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Review Article

Exploiting SARS-CoV-2 Replication Cycle for COVID-19 Therapies

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Abstract

The tail end of 2019 saw the identification of SARS-CoV-2 as the causative virus of COVID-19, which was followed in March 2020 by the assignment of pandemic status to this disease. COVID-19 has exacted terrible tolls on the lives, health, and economies of nearly every country on the planet since then. The major focus in fighting the pandemic has been on the fast development and deployment of vaccines. Despite the undoubted success of vaccines, a few COVID-19 cases will continue to be encountered that require medical interventions. The field of pharmacological treatment has been largely set aside with no emerging specific and effective therapies that are tailored and designed to combat SARS-CoV-2. This narrative review looks at pharmacological therapies that target parts of the viral replication cycle or counteract the body's response to the presence of the virus. A literature search was undertaken using PubMed and Google Scholar databases to identify relevant medicinal therapies and clinical studies for the management of COVID-19.

Keywords: COVID-19 treatments, SARS-CoV-2 replication, SARS-CoV-2.

استغلال دوره تكرار فيروس الكورونا المستجد لايجاد علاجات لمرض كوفد-١٩

الخلاصة

شهدت نهاية عام 2019 التعرف على SARS-CoV-2 باعتباره الفيروس المسبب لمرض COVID-19. تبع ذلك، وفي شهر آذار من عام 2020 أعتبار هذا المرض حالة وبائية عالمية. منذ ذلك الحين، أدى مرض COVID-19 الى خسارة كبيرة في حياة الكثير من البشر بالأضافة الى تدهور أقتصاد كل دول العالم تقريبا. كان التركيز الرئيسي في مكافحة الوباء يتركز على التطوير السريع للقاحات مناسبة وانتاجها بكميات كبيرة. وعلى الرغم من النجاح المؤكد لهذه اللقاحات، سوف تستمر مواجهة عدد قليل من حالات COVID-19 التي تتطلب تدخلات طبية. الا ان التركيز على تطوير وانتاج اللقاحات قد ادى الى وضع مجال العلاج الدوائي جانبا الى حد كبير مع عدم وجود علاجات ناشئة محددة فعالة ومصممة خصيصا لمكافحة SARS-CoV-2. تبحث هذه المراجعة السردية في العلاجات الدوائية التي تستهدف أجزاء من دورة تكرار الفيروس أو تتصدى لاستجابة الجسم بسبب وجود الفيروس. لهذا الغرض، تم أجراء بحث باستخدام قواعد بيانات PubMed و Google Scholar لتحديد العلاجات الطبية والدراسات السريرية ذات الصلة بالتعامل مع COVID-19.

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INTRODUCTION

A number of the Coronaviridae viruses are constantly circulating in the human population, causing mild respiratory symptoms. However, in 2002, a more virulent member emerged in humans, causing severe acute respiratory conditions and being given the name SARS-CoV. This virus resulted in 8096 cases and 774 deaths before it was brought under control. No specific therapies or vaccines were developed against this virus and its spread was only halted using conventional control measures [1-3]. In 2019, a new acute respiratory disease was diagnosed in China and termed COVID-19 (coronavirus disease-19, after the year 2019 when it was first diagnosed). Soon after, the causative agent for this condition was found to be a virus and a member of the Coronaviridae family, which subsequently was given the name SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) [3]. The fast worldwide spread of this virus prompted the World Health Organisation (WHO) to classify COVID-19 as a pandemic in March 2020. Since then, this pandemic has reached nearly every corner of the globe and necessitated wide-reaching health controls with economic and social implications [4]. Up to December 3rd 2021, the time of writing this paragraph, there had been an estimated 263,563,622 cases and 5,232,562 deaths, with a mortality rate of around 5% (WHO website 2021 and reference [5]). To protect individuals and reduce the risk of infection, vaccine development was undertaken. This has led to the speedy and successful introduction of several vaccines for COVID-19 with excellent protective efficacy. However, although vaccination is an effective approach for prevention, current COVID-19 vaccines are based on the original (wild type-WT) virus first encountered in China, and given the relatively high mutational rate of SARS-CoV-2, the vaccine will no longer elicit such a good immune response [6,7]. Moreover, immunity can decline with time, thus requiring re-vaccination for continued protection. Nevertheless, to halt the advancement of the COVID-19 pandemic, global vaccine development programs were initiated. The fruits of these programs are now obvious and vaccination is seen to be weakening the link between infection with SARS-Cov-2 and hospitalization/mortality. However, SARS-Cov-2 is predicted to remain circulating in humans and cause cases of severe COVID-19 well beyond the end of the pandemic. This will necessitate administering therapeutic agents to patients who become ill with COVID-19. Unfortunately, the scientific community is still searching for that magic medicine that can fight and eliminate the virus following its successful invasion of the body [8]. Numerous studies have been published since the start of the pandemic to help in the fight against SARS-CoV-2. A wealth of information has been accumulating in this respect, and no single review article can cover the subject adequately. This article aims to give a simplified view of the SARS-CoV-2 replication cycle and highlights the various steps that were exploited to reduce its morbid impact. The review will focus on treatment options connected to the replication of the virus and not on the prevention strategy and the excellent gains made through the successful deployment of vaccination programs.

SARS-CoV-2 structure and genome

SARS-CoV-2 is an enveloped positive-sense (translatable) single-stranded RNA virus that measures 65 nm to 125 nm in diameter [9-11]. The virus has crown-like spikes on its outer surface (Figure 1) made up of the Spike protein (S). In addition to the S protein, it has three other main structural proteins, including the envelope protein (E), the membrane protein (M), and the nucleocapsid protein (N).

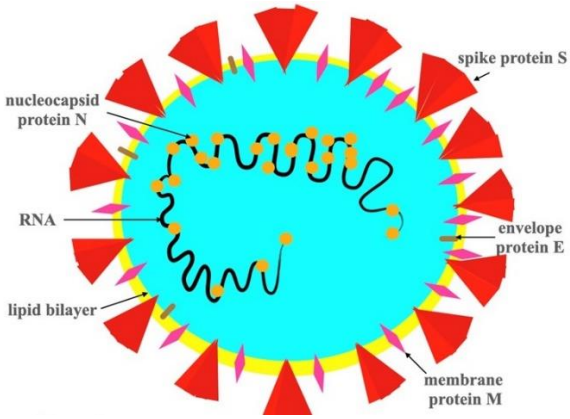

Figure 1: SARS-CoV-2 structure.

These structural proteins share around 90% amino acid sequence identity with SARS-CoV except for the S protein, which diverges and shares only 73% sequence identity [12,13]. The genomic material (RNA) is housed inside the assembled structure. The mature virus particle, often referred to as a virion, will surround itself with a lipid bilayer derived from the infected host when exiting the cell. The genome size is about 29.9 Kb for the original variant, first discovered in China, as a (+) ss-RNA molecule with a 5′ cap and a 3′ poly (adenine-A) tail [14,15]. These features allow the genomic RNA molecule to act as a functional messenger mRNA for translation once it is released into the cytosol. Twenty-nine different proteins are encoded by the genomic RNA and of these, only four make up the external structure and the remainder participate in the replication cycle [16]. The spikes protrude from the viral surface to facilitate binding to the host cell's angiotensin-converting enzyme 2 (ACE2) receptors. The S protein is crucial for the attachment of the virus to cell-surface receptors and is often selected for the development of vaccines against SARS-CoV-2 [17]. Three molecules of the S protein (homotrimer) come together to form a single spike. The full size of a single S protein is 1273 amino acids in the form of two functional segments termed S1 and S2 [18]. These segments, S1 and S2, are separated by a particular sequence of four amino acids (proline, arginine, arginine and alanine) to enable cleavage of the spike protein at this junction by host protease enzymes upon cell entry. The acquisition of a cleavage site has been proposed as a key event in the

