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COVID-19: An Update on the Latest Therapeutic Agents

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Abstract: The COVID-19 pandemic has plagued the world for over three years since discovering the causative virus, SARS-CoV-2, in China. The rampant spread of the virus led to the loss of livelihoods of millions across the globe. This public health emergency prompted the rapid development of vaccines and treatments to fight against viral infection. Vaccines against the viral infection started rolling out in late 2020, and the distribution of the vaccines worldwide managed to reduce the symptoms of COVID-19 and prevent outbreaks in local communities. However, COVID-19 infections are still prevalent, with patients suffering from severe symptoms which require oxygen support or mechanical ventilation. Thus, therapeutic agents for COVID-19 play a significant role in reducing the risk of disease progression into severe disease and improving hospitalized patients' clinical outcomes. Existing drugs such as remdesivir, molnupiravir, baricitinib, anakinra, and tocilizumab have been repurposed to treat COVID-19 earlier during the pandemic to meet the urgent demand for treatment. There

are also novel antiviral and immunomodulating treatments (nirmatrelvir plus ritonavir, ensitrelvir, regdanvimab, sotrovimab, and vilobelimab) that were developed during the pandemic to fight against COVID-19 infections. These therapeutic agents have been reported to be effective and safe for use to treat COVID-19 infections of different severity. Nevertheless, continuous surveillance is imperative in ensuring that these treatment methods maintain efficacy and safety profiles in treating COVID-19 caused by different variants of the virus.

Keywords: COVID-19; antiviral; immunomodulator; hyperinflammation; therapeutic agents

1. Introduction

The coronavirus disease 2019 (COVID-19) has plunged the world into a public health and economic crisis since its discovery in late 2019, when it was first discovered during an outbreak of pneumonia in China [1]. Patients infected presented symptoms such as fever, dry cough, fatigue, and occasional gastrointestinal symptoms [2, 3]. Upon further genomic characterization, the pathogen from the outbreak was identified as the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4, 5]. By February 2020, the coronavirus had spread to other countries and confirmed cases outside China were steadily increasing [6, 7]. The virus is highly infectious as it is easily transmitted from an infected individual to close contacts via respiratory droplets [8]. The population at a higher risk of getting infected by the coronavirus are the elderly, male sex, immunocompromised, and individuals with existing comorbidities such as diabetes, cardiovascular disease, hypertension, kidney failure, and chronic respiratory disease [9, 10]. As the virus continued to spread to every corner of the world, the World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020, eleven years after the previous H1N1 pandemic in 2009 [11]. As of April 2023, approximately 762 million confirmed cases and over 6.8 million deaths due to COVID-19 have been reported [12]. The COVID-19 pandemic has put immense pressure on the global healthcare system, particularly in resource-limited countries. In addition to managing many patients with COVID-19, healthcare facilities struggled to provide essential services to the public, e.g., preventive and curative services for communicable and non-communicable diseases [13-16].

At the beginning of the pandemic, world leaders quickly implemented strategies to prevent the spread of the disease, such as travel restrictions, quarantine, wearing of masks in public, contact tracing, and frequent screening for the coronavirus within local communities [17, 18]. Meanwhile, researchers were working towards developing a safe and effective vaccine to fight against SARS-CoV-2. In December 2020, the first vaccine against COVID-19, Comirnaty by BioNTech and Pfizer, received approvals and authorizations for use in several countries [19, 20], thus kickstarting the distribution of COVID-19 vaccines to meet global demands. Following Comirnaty, other vaccines such as Covishield by AstraZeneca, Spikevax by Moderna, Coronavac by Sinovac, Covaxin by Bharat Biotech, Covovax by Novavax, and Jcovden by Johnson & Johnson were also approved for emergency use by WHO [21]. Vaccines

were deployed to reduce the risk of developing severe symptoms when infected with COVID-19 and to prevent the rampant spread of the virus in the community. Moreover, herd immunity can be achieved with mass immunizations with the COVID-19 vaccines to protect individuals who are ineligible to get the vaccines. The increase in vaccine production has resulted in over 13 billion vaccine doses administered worldwide as of April 2023 [12]. As the vaccines continue to be distributed and the virus is under better control than at the beginning of the pandemic, stringent rules regarding travel restrictions, social distancing, and quarantine have been loosened worldwide. The world was slowly recovering from COVID-19, and society was trying to resume a sense of normality pre-pandemic. Although 69.9% of the world has received at least one dose of a COVID-19 vaccine at the time of writing [22], outbreaks are still being reported, and the number of confirmed cases and deaths due to COVID-19 are still fluctuating across continents [23-33].

