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Biosafety and Health 3 (2021) 148–155

Contents lists available at ScienceDirect

Biosafety and Health

journal homepage: www.elsevier.com/locate/bsheal

Review of pharmacologic and immunologic agents in the management of COVID-19

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ARTICLE INFO

Article history:
Received 27 June 2020
Received in revised form 1 January 2021
Accepted 7 January 2021
Available online 9 January 2021

Keywords:
SAR-CoV-2
COVID-19
Respiratory
Drug repurposing
Antiviral
Supportive therapy
Immunotherapy

ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is the third coronavirus outbreak in the last two decades. Emerging and re-emerging infections like COVID-19 pose serious challenges of the paucity of information and lack of specific cure or vaccines. This leaves utilisation of existing scientific data on related viral infections and repurposing relevant aetiologic and supportive therapies as the best control approach while novel strategies are developed and trialled. Many promising antiviral agents including lopinavir, ritonavir, remdesivir, umifenovir, darunavir, and oseltamivir have been repurposed and are currently trialled for the care for COVID-19 patients. Adjunct therapies for the management of symptoms and to provide support especially in severe and critically ill patients have also been identified. This review provides an appraisal of the current evidence for the rational use of frontline therapeutics in the management of COVID-19. It also includes updates regarding COVID-19 immunotherapy and vaccine development.

1. Introduction

In December 2019, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported to be the causative agent of a pneumonia outbreak in a cluster of patients in China [1]. The disease, named coronavirus disease 2019 (COVID-19), spread around the world resulting in a global pandemic and disruption of activities. The novel coronavirus was named SARS-CoV-2 as it was found to be a strain of SARS-CoV [2]. SARS-CoV-2 is transmitted mainly through droplets of saliva and respiratory discharges or contact with contaminated objects [3]. SARS-CoV-2 showed a proximate phylogenetic relationship to a bat coronavirus isolate (RaTG13), indicating a possible origin from bats [4]. COVID-19 presents clinically as a mild, moderate, severe or critical form [5]. The most common symptoms of the disease include fever, cough, dyspnoea, myalgia, headache, and diarrhoea [6]. COVID-19 lacks specific and defined therapy, and interventions depend entirely on presentation. Asymptomatic and mildly symptomatic forms need little or no medical intervention but should be monitored and required to isolate [7]. The clinical management of moderate, severe, or critical COVID-19 cases mainly revolves around symptomatic and supportive treatments, including hospitalisation or intensive care [5]. Biomedical and clinical data on the coronaviruses suggest a potential list of new and existing drugs with potential therapeutic effects on COVID-19 patients [8]. This review appraises the major repurposed interventions and potentially promising pharmacologic and immunologic agents in the management of COVID-19. These drugs were categorised into three groups: agents with antiviral activity, drugs for symptomatic and supportive treatment, and immune-based therapies (Table 1). It also includes updates in the development of vaccines for COVID-19, mainly in the trial stages.

2. Drugs with antiviral activity

Antiviral and antimalarial agents with activities against related coronaviruses are at the forefront in the management of COVID-19

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http://dx.doi.org/10.1016/j.bsheal.2021.01.001

Table 1
Commonly repurposed drugs in the management of COVID-19.

Name of the drug	Pharmacological class	Rationale for use in COVID-19	Reference
Lopinavir-Ritonavir	Antiviral	Inhibit viral protease	[12]
Remdesivir	Antiviral	Active against SARS-CoV2 with low toxicity to mammalian cells.	[16]
Umifenovir	Antiviral	Active against widely spreading viruses.	[20]
Favipiravir	Antiviral	Binds to and inhibits viral RdRp. Used in the treatment of RNA viral infections such as EVD and influenza.	[23]
Darunavir	Antiviral	An antiviral protease inhibitor. Shown to inhibit SARS-CoV-2 replication at 300 μM with inhibition efficiency 280-fold higher than placebo *in vitro*.	[19,25]
Oseltamivir	Antiviral	Used to treat influenza A and B.	[26]
Chloroquine and Hydroxychloroquine	Antimalarial with antiviral effect	Inhibited SARS-CoV-2 *in vitro*. Prevent virus-host cell fusion through ACE2 receptor.	[16]
Azithromycin	Second-generation macrolide and broad-spectrum antibacterial	Effective against many respiratory bacterial infections. Shown activity against Zika and Ebola viruses.	[39,40]
Nitric oxide (iNO) and Epoprostenol	Pulmonary vasodilator	Inhibited SARS-CoV replication *in vitro* and improved arterial oxygenation in SARS patients.	[35,36]
Corticosteroid	Anti-inflammatory and immunosuppressants	Used to treat ARD and sepsis. Previously used in management of H1N1 viral pneumonia and SARS.	[43,45]
Vitamin C	Vitamin	Antioxidant and immunomodulatory properties. Shown to be essential in antiviral immune response	[60,61]