SARS-CoV-2 evolution, enabling it to overcome species barriers [19–21]. The S1 subunit is further subdivided into two domains: An N-terminal domain and a C-terminal domain. There are 211 amino acids (amino acids 319 to 529) at the C-terminal that act as a receptor binding domain (RBD), which has a crucial role in viral entry into the cell as it engages the host receptor. Part of the RBD is called the receptor binding motif (RBM) between amino acids 437 to 509 and mediates the actual contact with the ACE2 receptor [18]. The S2 subunit mediates subsequent membrane fusion, thus enabling the virus to enter the host cytoplasm. Currently, the S protein is the antigen of choice in the development of vaccines against COVID-19 as it enables the virus to enter the cells and is surface-exposed [17]. The envelope protein (E) is the smallest protein in the structure, containing about 75 amino acids. It forms an ion channel in the viral membrane and participates in viral particle assembly [22,23]. The membrane protein (M) plays a role in determining the shape of the virus particle envelope and can bind to all other structural proteins. Binding to the M protein helps to complete the viral assembly and provides a distinct shape to the virus. The M protein is 222 amino acids in size [22,23]. The nucleocapsid protein (N) is a relatively large protein made up of around 419 amino acids and provides a critical role in viral genome packaging. It is a dynamic and disordered protein which is structurally bound to the single-stranded RNA of SARS-CoV-2 [23]. It has further functions during the replication cycle and cellular responses. The N protein is highly immunogenic and expressed abundantly during infection, making it a possible candidate for the development of vaccines and serological assays [24]. Following SARS-CoV-2 infections, the body actually makes the most antibodies against this protein and not against the spike protein [25]. However, the way these N protein antibodies protect against future infections remains a mystery.

SARS-CoV-2 REPLICATION CYCLE

SARS-CoV-2 enters its human host mainly through the nasopharyngeal cavity. Some viral particles will randomly collide with cells lining the upper respiratory tract as a result of breathing and inhalation, and some may be sucked down into the lower respiratory tract as a result of breathing and inhalation. Mild electrostatic attractions might play a part in allowing a few of the viral particles to stick to the membrane of target cells. However, this on its own does not necessarily lead to viral cell entry [10,18,26]. The strategy for SARS-CoV-2 to enter host cells relies on the engagement of its S protein with the host cell-surface receptors. It involves the direct binding of the RBD of the S1 subunit with the angiotensin-converting enzyme 2 (ACE2) receptors of the epithelial cells in the nasopharynx [27]. This is usually followed by the activation of the S protein fusion activity, which requires prior proteolytic cleavage at two sites [12]. The first site is at the S1/S2 junction, which leads to structural changes in the "spring-loaded" S2 subunit, placing it in the "ready-to-fuse" state [22,28]. This cleavage also separates S1 from S2, though they remain non-covalently linked. The second cleavage site is at S2' (Figure 2), which drives the fusion of the viral and cellular membranes, thus facilitating the release of the viral genome into the cytoplasm [29].

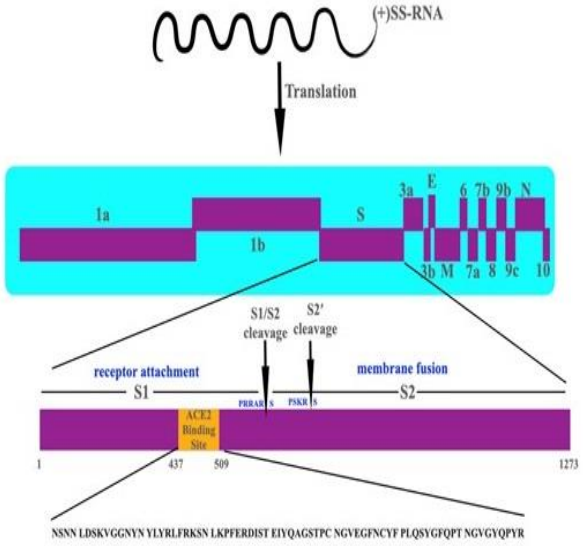

Figure 2: A schematic representation of the translation SARS-CoV-2 genome. The diagram illustrates the translation of the genomic material of the virus (positive sense single-stranded RNA, (+) ss-RNA). 1a: polyprotein1a, 1b: polyprotein1b. The structural proteins are S: spike, E: envelope, M: membrane and N-nucleocapsid). The non-structural proteins are 3a, 3b, 6, 7a, 7b, 8, 9b, 9c and 10.

The proteolytic cleavage of the S protein is accomplished by the host cell-surface protease, the transmembrane protease serine 2 (TMPRSS2) enzyme at S1/S2/ and at S2'. This enzyme, TMPRSS2, has an important and highly conserved role in the pathogenesis of COVID-19. This mode of entry into the host cell is termed "early entry" as it is also possible for the virus to enter by a slightly different process through endocytosis using host proteases such as cathepsins L/B in what is conveniently called "late entry" [30,31]. The "late entry" mode still uses ACE2 receptors for attachment, but fusion to the cell membrane is facilitated by cathepsins L/B instead of TMPRSS2 [30]. Within the endosome, the low pH activates cathepsins and facilitates cleavage at S2′. Almost all of the amino acid residues in the RBD of SARS-CoV-2 are not conserved [32], and the virus has 10–20 times the binding efficiency to ACE2 compared to that of SARS-CoV [33]. Possible reasons for this are the presence of unique salt-bridge interactions between S and ACE2 in SARS-CoV-2 as well as a polybasic site at the S1/S2 junction. The latter site contains a stretch of amino acids having a Furin recognition motif, which could be cleaved by host Furins in producer cells [20,27]. This pre-cleavage event could potentiate the membrane fusion process of SARS-CoV-2 with the host-cell membrane. Cleavages of the S protein at either S1/S2 or at S2′ or both are associated with viral entry depending on cell type. The multibasic amino acids at the S1/S2 cleavage site can be cleaved by the abundant Furins

proteases, which appear to extend the viral tropism of SARS-CoV-2 [20,27,34]. After fusion of the S protein with the ACE2 receptor, there is a subtle conformational change that allows the virus to enter the host cell and to release the N protein together with the RNA into the cytoplasm [35,36]. The viral genome is a single-stranded positive sense RNA, which implies that it is ready to be translated by the host machinery into the appropriate proteins. The ribosome of the host cell usually scans the mRNA from the 5′ end during translation and has evolved to allow one protein to be made from one mRNA. The way SARS-CoV-2, and other coronaviruses in general, circumvent it is through the production of a large polyprotein, which is subsequently processed into smaller proteins, as well as the transcription of several sizes of subgenomic mRNAs [14,37]. All of the non-structural proteins (nsps) are encoded in two open-reading frames (ORFs), namely ORF1a and ORF1ab, and these two ORFs alone span around 65% of the genome. ORF1a and ORF1ab are translated into polyprotein 1a (pp1a), which contains nsps 1–11, or a longer polyprotein 1ab (pp1ab), which contains nsps 1–16 [38]. Translational skipping depends on whether a stop codon at the end of ORF1a is recognized or not. If it is recognised, pp1a will be synthesised, whereas if it is bypassed, pp1ab will be produced. The bypassing event occurs through a frameshift where the ribosome does a –1 shift at the ORF1a/ORF1b junction [29]. Frameshifting is triggered by the presence of a slippery sequence UUUAAAC followed by a pseudoknot structure, and the disruption of this structure affects the frameshifting efficiency [39,40]. It is thought that the virus keeps a precise ratio of pp1a/pp1ab optimal for infectivity and replication, and this particular area was explored as a possible drug target [41-43]. To liberate individual nsps, pp1a and pp1ab are proteolytically processed via cis (autoproteolysis) and trans means by the encoded proteases. The nsp3 contains the papain-like protease (PLpro) and the nsp5 contains the chymotrypsin-like protease (3CLpro). 3CLpro cleaves all nsps downstream of nsp4 and is thus referred to as the main protease. Inhibitors of 3CLpro and PLpro are potential drugs for COVID-19. The other ORFs in the genome encode the remaining structural and accessory proteins. A group of these translated non-structural proteins, including nsp12 (RNA-dependent RNA polymerase, RdRp), nsp13 (helicase), nsp7 and nsp8 come together to form what is known as the replication/transcription complex (RTC) [44], which undertakes to transcribe more copies of the viral genomes (Figure 3). The RNA-dependent RNA polymerase, which is the core of the RTC, comprises three subdomains, namely finger, palm and thumb subdomains. The nsp7 binds to the thumb subdomain and the nsp8 binds to the thumb and finger subdomains [45], and by doing so, they significantly improve the binding of RdRp to the RNA. The RTC participates in the transcription of the genomic (+) ss-RNA into (-) ss-RNA and further into RNA molecules of varying lengths (subgenomic RNAs, sgRNAs), including the full-length "genome-ready" RNA.