The available COVID-19 vaccines are not 100% effective at preventing SARS-CoV-2 infections, i.e., individuals who have received their vaccinations may still get infected [34]. They can be asymptomatic or develop common symptoms such as fever, cough, fatigue, sore throat, and sputum production [35]. In moderate cases, the individual may have difficulty breathing or mild pneumonia, while severe pneumonia, acute respiratory distress syndrome, and organ failure can occur in severe COVID-19 infections [36]. These symptoms have a negative impact on the quality of life of those infected. Hence, studies have been done to explore the potential treatment options for COVID-19 infections. In addition, the emergence of new variants of SARS-CoV-2 raises concern as the efficacy of the vaccines and treatments may be altered due to the ability of the virus to evade host immunity [21, 37-40]. Therefore, by understanding the currently available treatments for COVID-19, and their safety and efficacy profiles, healthcare professionals can determine the best option to manage the viral infection based on the patient demographic and disease severity.

2. Mechanism of action of SARS-CoV-2

Coronaviruses are pleomorphic, enveloped particles with a single-stranded positive-sense RNA as their nuclear material. They belong to the family of Coronaviridae and are under the order Nidovirales [41]. The SARS-CoV-2 genome encodes for four structural proteins, nucleocapsid (N) protein, membrane (M) protein, spike (S) protein, and envelop (E) protein and several non-structural proteins. The virus targets the multiciliated cells in the nasopharynx or trachea, or sustentacular cells in the nasal olfactory mucosa, and replicates mainly in the respiratory system of humans [42, 43]. It is suggested that COVID-19-related anosmia is because of the virus targeting the sustentacular cells of the host. Upon exposure to SARS-CoV-2, the S-protein attaches to angiotensin-converting enzyme 2 (ACE2) receptors on the surface of human cells. The S-protein is made up of the S1 subunit, which is responsible for binding to ACE2 receptors, and the S2 subunit mediates membrane fusion [44]. The S2 subunit of the S-protein then undergoes proteolytic cleavages by transmembrane serine protease (TMPRSS2) to facilitate virus entry into the host cells [45, 46]. After entry into the host cell, there is uncoating of the N-protein from the viral RNA genome, fully releasing the viral RNA into the cell cytoplasm [47]. Replication and transcription processes mediated

by replication/transcription complex (RTC) made up of non-structural proteins can occur within the cell. Structural proteins of the virus M, S, and E are subsequently synthesized in the cytoplasm, and nucleocapsids also form in the cytoplasm from the encapsulation of replicated genomes by the N protein. The E-proteins are small membrane proteins that are important in virus assembly, membrane permeability of the virus particle, and virus-host cell interaction [48]. After the assembly of the virions, they are transported out of the infected cells via exocytosis. Stress from viral production on the endoplasmic reticulum within the host cells typically leads to cell death.

Viral exposure of host epithelial cells in the upper respiratory tract is detected by pattern recognition receptors (PRRs) in the cytoplasm, triggering a signaling cascade for the transcription of type I and type III interferons. Toll-like receptors (TLRs) of bystander epithelial cells and local immune cells also detect SARS-CoV-2, thus initiating the production of chemokines and interferons. The paracrine effect of locally produced interferons further enhances the production of chemokines and interferons [49, 50]. The autocrine and paracrine effects of interferons induce an antiviral cellular state by attracting immune cells to the infected site. The development of adaptive B cell and T cell responses is also promoted via the production of cytokines. When the innate or adaptive immune responses fail to clear the viral infection, the virus particles can travel to the lower respiratory tract via inhalation or dissemination along the tracheobronchial tree. The lower respiratory tract can also be the initial site of infection in COVID-19 which can result in infections in the alveoli. Inflammation of the alveoli limits its functionality in terms of gas exchange as SARS-CoV-2 primarily attacks the alveolar type 2 (AT2) cells during infection [51-53]. AT2 cells are responsible for lubrication in the lung by secreting pulmonary surfactants to reduce surface tension in the alveoli during respiration. Moreover, they are the progenitor cells for alveolar type (AT1) that mediate gas exchange [54].