worldwide (Table 1) [9]. Due to the urgent need to treat and control COVID-19, most of these repurposed drugs were accelerated to phase III clinical trials, and include lopinavir, ritonavir, remdesivir, oseltamivir, ASC09F, and darunavir [10,11]. The majority of these antiviral agents limit or inhibit viral binding and entry into host cells, viral replication, transcription, and metabolism (Fig. 1) [10].

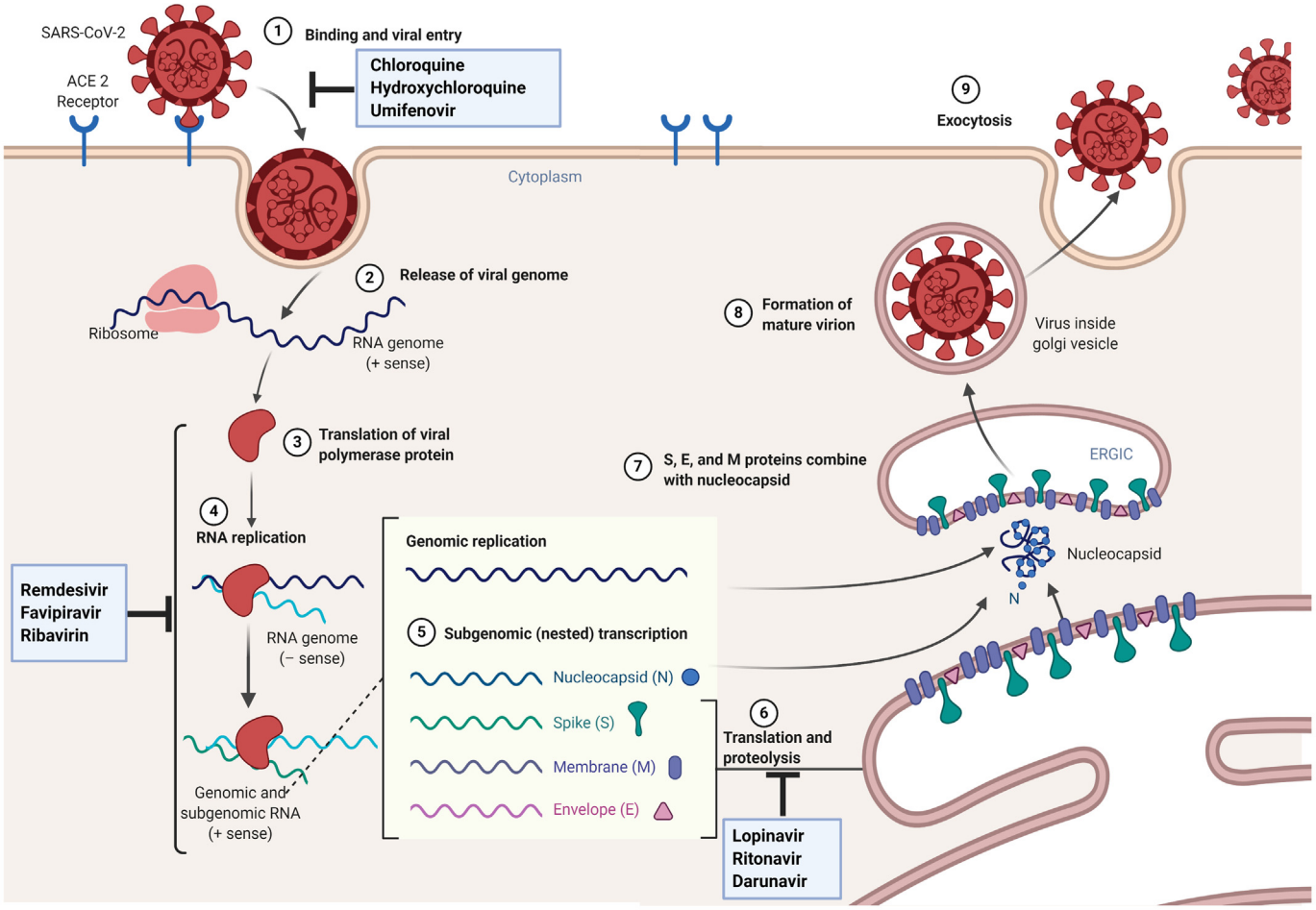

Fig. 1. SARS-Cov-2 replication cycle and targets of drug action. Drugs such as chloroquine, hydroxychloroquine and umifenovir prevent viral binding and entry into host cells. Remdesivir, favipiravir, and ribavirin inhibit viral RNA replication. Other drugs including lopinavir, ritonavir, and darunavir inhibit viral protease. (Figure created with Biorender.com)

2.1. Lopinavir-Ritonavir

Lopinavir is an antiretroviral protease inhibitor while ritonavir inhibits the enzymes that metabolise lopinavir. This combination acts by inhibiting viral protease enzyme through the formation of an inhibitor-enzyme complex [12]. Lopinavir has poor oral bioavailability due to extensive biotransformation, thus, it is co-administered with lopinavir with ritonavir to improve its bioavailability and efficacy [8]. In an open-label individually randomised controlled trial (RCT) conducted in Wuhan, China, lopinavir-ritonavir treatment showed no significant benefit in COVID-19 patients compared to standard care. The combination also resulted in adverse effects including diarrhoea, nausea, and asthenia [13]. In contrast, the COVID-19 index case in Korea showed a significant decrease in coronavirus titre following the administration of lopinavir-ritonavir [14].

2.2. Remdesivir

Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerases developed in 2017 as a treatment for Ebola virus infection. The activated form of remdesivir obscures viral RNA polymerase to evade proofreading by viral exonuclease. This causes a decrease in viral RNA production, thus delaying chain cessation of nascent viral RNA [15]. Remdesivir has shown potent activity against SARS-CoV-2 recently with a half-maximal effective concentration (EC_{50}) of 0.77 μM and low toxicity to mammalian cells [16]. Although remdesivir has indicated a promising therapeutic effect on SARS-CoV-2 viral loads in the respiratory tract of some patients, its safety and efficacy are yet to be elucidated [17].