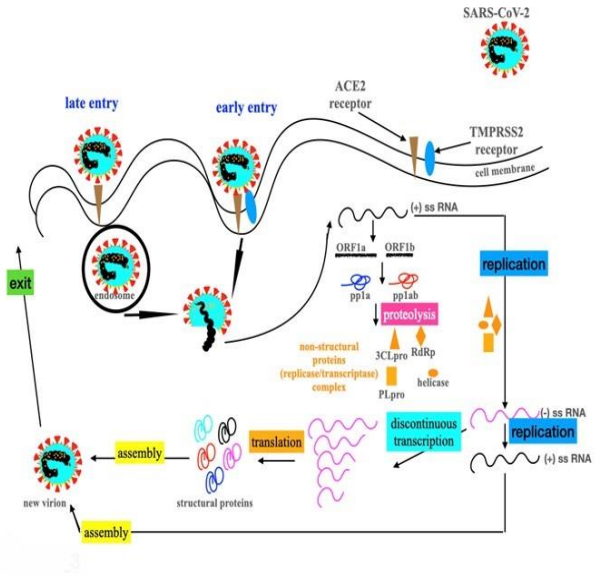

Figure 3: The replication cycle of SARS-CoV-2. ACE2: angiotensin converting enzyme 2, TMPRSS2: transmembrane protease serine 2, (+) ss RNA: positive sense single-stranded RNA, (-) ss RNA: negative sense single-stranded RNA, ORF1a: open reading frame 1a, ORF1b: open reading frame 1b, pp1a: polyprotein 1a, pp1ab: polyprorein 1ab, 3CLpro: 3 chymotrypsin-like protease, PLpro: papain-like protease.

The latter can be incorporated into the assembly of the new virions. The RTC also helps in rearranging the endoplasmic reticulum (ER) to form double-membrane vesicles, which are involved in the regulation of replication and transcription of the virus's subgenomic RNAs (sgRNAs). The translation of sgRNA results in the formation of structural and accessory proteins which are inserted into the ER and then moved to the ER–Golgi intermediate compartment (ERGIC) for viral budding [38]. Following successful virion assembly, the virus is then released from the infected cell via exocytosis.

Taking advantage of the SARS-CoV-2 replication cycle for therapies

Generating protective immunity, through vaccination, against SARS-CoV-2 has been the major focus in the fight against this virus [46,47]. However, the different vaccine technologies and platforms are outside the scope of this review, which focuses only on pharmacological treatments. To this end, all virus proteins can be potential targets for the treatment of COVID-19. Additionally, a few of the host proteins that are essential for the viral life cycle and are reasonably dispensable for the normal functioning of the cell can also be possible targets. The current pandemic triggered an unprecedented number of CTs on repurposed and investigational molecules to evaluate their efficacy and safety for the treatment of COVID-19. All of these molecules are thought to interfere with the replication cycle of SARS-CoV-2, from entering the host through attachment and cell entry to replication and release, together with the consequences of the viral presence on the host immune system. For simplicity, the molecules targeting the SARS-CoV-2 replication cycle and host response in this review will be classified into two main

categories. The first category is that of therapies acting primarily before cell entry, and the second category is that of treatments acting after cell entry.

Therapies acting primarily before viral cell entry

An obvious choice of therapy is to intercept the virus before entering the cell and initiating its replication cycle, which, of course, is the foundation of vaccination. However, immune escape can happen, and the virus may overwhelm the human defences and be in a position to enter the cells in sufficient numbers to cause an infection. To counteract this, pharmacological interventions are required, and those primarily acting before the virus makes its way to the inside of the cell are discussed in the sections below (Figure 4).

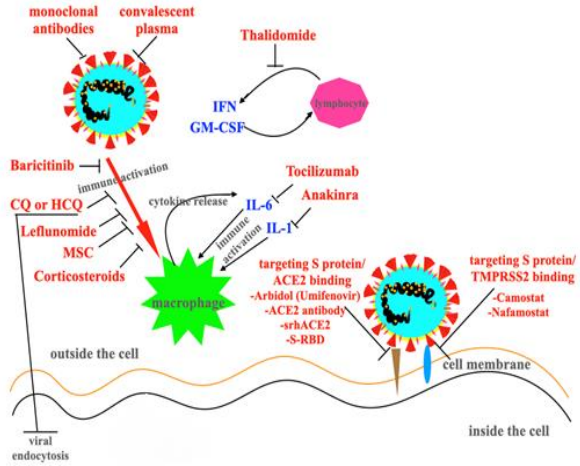

Figure 4: COVID-19 therapies acting primarily before viral cell-entry. IFN: interferon, GM-CSF: granulocyte-macrophage colony-stimulating factor, IL-1: interleukin 1, IL-6: interleukin 6, CQ: Chloroquine, HCQ: Hydroxychloroquine, MSC: mesenchymal stem cells, S: spike, srhACE2: soluble recombinant humanised angiotensin converting enzyme 2, SRBD: spike receptor binding domain.

Convalescent plasma

Convalescent plasma (CP) represents a rich source of multiclonal antibodies recovered from patients who have had COVID-19 infection. Any benefits of antibody treatments would be mainly observed within the first few days of infection when the level of the virus is at its peak and the immune response has not yet been sufficient [48]. Convalescent plasma has been used in previous viral pandemics [49-52] and appeared initially to have been a potential therapy for severe cases of COVID-19 with no serious side effects [53-55]. However, there are concerns regarding the dose and the need for standardisation due to varying antibody titres [53,54,56]. Several studies were carried out to assess the value of employing CP in the treatment of COVID-19, and only a select few are mentioned here. The results of these investigations are largely inconclusive, and it is often difficult to isolate the effect of CP when other therapies are also given in the intervention group. In one small study, six patients with COVID-19 were treated with convalescent plasma, and the results showed a reduction in disease-related symptoms without side effects [57]. In a larger study that used 20,000 COVID-19 patients, convalescent plasma was judged effective and safe [58]. However, another limited study on six patients found that convalescent plasma treatment in patients with severe COVID-19 could not reduce mortality [59]. Moreover, another open-label randomised clinical trial using CP that was carried out in several centres involving 103 severely-ill COVID-19 patients had to be terminated as no significant difference in 28-day mortality compared to standard therapy was obtained [60]. A new report on the results of the REMAP-CAP trial, where 2011 critically-ill COVID-19 patients were recruited to assess the efficacy of CP, concluded that CP had a low probability of providing improvement in the number of organ support–free days [61]. There is a lack of evidence supporting the routine use of CP, but the therapy could be useful in specific patient populations and disease severity [62,63]. Nevertheless, given that alternative effective therapies for COVID-19 are not yet available, CP is currently approved for critically ill COVID-19 patients in many countries around the world.