Individuals infected with SARS-CoV-2 can present with no symptoms, but a majority of COVID-19 patients present with mild to moderate symptoms such as cough, fatigue, myalgia, sore throat, and gastrointestinal symptoms [2]. However, as the disease severity progresses, hypoxemia occurs, resulting in dyspnea [55] which can quickly lead to progressive respiratory failure. In severe COVID-19 cases, there is a potential development of acute respiratory distress syndrome (ARDS) [56], characterized as severe hypoxemia and lung infiltration with an acute onset of 7 days upon exposure. In ARDS, inflammation, apoptosis, necrosis, and increased alveolar-capillary permeability damage the pulmonary epithelial and endothelial cells. This is followed by pulmonary vascular leakage, which ultimately results in alveolar oedema and proteinosis, a protein build-up in the alveoli that reduces gaseous exchange, causing difficulty in breathing [57]. Systemic hyperinflammation is often reported in severe COVID-19 with hypoxic respiratory failure and it is characterized by the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor (TNF). During hospitalization due to COVID-19, IL-6 and IL-8 serum concentrations are predictors of disease prognosis. There is also an increased concentration of inflammatory markers such as D-dimer, ferritin, and C-reactive protein (CRP). Severe COVID-19 can also

cause organ damage to the heart, liver, and kidneys which can lead to multiorgan failure, shock, and finally death [58].

The mechanism of action of SARS-CoV-2 has been studied extensively since its discovery to aid in the development of therapeutic agents which can target specific pathways in the pathogenesis of the virus to reverse the negative effects of the infection. However, developing a novel therapeutic agent to prevent or treat COVID-19 can be costly and time-consuming. Therefore, clinical trials have been done since 2020 to repurpose existing drugs for COVID-19. The interventions used in the clinical trials include, antivirals, antimalarials, immune modulators, inhaled gas, antifibrotics, and antioxidants [59]. As of April 2023, there have been approved treatment options that are currently being administered for the treatment of COVID-19 based on the disease severity. This review explores the approved therapeutic agents and provides insights into the safety and efficacy of these interventions.

3. Current therapeutic agents for COVID-19

Extensive research has been done to develop effective treatments with good safety profiles for COVID-19. As the process of developing a novel drug can be challenging and time-consuming, researchers looked to existing drugs for answers given the urgency of the current circumstance. Antivirals such as remdesivir and molnupiravir were found to have antiviral properties which could be advantageous in treating SARS-CoV-2 infections, thus, they have been repurposed to do so. In addition, immunomodulators such as baricitinib and anakinra were previously used in treating rheumatoid arthritis. By studying their mechanism of action and their targeted pathways in the immune system, these drugs were able to reduce inflammation in host cells, making them suitable for the treatment of COVID-19. This review provides an overview of the latest therapeutic agents available to treat COVID-19 (Table 1). and their respective mechanisms of action during treatment (Figure 1).

3.1. Antivirals

3.1.1. Remdesivir

The first drug approved for COVID-19 is remdesivir (Veklury®), which received emergency use authorization in the United States on 1 May 2020 [60]. This was followed by approval for emergency use in other countries, including Japan [61], Taiwan [62], Singapore [63], and Australia [64] in the following months. Remdesivir is a nucleotide analogue prodrug that elicits its activity when metabolizes in the host cell to form a pharmacologically active nucleoside triphosphate [65]. It was first developed to target emerging pathogenic RNA viruses and has broad antiviral activity. It has demonstrated antiviral activity against filoviruses, coronaviruses, paramyxoviruses, and *Pneumoviridae* [66]. Remdesivir targets the viral RNA dependent RNA polymerase (RdRp) of SARS-CoV-2 by competitively inhibiting the binding of adenosine triphosphate (ATP) during the formation of new strands of RNA. This prevents the elongation step in RNA synthesis, ultimately putting a halt to further transcriptional and translational processes for the synthesis of new virions [65]. In addition, it has been suggested that the vehicle used for Veklury®, namely sulfobutylether-β-

cyclodextrin (SBECD), can inhibit the binding of spike proteins to ACE2 receptors, thereby preventing the entry of the virus into host cells [67].

In a clinical study to evaluate the efficacy of remdesivir, it was reported that the antiviral drug could reduce the recovery time from a median of 15 to 11 days in patients hospitalized for COVID-19. The study also found that the intervention was associated with fewer days of subsequent oxygen use for patients who required supplemental oxygen during their hospitalization [68]. In moderate to severe cases of COVID-19, remdesivir can be useful in reducing recovery time, mortality, adverse events, and the need for oxygen support [69]. In adults, remdesivir is given as a single 200 mg dose on the first day via the intravenous route, followed by 100 mg once daily for the rest of the treatment. Remdesivir can also be given to infants who weigh more than 3kg, children, and adolescents. The duration of treatment and dose of Veklury® should also be adjusted based on disease severity, comorbidities, or ongoing concurrent therapies of the patients [70]. Remdesivir is generally well tolerated by patients; however, the most reported adverse events involved the hepatic and renal systems, which included elevated liver enzymes, acute kidney injury, and increased blood creatinine levels [71-73].