2.3. Hydroxychloroquine and chloroquine

Chloroquine and its analogue, hydroxychloroquine, have been used clinically for the treatment of malaria and arthritis. They are of profound attraction as potential therapeutic agents against COVID-19 following promising results from preclinical and early clinical testing [18]. Hydroxychloroquine share a similar mechanism of action with chloroquine, but has proved to be safer and most preferred in the treatment of malaria, viral infections, and autoimmune conditions [19]. These drugs inhibit the entry of SARS-CoV-2 into host cells by interfering with glycosylation of the ACE2 receptor and its binding with the spike protein. Thus, chloroquine treatment might be more effective in the early stage of the infection, before COVID-19 reduces ACE2 expression and activity [16].

2.4. Umifenovir

Umifenovir has demonstrated *in vitro* antiviral efficacy in widely spreading viruses such as the Ebola virus, human herpesvirus, and Tacaribe arenavirus. It acts by blocking the virus-host cell membrane fusion as well as virus-endosome fusion through interference with the hydrogen bonding network of membrane phospholipids [20]. A retrospective study in China found that umifenovir might not improve the prognosis of COVID-19 or accelerate SARS-CoV-2 clearance in non-critically ill patients [21]. This suggests the need to assess the efficacy of umifenovir in COVID-19 patients in RCT [21].

2.5. Favipiravir

Favipiravir is a guanine analogue with a pyrazine carboxamide structure that binds to and inhibits viral *RNA dependent RNA polymerase* (RdRp). Its antiviral activity is decreased in the presence of purine nucleosides due to competitive inhibition [22]. In an open-label controlled study in China, favipiravir showed better outcomes in COVID-19 patients in terms of disease progression and viral clearance, compared to Lopinavir-Ritonavir therapy [22]. Favipiravir also demonstrated a better recovery rate and relief time over umifenovir in a superiority RCT in China [23]. Favipiravir is currently under Phase III controlled, multi-centre clinical trial as a treatment for a moderate form of COVID-19 in Italy [24].