Monoclonal antibodies against the spike protein

Human monoclonal antibodies (mAbs) that neutralise SARS-CoV-2 and its variants are attractive therapies [64]. These antibodies are predicted to reduce viral loads and prevent severe illness and hospitalisation. The S protein is, by far, the primary target of mAbs. The S protein exists in two main conformations; the "up" state or the "down" state [65]. Since there are three monomers of the S protein per spike, the spike conformations will take one of four sub-conformations and these are (a) all three monomers are "down", (b) one monomer is "down" and two are "up", (c) two monomers are "up" and one is "down", and (d) all three monomers are "down" [66]. Different mAbs can have different effects depending on the type of spike's sub-conformation they best bind to. Currently, eight mAbs have been approved by the food and drug administration (FDA) under an emergency use authorization (EUA) to treat non-hospitalized patients with a high risk of severe COVID-19. These eight mAbs are Bamlanivimab, Etesevimab, Casirivimab, Imdevimab, Tixagevimab, Sotrovimab, Cilgavimab, and Regdanvimab. Bamlanivimab + Etesevimab (REGEN-COV2 antibody cocktail) and Casirivimab + Imdevimab (REGEN-COV2 antibody cocktail) are two popular combinations for extending the antibody range of binding and thus its action [66]. Cohen *et al*. found that Bamlanivimab monotherapy, compared to a placebo, reduced the risk of COVID-19 in residents and staff in assisted living facilities [67]. In two animal models (Rhesus macaque and golden hamsters), prophylactic Casirivimab-Imdevimab reduced viral load and limited disease progression, indicating possible human therapeutic potential [68]. This combination later revealed a greater reduction in viral load for patients whose immune response had not yet started or at a baseline viral load [69,70]. A randomised CT (BLAZE1 study), including over 1000 participants,

compared Bamlanivimab+Etesevimab with a placebo [71]. The group that received that combination showed a 70% relative reduction and a 5% absolute reduction in COVID-19 related hospitalisation or death compared to those on a placebo [72]. Ge *et al*. very recently identified a potent antibody called P2C-1F11 that most closely mimics the binding of SARS-CoV-2 S protein to the ACE2 receptors. This offers the potential for potent neutralization of the virus before cell entry [73].

Baricitinib

Baricitinib is a small molecule inhibitor of Jak1 and Jak2 tyrosine kinases (members of the Janus kinase family). These are non-receptor intracellular tyrosine kinases that transduce signals mediated by cytokines via the JAK-STAT pathway. This pathway has been recognised as a key driver of several inflammatory diseases, and its inhibitors are predicted to have anti-inflammatory effects [74]. Baricitinib is one such inhibitor that has been successfully used for the treatment of mild and severe rheumatoid arthritis. In addition to its anti-inflammatory properties, Baricitinib may prevent SARS-CoV-2 cell entry by inhibiting AP2-associated protein kinase 1 (AAK1), making it a promising candidate for COVID-19 treatment [75,76]. A small non-randomised trial using Baricitinib for the treatment of COVID-19 showed significant improvements in disease outcomes [77]. However, the results of this trial were not considered conclusive due to the small sample size and trial design. A larger multicentre retrospective study comparing Baricitinib together with Lopinavir-Ritonavir combination (often referred to as Lop/r) versus Hydroxychloroquine (HCQ) plus Lop/r showed that the Baricitinib group had lower intensive care need and mortality as well as a significant decline in C-reactive protein and IL-6 (interleukin-6) [78]. Another study comparing the effects of Baricitinib plus corticosteroids against corticosteroids alone found that the Baricitinib group had better improvement in respiratory function [79]. Other studies [80,81] suggested that Baricitinib could be clinically useful in reducing hyper-inflammatory reactions in some COVID-19 patients. The results of two large multicentre trials are now available. The first trial is called COV-BARRIER and was a double-blind, placebo-controlled randomised study to assess the efficacy and safety of Baricitinib for the treatment of COVID-19 hospitalised patients [82]. The primary outcome of this trial was the proportion of patients receiving ventilation or dying. COV-BARRIER trial showed no statistically significant difference in the primary outcome between Baricitinib or a placebo. However, the Baricitinib group had a significantly lower 28-day mortality compared to the control group. The second trial is called ACTT-2, which is a double-blind, placebo-controlled, randomised study comparing Baricitinib plus Remdesivir against a placebo plus Remdesivir [83]. This trial obtained a significantly shorter time to recovery from COVID-19 in the Baricitinib treated group. Therefore, the ACTT-2 trial suggested benefits in the time needed to recover but not in mortality, while the COV-BARRIER trial failed its composite primary endpoint and only found benefits in mortality. A meta-analysis of the two trials found potential benefits in terms of 28-day mortality and mechanical ventilation risk [74]. In light of the benefit observed in the ACTT-2 trial, the FDA issued an EUA for Baricitinib plus Remdesivir for hospitalized COVID-19 patients. Baricitinib, similar to corticosteroids, may hamper virus clearance through its immunomodulatory action. In summary, Baricitinib may be effective in hospitalised COVID-19 patients requiring oxygen therapy, especially those receiving non-invasive ventilation or high-flow oxygen therapy. However, given the mixed results of the two large randomised clinical trials, the exact benefits of Baricitinib need to be confirmed by further studies.

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are weak aminoquinoline bases with an established clinical history. Chloroquine is an antimalarial drug, and HCQ is an analogue of CQ for the treatment of autoimmune diseases, including rheumatoid arthritis. They were widely considered for the treatment of COVID, particularly during the early phase of the pandemic [62]. Both CQ and HCQ increase endosomal pH, thus inhibiting the fusion of SARS-Cov-2 with the cell membrane of the host cell and inhibiting viral release into the cell. They also obstruct the terminal glycosylation and proteolytic processing of ACE2 receptors [84,85]. Both CQ and HCQ also inhibit cytokine production and possess an immuno-modulatory action mediated by several mechanisms (see Fig. 4). All of these encouraged speculation on the use of HCQ to treat COVID-19. Previously, there were mixed results regarding the antiviral activity of HCQ against other viruses. Liu *et al*. reported that HCQ is effective in vitro against SARS-CoV-2 infections [86]. In an uncorroborated study on 100 COVID-19 patients, it was found that CQ is effective in the treatment of pneumonia associated with this disease [87]. Also, in an open-label non-randomized French study using 36 patients with COVID-19 (20 were given HCQ and 16 were acting as controls), Gautret *et al*. reported improved virological clearance with HCQ compared with control [88]. In this study, the addition of Azithromycin to the treatment of six patients resulted in better viral clearance compared with HCQ monotherapy. However, this study had major limitations, including the small sample size. Later on, a pilot observational study on COVID-19 patients conducted by the same group [89] reported a rapid fall in nasopharyngeal viral load and a shorter stay in intensive care following the use of a combination of hydroxychloroquine and Azithromycin. Most other clinical studies have not found HCQ to be effective in the treatment of COVID-19. This lack of supporting data has weakened the argument for using CQ or HCQ in the treatment of COVID-19, which led the FDA to withdraw its EUA in June 2020, three months after issuing it. There is clear information pointing to the

ineffectiveness of CQ and HCQ (alone or in combination with Azithromycin) in treating COVID-19 [62,90].

Leflunomide

Leflunomide is an isoxazole derivative and inhibitor of dihydroorotate dehydrogenase (DHODH) with broad-spectrum antiviral activity, including SARS-CoV-2 [91,92]. The compound has been used for the treatment of rheumatoid arthritis and psoriatic arthritis [93,94]. Leflunomide directly targets the host de-novo pyrimidine synthesis enzyme DHODH to cut off intracellular pyrimidine resources in a manner that is not affected by the proof-reading activity or viral mutations. [92]. Hu *et al*. in a small-scale open-label clinical trial, found that patients treated with Leflunomide had a shorter viral shedding time (median of 5 days) compared to control (median of 11 days) and showed a significant reduction in C-reactive protein levels [92]. In a slightly larger prospective controlled open-label trial, Wang *et al*. discovered that Leflunomide treatment (in combination with interferon IFNγ2a) was not associated with a reduction in viral shedding time when compared to interferon treatment alone [95]. Moreover, patients given Leflunomide did not have a substantially shorter length of hospital stay compared to patients with interferon alone.