3.1.2. Molnupiravir

Molnupiravir, sold under the brand name Lagevrio, was first approved for use in the United Kingdom in November 2021 to treat mild to moderate COVID-19 infections [74]. Molnupiravir has also been authorized for use in other countries, such as the United States [75], Japan [76], Singapore [77], and China [78]. Lagevrio is an oral antiviral prodrug that is rapidly converted to ribonucleoside analogue N-hydroxycytidine (NHC) by host esterases [79]. NHC is then phosphorylated into the pharmacologically active compound, ribonucleoside triphosphate (NHC-TP) which is used by RdRp as a substrate instead of cytidine-triphosphate and uridine-triphosphate during RNA synthesis. Incorporating NHC-TP into the viral RNA induces errors in the viral genome, thus inhibiting further replication [79, 80]. Prior to repurposing molnupiravir for COVID-19, this antiviral has been used to treat infections caused by a range of viruses, including Chikungunya virus, Venezuelan equine Encephalitis virus, Respiratory Syncytial virus, Norovirus, and Influenza A and b viruses, Ebola virus, and human coronaviruses [80].

Jayk Bernal et al. reported that oral treatment of molnupiravir successfully reduced the risk of hospitalizations and deaths in at-risk, unvaccinated adults with COVID-19 [81]. Moreover, a study by Fischer et al. found that treatment of 800mg of molnupiravir twice daily for five days resulted in significantly lower isolation of SARS-CoV-2 by the end of the course of treatment, thus indicating rapid viral RNA clearance by molnupiravir [82]. In addition, multiple studies reported intervention with molnupiravir was well tolerated among participants, with similar incidences of adverse events across all groups [81-83]. Among the most reported adverse events during molnupiravir intervention were diarrhea, nausea, headache, and dizziness [81, 82, 84]. However, it has been shown that administration of molnupiravir in hospitalized COVID-19 patients did not yield clinical benefit [83], thus

indicating that treatment with Lagevrio should be given during early symptom onset to elicit its pharmacological effects effectively. Molnupiravir is given to patients aged 18 years old and above with mild to moderate COVID-19, at 800 mg twice daily for five days via the oral route [85].

3.1.3. Nirmatrelvir and Ritonavir

Nirmatlrelvir is a novel antiviral drug developed by Pfizer that acts as an orally active SARS-CoV-2 3C-like (3CLpro) protease inhibitor [86, 87]. In the generation of new virions, enzymes such as 3CLpro, otherwise known as Major protease (Mpro), play a role in the cleavage and maturation of proteins to facilitate the viral replication process for the generation of new virions. Nirmatrelvir binds directly to the active site of Mpro, thereby hindering the enzyme from processing the proteins needed for viral replication [86, 87]. However, nirmatrelvir is metabolized by the enzyme cytochrome P450 (CYP) 3A, hence ritonavir is added to the formulation to inhibit this process, thereby extending the half-life of nirmatrelvir in the host [88]. The formulation which constitutes nirmatrelvir and ritonavir is known as Paxlovid®, with nirmatrelvir as the antiviral and ritonavir as the pharmacological enhancer. Since December 2021, Paxlovid® has been authorized in countries such as the United States, South Korea, the United Kingdom, Canada, Australia, Europe, and Japan [88].

Paxlovid® is given orally as 300mg of nirmatrelvir with 100mg of ritonavir twice daily for five days for individuals with mild to moderate COVID-19 [89]. It has been reported to effectively reduce the risk of progression to severe COVID-19 in non-hospitalized, symptomatic adults. By day 5 of treatment, the viral load was lower with nirmatrelvir plus ritonavir compared to the placebo group [90, 91]. Adverse events commonly reported with the use of Paxlovid® were dysgeusia, diarrhea, nausea, and myalgia, with no serious adverse events reported [88, 90, 92]. However, ritonavir as a CYP3A inhibitor raises concern for potential drug-drug interactions that may occur with other drugs metabolized through this pathway. For example, the conversion of clopidogrel to its active metabolite can be reduced by ritonavir which leads to insufficient inhibition of platelet aggregation. This increases the risk of blood clot formation, strokes, and heart attacks [93]. Therefore, healthcare professionals need to identify any potential drug-drug interactions between Paxlovid® and the current medications taken by patients to avoid causing harm during treatment.

3.1.4. Ensitrelvir

Enstirelvir (Xocova®) is a novel non-covalent, non-peptidic oral antiviral that targets the Mpro in SARS-CoV-2 developed in Japan by Shionogi in collaboration with Hokkaido University [94]. By targeting Mpro, corresponding inhibitory effects on RdRp can occur, thus hindering viral replication. The discovery of ensitrelvir could overcome issues of low bioavailability due to low cell permeability, low metabolic stability, and low stability in the blood of its predecessors due to its non-covalent, non-peptidic features. In animal studies, Xocova was found to have a long elimination half-life, good oral bioavailability, and it was effective in inhibiting intrapulmonary replication of SARS-CoV-2 in mice [94]. Moreover,

ensitrelvir has is highly selective towards coronavirus proteases, as it did not show any inhibitory effects on human cell proteases even at high concentrations [95]. As the discovery of Xocova is fairly recent at the time of writing, it has only received authorization for use in Japan [96], and it remains an investigational drug outside of Japan.

