficacy in COVID-19 infected patients (Henriksen, 2020).

4.4.2. Itolizumab (ALZUMAb)

It is a humanized recombinant IgG1 anti-CD6 monoclonal antibody, used for the treatment of moderate to severe plaque psoriasis, rheumatoid arthritis and autoimmune disorders (Saavedra et al., 2020). Initially, it was developed by Biocon in Bengaluru and approved in 2013 in psoriatic patients. Recently, Biocon repositioning the drug into patients with moderate to severe COVID-19 associated with Cytokine release syndrome (CRS) and acute respiratory distress syndrome (ARDS). In addition, Drug controller General of India (DCGI) allowed use of ALZUMAb (25 mg/5ml injection) in SARS-CoV-2 patients as an emergency treatment and capable to save numerous seriously sick patients with COVID-19 (<https://www.pharmaceutical-technology.com/news/biocon-itolizumab-approval/>).

Itolizumab is also acts as a immunomodulator and binds with CD6 receptor along with suppress many proinflammatory mediators (cytokines) and downregulates the T-cell activation at site of inflammation (Saavedra et al., 2020). An open-label randomized and controlled study performed by Biocon, in 30 participants associated with moderate to severe symptoms of SARS-CoV-2 virus. The study being conducted in two groups, first group taken itolizumab + supportive care while second group only with supportive care. The overall outcomes showed there is no mortality rate and all patients are recovered well as compared to second group. Further, clinic-pathological observations i.e release of pro-inflammatory cytokines (IL-6 & TNF- α) significantly decrease in first group when compared to second group (Jolla, 2020; Uttamani et al., 2020). Moreover, several clinical studies are required to confirm its safety and efficacy in COVID-19 patients.

4.5. Aviptadil

It is a vasoactive intestinal polypeptide (VIP) analogue used in the treatment of erectile dysfunction, acute lung injury and Besnier-Boeck-Schaumann disease. The significance of aviptadil in ARDS, because it has been documented by animal studies that VIP is extensive concerted in the lungs and inhibits NMDA-induced caspase-3 activation, IL6 and TNF- α production and also protects against acidic (HCl)-induced lung edema. In the various animal models, aviptadil protects lungs and other organs from damage or failure by restoring barrier function at the alveolar interface (Petkov et al., 2003; Said, 2012). In a phase 2 clinical trials, conducted under European regulatory authority (ERA), patients

were successfully treated with intravenous infusion of aviptadil on escalating doses and restores all the functioning of pulmonary hypertension, acute lung injury and ARDS. Few adverse effects related to cardiovascular system such as change in blood pressure, heart rate or ECG was noticed.

4.6. Eculizumab

Eculizumab is a monoclonal protein based monoclonal antibody (mAb) used to treat paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and neuromyelitis optica (Wong and Kavanagh, 2015). The main target of eculizumab is complement protein C5, preventing cleavage to C5a and C5b, and the formation of the terminal complement complex C5b-9, which is involved in many autoimmune diseases (Gralinski et al., 2018). Based on case study of patients with SARS-CoV2 infection and also confirmed severe pneumonia and ARDS treated with i.v. infusion of eculizumab along with anticoagulant therapy (Enoxaparin 4000 IU/day s.c), antiviral therapy (LPV 800 mg/day + RTV 200 mg/day), hydroxychloroquine 400 mg/day, ceftriaxone 2 g/day IV, vitamin C 6 g/day for 4 days. All patients showing decrease in the inflammatory markers including C-reactive protein (CRP) (Diurno et al., 2020). More clinical study is needed for confirmation its safety and efficacy as an anti-inflammatory in the treatment of COVID-19.

4.7. Janus kinase (JAK) inhibitors

JAK are the intracellular enzymes located on cellular membrane, transmits signal by binding with various cytokines and growth receptors. After binding with receptor, enzymes phosphorylation occurs, which modulating the changes in the gene expression and thus, activates the signal transducers and activators of transcription proteins (STATs) (Seif et al., 2017). JAK pathway is key enzyme and plays a crucial role in the activation of immune system, hematopoiesis and inflammation. Inhibitors of JAK, prevents the enzymes phosphorylation and activation of STATs proteins (O'shea et al., 2015).

4.7.1. Baricitinib

It is reversible and competitive inhibitor of JAK1 & JAK2, and firstly accepted by US FDA in the treatment of autoimmune disorder i.e. rheumatoid arthritis. It also have broad immunosuppressive effect, and used in many autoimmune disorders (Winthrop, 2017). It blocks the enzymes protein kinase 1 related with AP2 (AAK1), thus inhibits the entry and binding of virus into the epithelial cell of the alveoli (Mayence and Vandeneynde, 2019). A non-randomized open label trial of baricitinib + LPV/RTV in 12 COVID-19 patients and a control group treated with HCQ + LPV/RTV. The respiratory function parameters in baricitinib-treated patients improve as compared to control group. No significant adverse effect reported in baricitinib-treated patients (Cantini et al., 2020). Further studies are needed to confirm its clinical safety and efficacy in the treatment of COVID-19 infection. Others JAK inhibitors are also under clinical development and data are being evaluated in the treatment of COVID-19 are *ruxolitinib* and *tofacitinib* (Smith and Prosser, 2020).