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are self-renewing, multipotent stem cells that can migrate to any part of the body where they modulate an immune response or differentiate into several cell types [96-98]. They can be isolated from peripheral blood, umbilical cord, adipose tissue, as well as bone marrow and can be expanded in vitro, under certain conditions [98]. Mesenchymal stem cells may present a therapeutic option to control hyper-inflammatory responses to viral infections. Their safety and efficacy have been demonstrated in clinical trials for immune-mediated inflammatory diseases, as well as influenza-infected animal models and humans, and they appear to be a promising candidate for reducing inflammation, assisting lung-tissue recovery, and lowering mortality [99-102]. A major challenge with their use remains the standardisation of the product. So far, there are several small clinical trials and case reports highlighting their usefulness in the management of COVID-19 and indicating that MSC can ameliorate disease severity and help reduce the need for ventilators [103,104].

Corticosteroids

Corticosteroids (CSs) are widely used as standard treatments for inflammatory disorders. The severe inflammation that is often seen with COVID-19 infections makes them good candidates to consider in the management of this disease. In addition to their immunosuppressive action, CSs display potent anti-inflammatory properties, suppress exudative fluid in lung tissues, promote absorption of inflammasome and prevent further alveolar damage [105]. Through these mechanisms, CSs can relieve hypoxemia and effectively protect the lungs by preventing further progression of respiratory insufficiency [106]. Corticosteroids can also reduce body temperature and alleviate the effects of hyperthermia [107]. Several meta-analyses of clinical trials where corticosteroids were used in the treatment of COVID-19 concluded that these drugs are beneficial in patients and can curb the overwhelming inflammation [74,108-109]. However, corticosteroids may also induce immunosuppression and further aggravate the infection. Whether these drugs should be used routinely for COVID-19 treatment has been debated since the start of the pandemic. The RECOVERY trial shed a little light on this matter [112]. In this trial, dexamethasone was used as the corticosteroid and was found to be associated with a 17% reduction in 28-day mortality. Dexamethasone also reduced the risk of mechanical ventilation by 21%. These results were further validated by a meta-analysis of 7 RCTs which suggested that corticosteroid treatment resulted in a marked reduction in 28-day mortality for critically ill patients [113]. Sub-group analysis of the RECOVER trial indicated that the mortality benefits are better in patients receiving CSs after 7 days of symptom onset. This is to be expected since the direct viral injury appears to dominate the early phase of the infection while the immune insult occurs later in the second stage. Moreover, it has been reported that ACE2 expression decreases with the use of inhaled corticosteroids [114]. This outcome needs further validation and assessment with systemic CSs but may provide additional support for the use of corticosteroids for the treatment of COVID-19. Sanders *et al*. argued that corticosteroids should be avoided because they may cause delayed viral clearance and an increased risk of secondary infection [48]. Additionally, a small trial in France showed that hydrocortisone did not reduce mortality or respiratory support in patients with COVD-19 compared to those on placebo [115]. This trial was terminated early, making the drawing of meaningful conclusions difficult. Ciclesonide, a corticosteroid that does not enter the bloodstream in any significant amounts after inhalation, could be a good candidate that warrants further investigation as in vitro data showed that it can suppress SARS-CoV-2 replication [116]. As the pathogenesis of COVID-19 is driven by viral replication in the early stages followed by an excessive inflammatory response in the secondary phase, it is speculated that a good therapy option will include an antiviral together with an immunomodulatory drug. A recent study reported on the effectiveness of Remdesivir with and without Dexamethasone in hospitalised patients with COVID-19 and concluded that such a combination is worth assessing further [117].

Thalidomide

Thalidomide is a repurposed controversial molecule with a bad reputation stemming from its well-known teratogenic side effects and possessing immunomodulatory and anti-inflammatory properties.

These properties are associated with the suppression of excessive TNF-α production and the down-regulation of cell-surface adhesion molecules involved in leukocyte migration [105]. Two clinical trials were commissioned in China, and one reported its outcomes recently [118]. In this study, a case-series investigation was carried out in which Thalidomide was given with short-term low-dose corticosteroids. It was found that Thalidomide significantly accelerates the negative conversion of SARS-CoV-2, shortens hospital stays and reduces the requirement for mechanical ventilation. Further studies regarding efficacy and safety are needed before Thalidomide can be considered as a viable therapeutic option for the treatment of COVID-19.

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody that is currently licensed for the treatment of certain immune disorders. It is a potent antagonist of IL-6 (interleukin-6) whose elevated levels are associated with severe COVID-19 and mortality [74]. Some prognostic models of COVID-19 include measuring the level of IL-6 as a biomarker of the disease and its severity [119-121]. In the pathogenesis of COVID-19, there is a considerable release of pro-inflammatory cytokines such as IL-6, possibly due to the stimulation of immune cells. The receptors for IL-6 are usually found in hematopoietic cells and they are either membrane-bound (IL-6Rα) or in a soluble form (IL-6Rβ) [8]. Upon binding of IL-6 to these receptors, an intracellular signaling cascade is initiated, which can be classical signaling upon the binding of IL-6 to IL-6Rα or trans-signaling upon the binding of IL-6 to IL-6Rβ. The classical signaling is vital as an anti-inflammatory and regenerative mechanism, while the trans-signaling is associated with pro-inflammatory responses and is considered important in the cytokine release syndrome "cytokine storm" [122]. Tocilizumab can bind to both IL-6R and IL-6R receptors and inhibit IL-6 signal transduction, providing a new therapeutic strategy to combat COVID-19 and alleviate hypoxemia, lymphopenia, and lung infiltration associated with this disease [105,114]. However, IL-6 antagonists can increase the risk of infections and might suppress immune responses that the body requires to fight the virus [8]. Several studies and case reports [123–131] found that Tocilizumab treatment resulted in good clinical outcomes in COVID-19 patients. Even though observational studies provided positive signals, only one out of the five randomized clinical trials reported in 2020 met the primary endpoint [74]. A meta-analysis of the five trials found no clinical benefits for Tocilizumab in reducing mortality [132]. Two randomized clinical trials reported in 2021, REMAP-CAP and RECOVERY, had larger sample sizes and showed a decrease in mortality and a lower risk of mechanical ventilation among patients receiving Tocilizumab [74].

Anakinra

Anakinra (Kineret™) is a recombinant immunosuppressive IL-1 receptor antagonist that blocks the activity of this interleukin in the regulation of inflammatory responses and has been used for the treatment of immune-mediated disorders [108]. Anakinra, like corticosteroids, is involved in suppressing the immune response and, thus, precautions are necessary for its administration [114]. Several case studies discovered that Anakinra can be used in conjunction with other therapies to alleviate COVID-19 symptoms, reduce the need for mechanical ventilation, and improve overall clinical outcomes [133–138]. An observational study that compared the use of a combination of Anakinra and Methylprednisolone versus untreated controls reported a significant reduction in mortality in the treatment group compared with controls (13.9% compared with 35.6%, respectively) [139]. Another retrospective study showed that the addition of Anakinra to standard treatment involving the use of an antiviral plus HCQ was associated with better clinical outcomes compared to the use of standard treatment [140]. A recent prospective open-label interventional study shows that the use of Anakinra was associated with a reduced need for mechanical ventilation, a shorter duration of oxygen needs, and a reduction in inflammatory markers [141].