Clinical trials for Xocova® have yielded promising results, with multiple studies reporting that ensitrelvir treatment has a favorable antiviral efficacy with an acceptable safety profile. Hiroshi et al. showed that intervention with ensitrelvir in mild to moderate cases significantly improved respiratory symptoms and pyrexia which are common symptoms of COVID-19 [97]. Ensitrelvir also decreased the median time for viral clearance by approximately 50 hours with minimal adverse events [98]. A study by Shimizu et al. that included healthy Japanese and white participants also showed that ensitrelvir is well-tolerated as it only elicited mild adverse events that resolved without treatment [99]. Xocova® aims to treat mild to moderate COVID-19 in adults and children above 12 years of age. It is to be given in a 5-day course, starting with a loading dose of 375mg (3 tablets) on the first day, subsequently followed by 125mg (1 tablet) daily [100]. Given the similarities in their mechanisms, Xocova® can be a potential treatment alternative for patients who are allergic or cannot tolerate Paxlovid®.

3.2. Immunomodulators

3.2.1. Baricitinib

Baricitinib (Olumiant®), by Lilly, first gained approval for the treatment of rheumatoid arthritis. Still, its ability to control inflammatory responses via inhibition of Janus-associated kinases (JAK) renders it a potential candidate for treating COVID-19 [101]. During inflammation, cytokines bind to their respective receptors on the cells' surface, triggering the activation of JAK enzymes to phosphorylate recruited signal transducers and activators of transcription (STAT) molecules. The phosphorylated STAT molecules translocate to the cell nucleus for gene transcription, enhancing immune responses [102, 103]. Inhibition of JAK by baricitinib blocks the subsequent JAK/STAT pathway and reduces cytokine signaling, thereby preventing the progression of cytokine storm in COVID-19. In addition, it has been reported that baricitinib also interrupts the passage and intracellular assembly of SARS-CoV-2 into target cells mediated by ACE2 receptors. Baricitinib binds to numb-associated kinases (NAK), AP2-associated protein kinase 1 and cyclin G-associated kinase to prevent viral propagation in host epithelial cells [104, 105].

To support the use of baricitinib in COVID-19, a randomized controlled trial done to determine the efficacy of baricitinib in hospitalized COVID-19 found that treatment with baricitinib reduced the risk of mortality in these patients by approximately 20% [106]. A separate study by Marconi et al, reported similar findings and that treatment with baricitinib had a similar safety profile with standard care alone [107]. It has also been shown that combining baricitinib and other COVID-19 treatments can yield favorable results. A COVID-19 patient, aged 50 with non-Hodgkin lymphoma successfully recovered from

COVID-19 after receiving a combination treatment of remdesivir, baricitinib, tocilizumab, hydroxycholoroquine, and broad-spectrum antibiotics [108]. A separate study showed that combination therapy with baricitinib, remdesivir, and dexamethasone reduced hospitalization and recovery time, with minimum adverse events [109]. Given its efficacy in treating COVID-19, the rheumatoid drug has since been approved for use in Japan [110], the U.S. [111], and Singapore [112]. Baricitinib is currently administered to hospitalized patients of COVID-19 at 4mg once daily as part of an appropriate combination regimen for 14 days or until discharge [113].

3.2.2. Anakinra

Like baricitinib, anakinra (Kineret®) treats rheumatoid arthritis and has been repurposed for COVID-19 in the U.S. and Europe [114, 115]. It acts as an IL-1 receptor antagonist to block the activity of IL-1α and IL-1β to reduce inflammation in the host. In severe cases of COVID-19 where ARDS occurs, IL-1α and IL-1β are the major proinflammatory cytokines that facilitate the recruitment of immune cells and induce the production of secondary cytokines. In ARDS, the damaged epithelial cells release IL-1α causing the recruitment of immune cells and the production of IL-1β. Consequently, a cascade of proinflammatory cytokines secretion is initiated, resulting in hyperinflammation, further exacerbating the infection [116]. From a pharmacokinetics perspective, anakinra has a short half-life and has rapid clearance after drug continuation. This allows for flexible dosing without excessive immunosuppression, and adverse effects such as hepatotoxicity can be better managed [117].