2.6. Darunavir

Darunavir inhibits viral protease and interferes with viral replication [19]. At a concentration of 300 μM, darunavir was shown to inhibit SARS-CoV-2 replication with inhibition efficiency 280-fold higher than placebo [25].

2.7. Oseltamivir

Oseltamivir, an approved drug for the treatment of influenza, targets the neuraminidase distributed on the surface of the influenza virus to inhibit its spread in the human body [26]. A Japanese study reported that early treatment with oseltamivir has benefit in suspected COVID-19 patients with fever [27]. However, in another study in Wuhan, China, treatment with oseltamivir did not produce positive outcomes [28].

2.8. Niclosamide and ivermectin

Niclosamide is a narrow-spectrum anthelminthic that inhibits glucose uptake, oxidative phosphorylation, and anaerobic metabolism in tapeworms. Arecent study suggests that niclosamide inhibits replication of several viruses including coronaviruses [29]. Another study showed that niclosamide inhibit MERS-CoV the replication in VERO B4 cells [30]. On the hand, ivermectin, a broad spectrum anti-parasitic drug used widely in animals and humans, inhibits the interaction between human immunodeficiency virus (HIV)-1 integrase, importin and integrase nuclear import. Ivermectin has recently shown inhibition of SARS-CoV-2 [31].

2.9. Nitazoxanide and tizoxanide

Nitazoxanide, a thiazolide compound with broad spectrum anthelmintic and antiprotozoal activities, exhibits broad antiviral activity and a relatively favourable safety profile. Nitazoxanide and its metabolite, tizoxanide, have demonstrated inhibitory effects against MERS-CoV and SARS-CoV-1 [32]. Furthermore, the inhibition of murine coronavirus, bovine coronavirus strain L9, human enteric coronavirus 4,408, and mouse hepatitis virus strain A59 by nitazoxanide has been reported *via* suppression of viral N protein [33]. However, there is need for further studies into the efficacy and safety profile of nitazoxanide as a potential as a treatment option for COVID-19.

3. Drugs for symptomatic and supportive treatment

In the absence of a vaccine or specific antiviral therapy proven against SARS-CoV-2, many adjunctive therapies are used as supportive care for COVID-19 patients (Table 1). These adjunctive therapies are used wholly based on patient symptoms presentation and underlying conditions.

3.1. Nitric oxide and epoprostenol

Inhaled nitric oxide (iNO) and epoprostenol (iEPO) are two common pulmonary vasodilators that have been widely studied [34]. They are used in severe hypoxemia that is unresponsive to conventional mechanical ventilation and are thus recommended for use in critical COVID-19 patients. Additionally, NO was shown to inhibit SARS-CoV replication cycle and viral protein and RNA synthesis [35]. In another study, six severely infected SARS patients receiving iNO therapy showed improved arterial oxygenation and reduced need for ventilator support [36]. The direct benefits of iNO or iEPO in COVID-19 patients are yet to be fully elucidated, and previous studies involving coronavirus-related acute respiratory distress syndrome (ARDS) did not report benefits on mortality [37]. However, considering the high incidence of pulmonary complications in critical

COVID-19 cases, pulmonary vasodilators may confer benefits in critically ill patients.

3.2. Azithromycin

Azithromycin, a second-generation macrolide and broad-spectrum antibacterial agent, has received increasing attention in recent years because of its additional effects on host defense [38]. Azithromycin binds to the 50s subunit of bacterial ribosome to inhibit the translation of mRNA into protein. It is used for the treatment of susceptible bacterial infections, including respiratory, dermal, urogenital, and sexually transmitted diseases. In addition, azithromycin has shown activity against Zika and Ebola viruses [39,40]. In a recent study, azithromycin enhanced the effect of hydroxychloroquine against viral load in COVID-19 patients [41]. However, the combination of hydroxychloroquine and azithromycin may increase the risk of cardiovascular mortality [42]. Therefore, azithromycin combination therapy should be critically evaluated in the management of COVID-19 patients, especially those with underlying cardiovascular conditions.