Umifenovir

Umifenovir (Arbidol) is a broad-spectrum antiviral agent and is currently approved in China and Russia for the prophylaxis and treatment of infections caused by influenza viruses types A and B [142]. It targets the S protein/ACE2 receptor interaction, thus inhibiting the fusion of the virus with the host cell membrane [143-145]. Umifenovir could stabilise the membrane and/or mask vital residues in receptor recognition, thus impairing attachment of the virus to the cell membrane [143,146]. In vitro studies showed Umifenovir to have antiviral activity against human herpesvirus, hepatitis C virus, Ebola virus, and SARS-CoV-2 [143,147,148]. The limited information available on the use of Umifenovir for the treatment of patients with COVID-19 paints a mixed picture. In one retrospective study, the use of Umifenovir appeared to have given significant clinical responses [149]. In another retrospective study, the viral cure was 100% when Umifenovir was used compared to 56% when a Lopinavir/Ritonavir combination was used, although disease progression was halted in both groups [150]. A third study that showed the potential efficacy of Umifenovir was an analysis of 62 hospitalised COVID-19 patients who received adjuvant treatment only (control group of 20 patients) versus a test group of 42 patients who received Umifenovir in addition to the adjuvant therapy [151]. Two other retrospective studies concluded that Umifenovir was not associated with better viral cure or any other better clinical outcomes in COVID-19 treatment [152,153]. Nojome *et al*. reported that Umifenovir treatment resulted in significant improvements in clinical outcomes [154]. However, a meta-analysis that included 12 clinical trials and 1052 patients showed no evidence of improvements when Umifenovir was employed [155].

Manipulating ACE2 receptors

ACE2 receptors are physiologically important, particularly for blood pressure control via homeostatic regulation of angiotensin II levels [156,157]. It follows that the complete blockade of these receptors, for example through anti-ACE2 antibodies, is not therapeutically desirable in the treatment of COVID-19. Therefore, the strategies for combating COVID-19 were focused on targeting these receptors in such a way as to maintain their main physiological functions. The SARS-CoV-2 virus, through its spike protein, makes use of the host receptors as a doorway for entry into the host cell. The S1 subunit of the SARS-CoV-2 S protein binds to the ACE2 receptor and then triggers the cleavage of the receptor by the tumour necrosis factor-alpha-converting enzyme (TACE)/ADAM17 at the ectodomain sites, producing a soluble form (sACE2) to maintain its catalytic activity and its ability to bind with the virus spike protein [158,159]. Recombinant humanised ACE2 (rhACE2) has the potential to treat acute respiratory distress syndrome (ARDS) [160]. During ARDS, the activation of ACE (not ACE2) causes vasoconstriction of the pulmonary vessels and lung injuries. ACE2 activation, on the other hand, appears to protect against lung damage in ARDS [105,160]. Therefore, soluble rhACE2 (also referred to as APN01) could act as a potential therapy for ARDS, which constitutes a significant complication of COVID-19. The soluble recombinant ACE2 mimics ACE2 for binding with the spike glycoprotein of SARS-CoV-2, thus diverting the S protein to bind to the soluble ACE2 instead of the cell membrane-bound form, retarding the ability of the virus to infect the cell. At the same time, the soluble form of ACE2 contributes to reducing the harmful inflammatory reactions in the lungs [160]. A small cohort of ARDS patients has been tested using recombinant ACE2 with encouraging results [161,162]. Studies conducted on organoids showed that rhACE2 can block SARS-CoV-2 replications by a factor of 1000–5000 times [163,164]. A recent investigation tested the potential of direct treatment with shACE2 in engineered human kidney organoids [163]. Huang *et al*. developed a humanised decoy antibody in the form of an ACE-Fc fusion protein that holds the prospect of preventing SARS-CoV-2 viral entry and infection [165]. Chen *et al*. reported a monoclonal antibody targeting ACE2 called 3E8 that can block the S1 subunit of a pseudo-virus construct of SARS-CoV-2 without markedly affecting other physiological activities of ACE2 in mice [166]. Other potential therapeutic strategies, which target ACE2, include blocking the surface ACE2 receptor using anti-ACE2 peptides or antibodies [160,162]. Recently, the use of a single-chain antibody fragment (scFv) or antibody to bind ACE2 and inhibit the interaction between the S protein and ACE2 has been proposed as a possible therapeutic method [167]. Understanding the mechanisms of ACE2 shedding, sACE2 function, and sACE2 plasma levels can contribute to the improvement of COVID-19 therapy and diagnosis.

Camostat and Nafamostat

These are proteolytic enzyme inhibitors that are marketed in Japan and other Asian countries for indications other than coronavirus infection. The proteolytic enzyme TMPRSS2 is central in mediating SARS-CoV-2 entry into host cells and has emerged as a better candidate to target than ACE2 because the latter has essential metabolic roles for the survival of the host cells [168]. Knockout mice without this enzyme have been confirmed to lack both coronavirus and influenza virus infections [169]. Both compounds were reported to inhibit SARS-CoV-2 infection of lung cell cultures in vitro, with Nafamostat possessing a higher inhibition efficiency compared to Camostat [3,170]. There have been some anecdotal reports associating Nafamostat with better clinical outcomes in patients with COVID-19 pneumonia, particularly when used with other treatments [171]. Clinical reports on 11 patients with COVID-19 showed reduced viral replication and enhanced recovery when used with Favipiravir [172]. Recent research predicted that combining TMPRSS2 and cathepsin B/L inhibitors would completely block viral entry [3,173,174]. Repurposing of a mucolytic agent called Bromhexine, which is a TMPRSS2 inhibitor, has also been proposed as a possible treatment for COVID-19 [175]. Furthermore, as TMPRSS2 expression in human lungs appears to be controlled by oestrogens and androgens, it was suggested that the activation of oestrogen pathways or the inhibition of androgen pathways may be a new target for clinical intervention in COVID-19 patients [176].

Anticoagulants

A mention must be made of the use of anticoagulants to counteract the blood clotting seen in some severe COVID-19 cases. Infections disrupt the function of the epithelial cells, resulting in high levels of thrombin production and inactivation of fibrinolysis, leading to coagulation [177,178]. It is, therefore, important to carefully consider the use of prophylactic anticoagulation, which must be weighed against the serious possible bleeding complications. A study in which 183 patients with COVID-19-associated pneumonia were evaluated for coagulation status revealed that abnormal coagulation outcomes were common [178]. Tissue plasminogen activator (TPA) is a thrombolytic agent that has been used as a supportive treatment for severely hypoxic COVID-19 patients. It is thought that TPA may help those patients experiencing thrombus formation by dissolving the thrombus, thereby improving oxygen levels [179]. However, no convincing therapeutic benefits have been reported, and a significant bleeding risk is anticipated. Heparin is another anticoagulant that was previously found to inhibit SARS-CoV infection of cultured cells [180]. In a study of 449 patients with severe COVID-19, of whom 99 were given heparin, the results showed that the 28-day mortality was lower in heparin users [181]. However, there is evidence that heparin use might lead to drug resistance and thrombocytopenia [182,183]. Nafamostat, mentioned previously, is indicated for

diffused (disseminated) intravascular coagulation (DIC) and has been reported to improve the clinical outcomes of COVID-19 patients needing supplementary oxygen therapy [171]. Diffused intravascular coagulation has been observed to occur in the majority of patients who died from COVID-19 [181].

Targeting SARS-CoV-2 inside the cell

Most of the effort in developing medicines to eliminate SARS-CoV-2 once it enters the cell is focused on its replication cycle and, in particular, on its RNA-dependent RNA polymerase (RdRp). This enzyme is conserved in structure and function among viruses with RNA genomes and mediates transcription and replication during infection [7]. The sequence identity in RdRp between SARS-CoV and SARS-CoV-2 is around 96% [184]. The fact that this enzyme has no human counterpart, together with its being essential for the replication cycle of the virus, makes it an ideal drug target for the development of antiviral therapies [185]. Approved nucleoside analogues for the treatment of other viral infections have been selected and are being trialled against SARS-CoV-2 (Figure 5). Of interest is the reported lack of activity of non-nucleoside analogues against SARS-CoV due to the absence of a hydrophobic pocket in the polymerase enzyme [186].