In patients requiring supplemental oxygen and are at risk of developing ARDS, anakinra is given as a subcutaneous injection of 100mg/0.67mL for 10 days [118]. This IL-1 receptor antagonist has been shown to reduce the need for mechanical ventilation, which was evident as 20% out of 15 patients receiving required endotracheal intubation compared to the control group with 66.7%, indicating that the intervention was able to improve the respiratory symptoms of the patients [119]. The improvement in oxygenation in patients allows for earlier recovery, thus shortening the length of hospitalization. Moreover, treatment with anakinra has been shown to reduce the mortality risk in patients with moderate to severe COVID-19 compared to standard care, further supporting drug use [120].

3.2.3. Regdanvimab

Regdanvimab (Regkirona®) is a recombinant human monoclonal antibody (mAb) that targets the receptor binding domain (RBD) of the spike protein of SARS-CoV-2. This neutralizing antibody effectively prevents the binding of SARS-CoV-2 to ACE2 receptors on host epithelial cells, thus inhibiting the virus's entry and stopping viral replication [121]. Regdanvimab is given as a single intravenous infusion of 40mg/kg. First approved in South Korea for treating COVID-19 in 2021, it is now available in Europe and Australia for mild to moderate SARS-CoV-2 infections [122]. The mAb has been indicated for use in mild to moderate COVID-19 as it was shown to significantly reduce the risk of disease progression

to severe infection during hospitalization [123]. Furthermore, a study done in South Korea showed consistent results with previous studies. In the earlier stages of COVID-19, treatment with regdanvimab can reduce the need for additional therapeutic options such as remdesivir, dexamethasone, and supplemental oxygen. Treatment with regdanvimab was generally well-tolerated, and no serious adverse events occurred throughout the study [124]. Regdanvimab has also been reported to be effective against mild to moderate COVID-19 caused by SARS-CoV-2 of the Delta variant [125]. Besides, a retrospective study showed that administering regdanvimab and remdesivir improved clinical outcomes of patients with severe COVID-19. The duration of oxygen supplementation was shortened with the combination of regdanvimab and remdesivir instead of remdesivir alone [126]. On that account, regdanvimab has the potential to be used in conjunction with other COVID-19 treatments to greatly improve the clinical outcomes in severe COVID-19.

3.2.4. Sotrovimab

Sotrovimab, marketed under the brand name Xevudy®, is a recombinant human mAb developed by GlaxoSmithKline that has been authorized for use in mild to moderate COVID-19 in Australia, Europe, the United Kingdom, and the U.S [127]. It binds to a highly conserved epitope in the S protein of SARS-CoV-2, thereby inhibiting the virus from binding to ACE2 receptors. Targeting the highly conserved epitope lowers the risk of developing viral resistance towards sotrovimab [128]. Binding of sotrovimab with high affinity to the ACE2 receptors prevents virus entry into host cells at the first stages of viral exposure. The subsequent viral replication and signaling cascades are prevented after which inflammation can be minimized to avoid developing severe respiratory symptoms and cellular damage in the respiratory system. To achieve effective treatment, sotrovimab is given as 500mg in a single intravenous infusion over 15 minutes in mild to moderate infections. In a study involving 1057 participants, a single dose of sotrovimab was shown to be effective in reducing the risk for hospitalization in high-risk mild to moderate COVID-19 patients and deaths compared to the placebo group [128]. A separate study involving 583 participants had consistent results, with sotrovimab reducing the risk of progression in high-risk patients with mild-moderate COVID-19 and a lowered risk of adverse events with sotrovimab compared to the placebo group [129]. In a rapid review and meta-analysis done by Amani et al., sotrovimab was also found to reduce mortality rates and hospitalizations in patients infected with the Omicron or Delta variants of the coronavirus [130]. All in all, sotrovimab is an effective treatment for mild to moderate COVID-19 which can prevent disease progression and its efficacy is broad enough to cover the newer variants of SARS-CoV-2.

3.2.5. Tocilizumab

Tocilizumab is a recombinant humanized mAb marketed under the brand name Actemra® which has been approved to treat COVID-19 in the U.S. [131], Japan [132], and Australia [133]. The Pan American Health Organization has also made the mAb available to 15 countries in Latin America and the Carribean [134]. Tocilizumab is an IL-6 receptor antagonist as it competitively inhibits the binding of IL-6 to its receptor. This inhibits further

signal transduction by IL-6, reducing subsequent signaling cascades that induce inflammatory responses [135, 136]. It has been shown that there is a significant increase in pro-inflammatory cytokines, such as IL-6, in patients with COVID-19. Therefore, the inhibitory effects by tocilizumab can prevent the initiation of hyperinflammatory responses to improve the symptoms of COVID-19. This can be useful in treating severe COVID-19 as the state of hyperinflammation can be reduced to mitigate the progression to ARDS. The recommended dose for tocilizumab in the treatment of moderate to severe COVID-19 is 8 mg/kg as a single intravenous infusion.