3.3. Corticosteroids

Due to their potent anti-inflammatory and antifibrotic properties, and the ability to suppress collagen deposition, corticosteroids are frequently used to treat ARDS and sepsis. Corticosteroids like methylprednisolone, dexamethasone, hydrocortisone, and prednisolone were previously used in H1N1 viral pneumonia [43] and severe community-acquired pneumonia [44]. This class of drugs was used in SARS to suppress cytokine storms and prevent clinical deterioration [45]. A low dose of corticosteroid has the potential to speed up the resolution of pulmonary and systemic inflammation associated with pneumonia [46]. The use of corticosteroids in the management of COVID-19 has been widely reported since the pandemic began [47,48]. Early administration of dexamethasone could reduce the duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS [49]. Interestingly, dexamethasone was recently identified as the first drug to reduce mortality in patients with COVID-19 requiring ventilator support [50]. However, current evidence suggests that adverse effects may outweigh the benefits of corticosteroids in some patients, suggesting the need for careful consideration [46,51].

3.4. Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have been extensively used to treat fever and pain. Indomethacin, an inhibitor of cyclooxygenase (COX), was shown to exhibit activity against SARS-CoV and canine coronavirus (CCoV) [52]. This suggests the possible efficacy of indomethacin against SARS-CoV-2. However, some NSAIDs including ibuprofen, are activators of ACE2 receptors and might increase the risk of contracting COVID-19 [53]. Nevertheless, there is so far no substantial evidence that links NSAID administration and the worsening of COVID-19 symptoms [8].

3.5. Angiotensin-converting enzyme 2 (ACE2) receptor

ACE2 is an aminopeptidase that plays essential role in cardiovascular and immune systems [54]. The binding of the spike protein of coronavirus to ACE2, which is highly expressed in the lungs, triggers infection cascade [53,55]. The resultant viral invasion of the alveolar epithelial cells of the lungs causes the respiratory symptoms, which are more severe in cardiovascular disease patients. Therefore, ACE2 receptor is considered a primary drug target in pathogenesis of coronaviruses including SAR-CoV-2 [56]. However, chronic treatment with ACE inhibitors such as lisinopril or angiotensin blockers like losartan in hypertensives can potentiate ACE2 overexpression [57,58]. Thus, safety and potential effects of these drugs in patients with COVID-19 should be carefully monitored. There is yet no evidence to suggest whether patients with COVID-19 and hypertension who are taking such medications should switch to another drug.

3.6. Vitamin C (Ascorbic Acid)

Vitamin C is an essential nutrient in the body that boosts immunity by stimulating IFN production and lymphocyte proliferation, and enhancing neutrophil phagocytic capability [59]. As a potent antioxidant, it neutralizes free radicals and prevents cellular damage as well as modulates cytokine network typical of the systemic inflammatory syndrome [60]. Moreover, vitamin C was shown to be essential in antiviral immune responses against influenza virus infection [61]. Clinical studies have demonstrated the protective activity of high dose oral vitamin C against COVID-19 [62]. Interestingly, high-dose vitamin C has been used clinically for several decades and documented to be safe with no significant side effects [62,63]. Given that COVID-19 patients frequently present with lung damage, the use of vitamin C could be beneficial.

3.7. Vitamin D

Vitamin D is known to modulate the innate and adaptive immune system, and its deficiency predisposes individuals to autoimmunity and infections [64]. Vitamin D can reduce the risk of infections by inducing cathelicidins and defensins, which can lower viral replication rates. It also reduces concentrations of pro-inflammatory cytokines that mediate lung injury and pneumonia, as well as increases the level of anti-inflammatory cytokines [65]. Thus, vitamin D3 might be useful in the management of COVID-19.

3.8. Zinc

Zinc is a trace mineral necessary for the normal functioning of the immune system [66]. Numerous reports have shown that loss of sense of smell and taste are common features in the early stages of COVID-19 [67]. Zinc deficiency has been associated with loss of taste and its supplementation has shown beneficial effects in subjects with ageusia [68,69]. Importantly, zinc is a potent inhibitor of some RNA viruses, including SARS-CoV [70]. Therefore, zinc may have beneficial effects in COVID-19 patients.