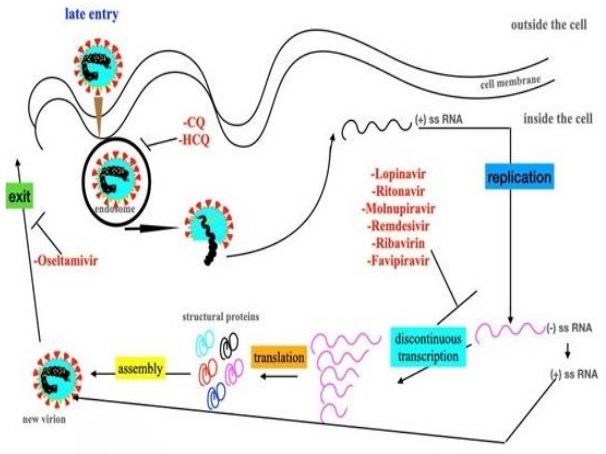

Figure 5: COVID-19 therapies targeting SARS-CoV-2 inside the infected cell. (+) ss RNA: positive sense single-stranded RNA, (-) ss RNA: negative sense single-stranded RNA, CQ: Chloroquine, HCQ: Hydroxychloroquine.

This study suggests that we should exclude non-nucleoside analogues when screening drugs that are suitable to target RdRp. Non-nucleoside analogues are predicted not to work against the RdRp of SARS-CoV-2 due to the lack of a hydrophobic pocket close to the polymerase active site or on the surface of the thumb subdomain and hence are unable to allosterically induce conformational changes to render the enzyme inactive. Therefore, targeting RdRp using nucleoside analogues became the widely accepted approach to disabling this enzyme [8,187].

Remdesivir

Remdesivir (Veklury™) is an adenosine nucleoside analogue with broad-spectrum antiviral activity [108]. It is a prodrug and, once activated by host kinases to remdesivir triphosphate, the active form competes with adenosine triphosphate for incorporation into the viral RNA, causing the termination of the transcription [62]. Remdesivir was previously developed for the treatment of Ebola infections but was found to have antiviral activity against SARS-CoV-2 [188-190]. It was one of the drugs used to treat the first case of COVID-19 in the USA, and since then, numerous case reports have documented improvements in viral loads and symptoms following its use [191]. In a prospective open-label study, Remdesivir was found to be effective in treating COVID-19-associated pneumonia [192]. Another clinical trial (SIMPLE) examined the effect of daily iv doses of Remdesivir after either 5 days or 10 days of treatment [193]. This investigation found that the length of treatment was insignificant and reported that both groups showed similar levels of clinical improvement. In a clinical trial (ACT) involving 1063 hospitalised patients with a broad mix of COVID-19 symptoms, Remdesivir outperformed placebo by showing a median time to recovery of 11 days compared to 15 days, thus demonstrating a 31% faster time to recovery [194,195]. The SOLIDARITY trial recruited 5475 people with the full spectrum of COVID-19 severity, and it found no significant clinical benefit in mortality, initiation of mechanical ventilation, or length of hospital stay [196]. It appears that, as for other antiviral drugs, earlier use may contribute to better effects. Remdesivir may improve clinical recovery and reduce mortality if given early, especially to patients with low flow oxygen. Despite the apparent variability of clinical responses to Remdesivir, the drug is judged safe and has an overall clinical benefit. Remdesivir is approved in many countries for the treatment of hospitalised patients with COVID-19. Remdesivir is able not only to inhibit the RdRp enzyme of SARS-CoV-2 but also to evade the action of the exoribonuclease (nsp14) [197]. This fact is important because the poor activity of some nucleoside analogues such as Ribavirin is attributed to their removal by the exonuclease from the growing chain of viral RNA during replication [198,199]. The current form of Remdesivir can only be administered intravenously and, at present (November 2021). Remdesivir is the only clinically approved antiviral for the treatment of COVID-19.

Molnupiravir

Viral RdRp enzymes are proven effective targets for inhibition with several licensed nucleoside analogues that are used therapeutically for other viral infections [200]. Similar to other nucleoside analogues, Molnupiravir targets the RdRp enzyme of SARS-CoV-2, which mediates replication and transcription of the virus genome. It is a prodrug that is converted to its active form, molnupiravir triphosphate (MTP), in the cell [200]. The active form competes most effectively with CTP (cytidine triphosphate) and less effective with UTP (uridine triphosphate) for incorporation into the growing viral RNA synthesis [201]. This leads to an increased frequency of G to A and C to U transition

mutations in the virus RNA [202,203]. After MTP incorporation, RNA synthesis proceeds without stalling, indicating that Molnupiravir does not act as a chain terminator. This lack of interruption to RNA synthesis may mitigate engagement of the proofreading complex. The RNA transcripts that contain MTP instead of CTP could be subsequently used as a template for a new round of RNA synthesis. Molnupiravir induces lethal mutagenesis and is minimally a two-step process characterized by the relatively high selectivity of MTP for incorporation as a CTP and the indiscriminate incorporation of either ATP (mutagenesis) or GTP [200]. The erroneous incorporation of ATP can subsequently template UTP, generating downstream C to U mutations. The accumulation of mutations derails viral replication as it goes beyond the replication fidelity required for viability. Molnupiravir can be administered orally, which is beneficial in tackling the quick spread of SARS-CoV-2. Off-target effects are of concern as the active form of the drug can be a substrate for the mitochondrial RNA polymerase, which can incorporate MNP instead of U or C. However, although the study by Sheahan *et al* [203] did not observe mutagenesis of host mRNA, the potential off-target effect of Molnupiravir on host genetic material requires further investigation [204]. Recently, Phase 1 safety, tolerability, and pharmacokinetics of Molnupiravir were recently reported [205]. The drug was found to be well tolerated with a lower incidence of adverse effects compared to placebo. In a statement released on October 1, 2021, Merck and Ridgeback announced an interim analysis of the phase 3 study. It showed that Molnupiravir reduced the risk of hospitalisation or death by approximately 50% compared to placebo for patients with mild or moderate COVID-19.

Lopinavir/Ritonavir

This is a common antiviral combination acting against the viral protease enzymes, thus preventing cleavage of the precursor polyproteins [108]. This combination is made up of Lopinavir as the main active ingredient and the protease inhibitor, and Ritonavir which is a potent inhibitor of p-glycoprotein and the cytochrome p450 3A4 enzyme which is responsible for breaking down Lopinavir [105,206]. This combination is used for the treatment of HIV infections and should be used cautiously with other drugs that can influence the levels of the CYP3A4 enzyme [207]. The combination of Lopinavir and Ritonavir, known as LPV/r, was tested during the 2003 coronavirus outbreak and was reported to significantly reduce the incidence of acute disease and death by day 21 [208]. Another study found that the use of LPV/r was associated with a decreased intubation rate and mortality from SARS-Cov-2 [209]. These studies have spurred interest in LPV/r as a therapeutic tool for COVID-19. However, published results revealed mixed outcomes. Ye *et al*. associated the use of LPV/r with a faster clinical response and a shorter course of the disease [210]. Cao *et al*. reported the results of a comparatively large open-label randomised clinical trial comparing the efficacy of LPV/r with standard treatment in 199 patients with COVID-19 [211]. This trial concluded that LPV/r neither shortened the time to clinical improvement nor reduced the mortality at 28 days. A study was carried out to investigate the interactions between LPV/r and Oseltamivir (a neuraminidase inhibitor) and found that these drugs function more effectively when used together than when used separately [212]. A further two studies from Korea found that LPV/r is helpful in the treatment of COVID-19 in relatively high-risk patients, particularly in the early stages of the disease [213,214]. Pfizer has very recently (November 2021) announced the interim results of the phase 2/3 trial of their new oral medicine, paxlovid (a combination of a protease inhibitor PF-07321332 and Ritonavir), for COVID-19. The trial found that paxlovid reduces the risk of hospitalisation or death by 89% compared to placebo in adults with COVID-19 if taken within three days of diagnosis.