Various studies on the efficacy of tocilizumab in patients with severe COVID-19 found a reduction in the likelihood of progression to mechanical ventilation [137, 138]. The time needed for clinical improvement was also reduced, along with a shorter duration of invasive ventilation [139]. However, one study showed that tocilizumab effectively improved symptoms of severe COVID-19 until day 14. Further, using up to 28 days did not produce significantly better clinical status or lower mortality than a placebo [140]. Therefore, in cases where tocilizumab is administrated, should the symptoms not improve by day 14, an alternative treatment should be considered. On the flip side, a systematic review and meta-analysis by Hariyanto et al. in 2021 found that tocilizumab reduced mortality rates. Still, the severity of the disease and length of hospital stay was not altered [141]. Nonetheless, the review did not standardize the dosing, route of administration, and timing of administration which might have affected the outcomes of their study. Given that tocilizumab had only recently been used to treat COVID-19, further research and clinical trials need to confirm its efficacy and safety.

3.2.6. Vilobelimab

Vilobelimab, a novel anti-C5a mAb is the latest addition to the list of approved COVID-19 treatments by the Food and Drug Administration (FDA) [142]. Marketed under the brand name Gohibic®, it targets C5a, a component in the complement system of patients with severe COVID-19 requiring invasive oxygen support ventilation. During severe SARS-CoV-2 infection, there is an activation of the complement system in the lungs, resulting in the proteolytic cleavage of the complement factor C5. This process generates C5a, an anaphylatoxin, which facilitates the recruitment of myeloid cells to the lungs. These immune cells then secrete pro-inflammatory cytokines, causing a cytokine storm. Prolonged inflammation caused by C5a can lead to neutrophil-mediated viral lung damage [143, 144]. Vilobelimab binds with high affinity to C5a to prevent binding to C5a receptors, thus inhibiting the subsequent signaling cascades, ultimately reducing inflammation and lung damage. A multicentre, double-blind, randomized, placebo-controlled, phase 3 trial showed that vilobelimab could improve the survival rates of patients receiving invasive ventilation. The intervention with intravenous vilobelimab at 800mg effectively decreased C5a concentrations in the vilobelimab group, significantly reducing mortality rates [144]. The clinical trials took place across multiple countries, and vilobelimab was given as an additional therapy to standard care based on the treatment guidelines in various countries. On that account, it is vital to ensure that standard care is already given to the infected patients prior

to administrating vilobelimab. The safety of vilobelimab was also evaluated by Bauer et al. in which the treatment was well tolerated with zero vilobelimab-specific adverse events reported [143]. Nevertheless, as vilobelimab suppresses the activity of the immune system to a certain extent, patients can be vulnerable to bacterial, fungal or viral infections when hospitalized.

Table 1. The various therapeutic agents for COVID-19.

Therapeutic agent	Mechanism of action	Route of administration and dosage	Indication (severity of COVID-19)
Antivirals			
Ensitrelvir (Xocova®)	Protease (3CLpro/Mpro) inhibitor	PO, 375mg on day 1, 125mg once daily on subsequent days for 15 days	Mild to moderate
Molnupiravir (Lagevrio®)	Viral genome disruption via integration into viral RNA genome	PO, 800mg once daily for 5 days	Mild to moderate
Nirmatrelvir and Ritonavir (Paxlovid®)	Protease (3CLpro/Mpro) inhibitor	PO, 300mg nirmatrelvir with 100mg ritonavir for 5 days	Mild to moderate
Remdesivir (Veklury®)	RdRp inhibitor	IV, 200mg on day 1, 100mg once daily on subsequent days	Moderate to severe
Immunomodulators			
Regdanvimab (Regkirona®)	Neutralising antibody against S protein of SARS-CoV-2	IV, Single infusioin of 40mg/kg	Mild to moderate
Sotrovimab (Xevudy®)	Neutralising antibody against S protein of SARS-CoV-2	IV, Single infusion of 500mg	Mild to moderate
Anakinra (Kineret®)	IL-1 receptor antagonist	SC, 100mg/0.67mL for 10 days	Moderate to severe
Baricitinib (Olumiant®)	JAK inhibitor	PO, 4mg once daily for 14 days	Moderate to severe
Tocilizumab (Actemra®)	IL-6 receptor antagonist	IV, Infusion of 8mg/kg	Moderate to severe
Vilobelimab (Gohibic®)	C5a inhibitor	IV, 800mg for maximum 6 doses on day 1, 2, 4, 8, 15, 22	Moderate to severe

*IV: intravenous infusion, PO: oral, SC: subcutaneous injection.