5. Adjuvant/supportive care

5.1. Isotretinoin

Isotretinoin, a retinoid derivative of vitamin A, is used in the treatment of severe acne. It is the strongest down-regulator of ACE-2 receptors. It has been documented that isotretinoin is a pro-

tease inhibitors and can be taken as a target therapy in COVID-19 (Wu et al., 2020a). Based on the above mechanism, isotretinoin currently tested under phase 3 clinical trials in the adult patients with positive SARS-CoV-2 viral infections. Current outcomes showing there is large difference at the onset of clinical signs and symptoms treated patients with isotretinoin, standard therapy or combined therapy and checked by on a daily basis.

5.2. Corticosteroids

Corticosteroid therapy is only used as supportive care in patients of COVID-19 with refractory shock or ARDS (Wu et al., 2020b). According to WHO, corticosteroids are recommended only for some conditions like asthma, chronic obstructive pulmonary disease (COPD), and septic shock (WHO, 2020b). Earlier studies showed corticosteroids i.e. methyl-prednisolone directly not supported the patients having symptoms of viral-pneumonia in COVID-19 (Jin et al., 2020), only act as an anti-inflammatory and reduces inflammatory mediators i.e. interleukin (IL-7 & IL-8), MCP1, Th1 chemokine, IP10 etc. (Sung et al., 2004; Wong et al., 2004).

Dexamethasone, another cheap and widely steroid drug used in the treatment of many inflammatory disease conditions and disorders like asthma, severe skin allergies, chronic obstructive lung disease and certain cancers. Recently, it has been documented that dexamethasone could be life-saving drug in critically ill patients with COVID-19 (WHO, 2020). A retrospective cohort study showed daily administered of dexamethasone (6 mg upto 10 days) reduces the mortality rate among patients with COVID-19 who needed supplemental oxygen and mechanical ventilation. There is no advantage of dexamethasone observed in patients who did not necessitate mechanical support or/ventilation (Horby et al., 2020).

5.3. Convalescent plasma

It is an antibody-rich plasma, collected from the patients who already have recovered from diseases caused by virus e.g. polio, measles, ebola, H1N1 influenza, hepatitis B, and now currently in SARS-CoV-2 responsible for COVID-19. On May 1, 2020, US FDA permitted issued guidelines to healthcare providers, make ensure the safety and efficacy of investigational product by collecting plasma from recovered patients under demand of public health emergency (Stephen and Hahn, 2020). A newly reports showed that use of plasma therapy in five ventilated coronavirus patients, all patients improved after one week of transfusion. Moreover, this report was not a clinical trial, further research is essential to confirm its potential and managing patients in SARS-CoV-2 infected patients (<https://clinicaltrials.gov/ct2/show/study/NCT04356534>).

5.4. Bronchodilators

Bronchodilators are preferred only as a supportive care for COVID-19 patients associated with COPD, asthma and other respiratory disorders (Lippi and Henry, 2020). Due to concern of safety precautions, both standard nebulizers and metered dose inhalers (MDI) are risky to COVID-19 patients, as it requires opening of ventilator circuit. Regular administration of bronchodilator may be needed, to minimize the virus transmission to others multiple health care patient. In order to alleviate these hazards, Aeroneb Solo (Aerogen©, Galway, Ireland) has been successfully made for COVID-19 patients which continuously delivers medication via inhalation without circuit opening and requires minimal health-care workers for handling (Miller and Epstein, 2020).

5.5. Fibrinolytics

These are the agents that breakdown plasminogen to plasmin on the surface of thrombi, thus produced fibrinolysis (Chapin and Hajjar, 2015). A study was done in seriously unwell patients, already suffered with ARDS and respiratory collapse/failure. Patients administered with alteplase along heparin improves PaO₂/FiO₂ (P/F) ratio momentary approximately by 11–100% (Moore, 2020). Further, detailed studies are required to check its clinical efficacy among large population. Others supportive fibrinolytic agents are also being evaluated for COVID-19 patients e.g. defibrotide (Fabio, 2020).

5.6. Anticoagulants

Coronavirus patients have a higher risk of venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (Porfida and Pola, 2020). Coagulopathy is one of the main reasons of mortality in the majority of COVID-19 patients. A recent report suggested anticoagulant therapy such as low molecular weight heparin (LMWH) administered to 449 patients showed low mortality risk (Kollias et al., 2020). Aspirin is also used as a prophylaxis treatment in case of post-discharge VTE COVID-19 patients (ASH, 2020). Further, additional data needed regarding its efficacy and safety in COVID-19 patients.

6. Conclusions

Due to pandemic of COVID-19 disease, no vaccine or drug is approved to eliminate the virus. Drug development and discovery is broad and extensive process, due to utmost necessity of the treatment, drug repurposing is suitable for treatment of COVID-19 infection. At present, numerous drugs are ongoing clinical trial and tested directly in patients with COVID-19, strict monitoring is mandatory at the time of treatment of patients to assure its safety and efficacy of unknown profile of drugs. Based on the exposed and revealed structure and transmission mechanisms of novel coronavirus, the available treatment option is antiviral, anti-inflammatory & immunomodulatory drugs. This review provides detailed description of all available *in-vitro* & *in-vivo* studies, mechanism, clinical spectrum of disease, symptoms and safety concern profile of currently available treatment and concerning drugs, which are progress under clinical development. In conclusion, while waiting for the most effectual pharmacological treatment with less adverse effects, many trials are currently ongoing and will available around at the end of 2020, according to clinical trials government website. Hope, their consequences will definitely provide us good outcome and help worldwide in significant the greatest approach to cure or treat COVID-19 along with symptoms and complications.

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