3.9. Low molecular weight heparin (LMWH)

In a cohort study involving COVID-19 patients, disseminated intravascular coagulation (DIC) and elevated d-dimer levels were identified as predictors of worse outcomes [71]. In addition to its anticoagulant and anti-inflammatory properties, heparin was shown to induce conformational changes in the surface protein (Spike) S1 receptor binding domain (RBD), indicating that it might interfere with viral attachment to host cell [72]. Furthermore, the use of LMWH in patients hospitalized with COVID-19 was associated with lower serum IL-6 concentrations, suggesting that this anticoagulant may provide other benefits besides the prevention of thrombosis [73]. In another study, severe COVID-19 patients with coagulopathy that received heparin had decreased mortality compared to control [74]. Based on current evidence, it is recommended to administer LMWH or heparin against venous thromboembolism in severe to critically ill COVID-19 patients [75]. In COVID-19 patients with rapidly developing respiratory failure or thrombosis, treatment with anticoagulants can also be instituted in the absence of contraindications [76].

4. Immunotherapy

The early host immune response to severe COVID-19 is defined by inflammatory cytokine storm (ICS), and an influx of activated immune cells to the lungs leading to severe lung damage and development of ARDS [77]. IL-6, which produces $CD14^+$ $CD16^+$ inflammatory monocytes, has been established to be the key inflammatory cytokine that mediates ICS associated with COVID-19 [78]. Despite the need for cytokines in viral clearance and control of pulmonary inflammation, rapid and massive release of cytokines could cause deleterious effects (like organs failure) in host [79].

Immunotherapy in form of immunomodulation, inflammatory cytokine neutralization, polyclonal antibody, convalescence plasma therapy, monoclonal antibodies and vaccines among other approaches constitutes promising adjuncts in management and prevention of COVID-19. These agents can alleviate inflammation or inflammation-associated lung damage, reduce viral load, prevent intensive care unit hospitalization, and might confer lasting immunity to control the pandemic [77]. However, immunosuppressants could affect host anti-viral immune response, hence, appropriate timing based on direct evidence from RCTs should be carefully considered before instituting these drugs in COVID-19 patients [80].

4.1. Tocilizumab

Tocilizumab is a recombinant humanised monoclonal anti-IL-6 receptor antibody that has been widely used in treatment of autoimmune diseases [81]. It is the first-line drug for the treatment of cytokine release syndrome (CRS). Tocilizumab was reported to improve clinical outcomes in severe to critically ill COVID-19 patients, with no adverse reactions observed [82]. There are many ongoing trials evaluating tocilizumab usage in COVID-19 [80,83].

4.2. Sarilumab

Sarilumab is another anti-IL-6 human monoclonal antibody similar to tocilizumab [77]. Several versions of this medication by different manufacturers are currently under RCTs for effective use in COVID-19 patients around the globe [84,85].

4.3. Siltuximab

Siltuximab this is a chimeric monoclonal antibody which specifically inhibits binding of IL-6 rather to its receptors. The use of drugs targeting either IL-6 or its receptor to enhance the resolution of CRS symptoms in COVID-19 has been reported [86]. Siltuximab is currently in phase III clinical trial for the management of COVID-19 patients with acute hypoxic respiratory failure and systemic CRS [87].

4.4. Baricitinib and ruxolitinib

These are small molecule immunosuppressants which selectively inhibit the activity of Janus kinases (JAK1 and JAK2). Baricitinib, approved for treatment of rheumatoid and psoriatic arthritis [88], and ruxolitinib, specifically approved for myelofibrosis and secondary haemophagocytic lymphohistiocytosis (sHLH) [89], are currently repurposed to manage COVID-19 patients [90].

4.5. Imatinib

Imatinib is an oral anticancer agent which inhibits the activity of tyrosine kinase, BCR-ABL1 fusion oncoprotein. Imatinib has shown *in vitro* antiviral properties against SARS-CoV-1, MERS-CoV and infectious bronchitis virus [91,92]. In addition, it has immunomodulatory effects, and an acceptable safety profile, which makes it a promising adjunct therapy in the COVID-19 management [93].

4.6. Convalescent plasma, polyclonal and monoclonal antibodies

Passive immunotherapy involves administration of preformed antibodies in form of either convalescent plasma, polyclonal or monoclonal antibodies to a non-immune individual. Convalescent plasma is normally employed as a therapeutic option in novel outbreaks especially when effective medications or vaccines are not available [94]. It has been successfully used to treat infected individuals during dreaded outbreaks like SARS [95] and Ebola viral disease [96]. Plasma from CRS-free recovered COVID-19 patients, prepared in freeze-dried or concentrated blood products was reportedly used to manage critical COVID-19 patients in China [97]. This therapy is aimed at direct neutralization of SARS-CoV-2, control of overactive immune system (cytokine storm, Th1/Th17 ratio, complement activation) and immunomodulation of a hypercoagulable state [98]. It has so far proved to be effective and safe in managing critical COVID-19 patients [99–101] and various clinical trials are currently ongoing worldwide. Recombinant human or humanized monoclonal antibodies are also effective, safe and highly specific in their ability to target a pathway, process, or invading pathogen [102]. They have been developed to treat several infections [103]. However, they are difficult and expensive to produce, and may not yield an appropriate infectious control in emergency situations [98].