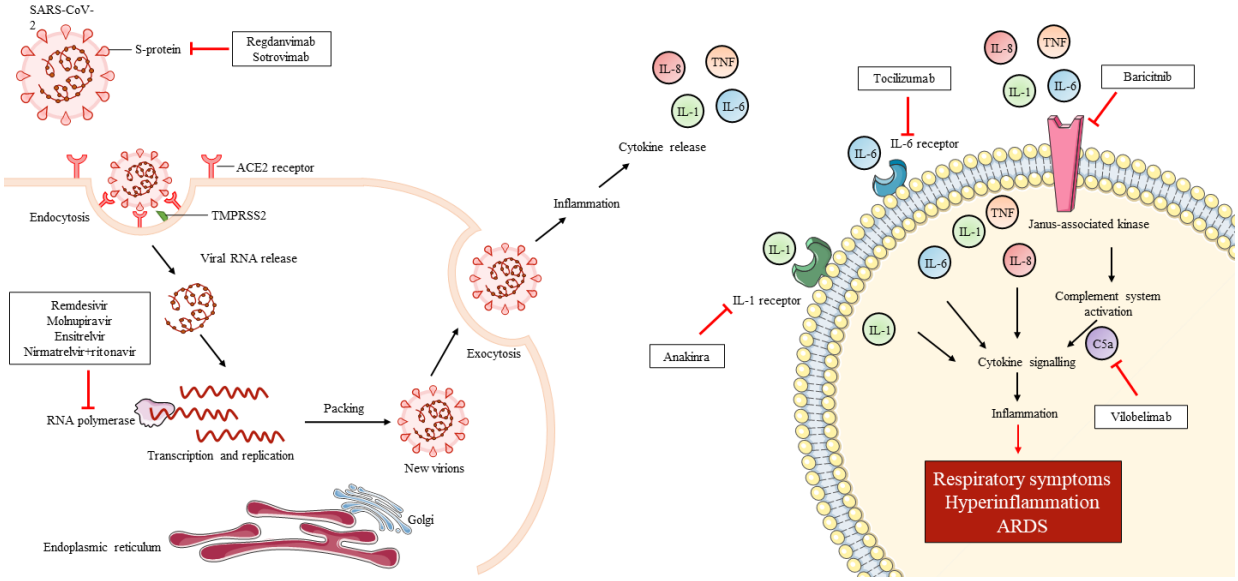

Figure 1. Illustration of the mode of action of SARS-CoV-2 and active site of COVID-19 treatments. This figure was partly generated using Servier Medical Art.

4. Conclusion

COVID-19 is the first documented coronavirus pandemic in the history of humankind. It has negatively affected the global economy and the physical and mental health of the public [145, 146]. The fluctuating numbers of confirmed cases and deaths caused by SARS-CoV-2 remain a concern as there is an underestimation and under-reporting of cases [147, 148]. Developing therapeutic agents such as antivirals and immunomodulators to manage COVID-19 infections provides a positive outlook for society in recovering from the pandemic. COVID-19 treatment should be administered during early symptom onset to reduce viral load, prevent disease progression into hyperinflammatory state, reduce respiratory symptoms, and ultimately prevent death.

Further studies can be done to explore the potential advantages of combining these treatments to achieve significantly beneficial results in COVID-19. Since the initial discovery of SARS-CoV-2, the virus has evolved into several variants: Alpha, Beta, Gamma, Delta, and Omicron. With each evolution, the virus has increased transmissibility and evasion of the host immune system, enabling it to continuously spread worldwide [21]. The increase in selective pressures on the coronavirus can potentially result in the generation of new variants which are resistant to the treatments for COVID-19 that are readily available. Moghadasi et al. found that mutations in Mpro of SARS-CoV-2 confer resistance towards nirmatrelvir and ensitrelvir [149]. In addition, the efficacy of the antivirals towards different variants of the coronavirus varies. For instance, antiviral drugs such as remdesivir and molnupiravir target the RdRp of SARS-CoV-2, but the mutation of RdRp in the Omicron variant potentially

decreases the efficacy of these drugs against the variant [150]. It is currently unclear what magnitude of resistance in the virus will render treatment failure. Therefore, genetic surveillance on emerging variants of SARS-CoV-2 and strategies to minimize the spread of viral resistance should be implemented to manage COVID-19 effectively. Moreover, research is ongoing to develop new therapeutic agents to treat COVID-19 at different stages of disease. With the equal distribution and effective use of vaccines and treatment for COVID-19 worldwide, there is emerging hope that society can transition into the endemic phase of COVID-19 at a global scale in the foreseeable future.

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