Ribavirin

Ribavirin is a guanosine analogue with a wide-spectrum antiviral activity against RNA and DNA viruses [215]. The compound is in use for the treatment of hepatitis C, respiratory syncytial virus and Lassa fever [216-218]. The proposed mechanism of action of Ribavirin against SARS-CoV-2 is through the inhibition of the synthesis of viral RNA and capping of the mRNA [219]. However, its mechanistic role against DNA viruses remains something of a mystery. The in vitro activity of Ribavirin against SARS-CoV was limited and required high concentrations to inhibit viral replication [48]. A systematic review of the clinical experience with Ribavirin for the treatment of SARS during the 2002/2003 outbreak revealed inconclusive results in 26 out of 30 studies, with 4 studies demonstrating possible harms in using this antiviral agent [220]. In a study using 115 patients with severe COVID-19, Ribavirin did not reduce the mortality rate compared with the control group [221]. An open-label clinical trial was conducted in Hong Kong in which the control group received LPV/r every 12 hours for 14 days, while the treatment group received Ribavirin every 12 hours and three doses of interferon beta-16 for 14 days in addition to LPV/r every 12 hours. In this trial, the combination therapy was well tolerated and reduced the time to negative nasopharyngeal swab and hospital stay in patients with mild-moderate symptoms [222]. The inconclusive efficacy data and its substantial safety concerns suggest that it has limited value for the treatment of COVID-19 as a stand-alone therapy [48,105].

Table 1: A selection of other drugs that were thought to play a role in the treatment of COVID-19

Drug	Main mode of action	Supportive findings	Non-supportive findings
Budesonide	Binds to glucocorticoid receptors and inhibits transcription of inflammatory genes	Budesonide reduced the need for urgent medical care and time to recovery after COVID-19 [230]	
Azithromycin	Macrolide antibiotic with antiviral effects and may reduce cytokine levels		Azithromycin did not increase likelihood of being symptom free at day 14 [231]. Adding Azithromycin to standard care treatment did not reduce the risk of subsequent hospital admission or death [232]. Adding Azithromycin to standard of care treatment did not improve clinical outcomes [233]
Doxycycline	Tetracycline antibiotic with possible antiviral anti-inflammatory effect		Doxycycline did not reduce time to recovery or hospital admissions or deaths [234]
Sarilumab	Monoclonal antibody inhibiting interleukin-6		Sarilumab did not show efficacy in patients admitted to hospital with COVID-19 and receiving supplemental oxygen [235]
Canakinumab	Monoclonal antibody inhibiting interleukin-1		Canakinumab did not increase the likelihood of survival [236]
Bamlanivimab	Neutralising IgG1 monoclonal antibody against the spike protein of SARS-CoV-2	Bamlanivimab monotherapy reduced the incidence of COVID-19 infection [237] Bamlanivimab appeared to accelerate the natural decline in viral load over time [238]	
Colchicine	Anti-inflammatory painkiller for gout	Colchicine reduced the length of supplemental oxygen therapy and hospitalisation [239] Colchicine improved time to clinical deterioration [240] Colchicine could be considered for use in those at risk of complications from COVID-19 [241]	Colchicine was not associated with reductions in 28-day mortality, duration of hospital stays, or risk of progressing to invasive mechanical ventilation or death [242]
Ascorbic acid (vitamin C) with or without Zinc	Ascorbic acid is an essential vitamin and Zinc is an essential mineral		Zinc, Ascorbic acid, or a combination of the 2 supplements did not decrease the duration of COVID-19 symptoms [243]
Cholecalciferol (Vitamin D3)	Essential vitamin		Colecalciferol did not reduce hospital length of stay [244]
Fluvoxamine	Selective serotonin reuptake inhibitor	Fluvoxamine had a lower likelihood of clinical deterioration over 15 days [245] Fluvoxamine reduced the need for hospitalisation [246]	
Ivermectin	Anti-parasitic with antiviral activity against a broad range of viruses	Ivermectin helped patients to recover earlier and were more likely to be PCR-negative on day 14 [247] Ivermectin is effective and safe in management of COVID-19 [248]	Ivermectin had no effect on preventing hospitalization of patients with COVID-19 [249] Ivermectin did not improve the time to resolution of symptoms [250]

Favipiravir

Favipiravir is a broad-spectrum antiviral agent that has been approved for the treatment of influenza, showed some promise with Ebola infections, and was deployed for the treatment of SARS and MERS infections during their outbreaks [38,108]. It is a purine analogue prodrug that is phosphorylated by host kinases to competitively inhibit the RdRp enzyme and eventually the replication of the virus [223]. Owing to its wide-range antiviral activity, Favipiravir was investigated for the treatment of COVID-19. In an open-label, non-randomised control study, Cai *et al*. compared the efficacy of Favipiravir to LPV/r in the treatment of COVID-19. The results showed Favipiravir to have better clinical outcomes and drug safety [224]. The results of a further clinical trial on COVID-19 patients showed a rapid antiviral response with Favipiravir [225]. Another randomised trial which compared Favipiravir and Arbidol in the treatment of 240 patients with COVID-19 concluded that Favipiravir did not significantly improve the clinical recovery rate at day 7, but relieved the pyrexia and cough associated with the condition [226]. It is recommended to use this drug in patients with respiratory and immunological problems and only in combination with drugs that have proven effectiveness [114,225].

Oseltamivir

Oseltamivir (Tamiflu^{TM}) is another antiviral agent that is widely considered for COVID-19 treatment [62]. It is

a neuraminidase inhibitor approved for the treatment and prophylaxis of influenza A and B but lacks evidence supporting its activity against SARS-CoV-2 [48]. During the initial outbreak of COVID-19 in China, which coincided with the peak influenza season, a large number of patients received oseltamivir until the discovery of SARS-CoV-2 as the causative virus of COVID-19 [48]. Oseltamivir exerts its antiviral action by inhibiting the viral neuraminidase activity and thus viral replication [227]. Coronaviruses are not known to use the neuraminidase enzyme in viral replication, therefore oseltamivir is unlikely to be of any therapeutic value. McCreary and Pogue concluded that oseltamivir is ineffective against coronaviruses in preventing SARS at even high concentrations of the drug [228]. A retrospective case series of 138 hospitalised patients with SARS-CoV-2-associated pneumonia showed no effective outcome in about 90% of patients who received oseltamivir [229].

The COVID-19 pandemic brought a new realization to the world and to healthcare systems that at times were on the brink of collapse due to being overrun with patients seeking medical help. Confronted with that reality and the lack of appropriate treatments, many people put forward their beliefs and remedies to combat this disease. Table 1 presents a selection of various medicines that did not form part of this narrative review, together with studies either in support or against their deployment in the treatment of COVID-19.

Concluding remarks

Intercepting the virus before cellular entry offers the advantage of blocking viral replication and the consequences that might have on the host. Antibodies that are specific to a viral protein appear to be promising in this regard and are being intensely scrutinized for their neutralizing abilities. Once the virus enters the cell, targeting its specific machinery, mainly RdRp and its proteases, is the focus of drug developers aiming to arrive at the magic bullet that disables the virus with minimum risks to the COVID-19 patient.

Conflicting interests

Nothing declared.

Data sharing statement

N/A

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