5. SARS-CoV-2 vaccine development

Spike protein fragments particularly RBD, S1 and S2 (as in MERS and SARS vaccines) are the prime targets for COVID-19 vaccine development. Rapid development of these vaccines avail from innovative and time-tested technologies used in developing vaccines against other highly evolving viruses like HIV and influenza virus [104,105]. The sequential SARS-CoV-2 vaccine development platforms involve the integration of computational and structural-based immunogen design strategies; production of immunogens (such as protein subunits); and immunogenic profiling in animal models, followed by vaccine manufacturing and testing in clinical trials [102]. Several strategies from conventional inactivated or live-attenuated virus vaccines, through nucleic acid (DNA, mRNA), recombinant protein, virus-like particle, peptide, viral vector (replicating and non- replicating) platforms, to newer approaches like novel Trimer-Tag technology are currently employed to develop vaccines against SARS CoV-2. As at August 2020, vaccine candidates including ChAdOx1 nCoV-19, CoronaVac, inactivated SARS-CoV-2 vaccine, mRNA-1273, BNT162b, Ad5-nCoV and recombinant new coronavirus vaccines are at the forefront of immunogenicity, safety and efficacy trials (Table 2). Regardless of the approach employed, careful evaluation of efficacy and safety of the vaccine candidates should be placed above the urgent need for a SARS CoV-2 vaccine.

6. Conclusions

The novel nature of COVID-19 has challenged the scientific research and development sector as well as pharmaceutical industries with unprecedented demand to accelerate therapeutics and vaccine development. Thank to advances in genetics and genomics, SARS-CoV-2 was detected early and its genetic sequence determined, which was made available worldwide. This has helped in many ways in the development of new drug molecules, vaccine development as well as repurposing existing therapeutics in the control of COVID-19.

The world is currently flooded with unprecedented efforts from governments, academics, and various private organisations to rapidly develop effective and safe vaccines against COVID-19. This might be our best bet for establishing long-lived immunity to prevent further spread and possibly control this pandemic. By the end of June 2020, the World Health Organisation (WHO) had identified more than 141 promising COVID-19 vaccine projects [106,107].

Among peculiar challenges in the management of COVID-19 is working with uncertainty. For most of the pharmacologic agents repurposed, there are still unanswered questions around efficacy, safety and cost-effectiveness [9]. Individual peculiarities and COVID-19 presentation are also critical issues to consider. It appears there is no gold standard single therapeutic option to treat COVID-19, and a combination therapy might be more beneficial in some cases of COVID-19 [108,109]. This brings about the question of drug-drug interaction especially in patients with underlying medical conditions or under other medications. Therefore, as efforts to provide cure and vaccines intensify, it is important that clinicians rationalise treatments on stratified or personalised basis and share outcomes and regimens with the medical and scientific community.

Table 2
Most advanced SARS-CoV-2 vaccines in clinical trials as in August 2020.

Vaccine candidate	Overview of the immunogen	Stage of development	Identifier	Trial location
Ad5-nCoV	Recombinant adenovirus type-5-vectore expressing spike (S) protein of the SARS-CoV-2.	Phase II randomized, double-blinded, placebo-controlled clinical trial	ChiCTR2000031781	China
Recombinant new coronavirus vaccine	Adjuvanted recombinant protein (RBD-Dimer)	Phase II randomized, blinded, placebo-controlled trial	NCT04466085	China
ChAdOx1 nCoV-19	Chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) that expresses spike protein of SARS-CoV-2	Phase III RCT	ISRCTN89951424	United Kingdom,
CoronaVac	Whole SARS-CoV-2 adsorbed (inactivated) vaccine	Phase III double-blind, randomized, placebo-controlled phase III clinical trial	NCT04456595	Brazil
Inactivated SARS-CoV-2 vaccine	Inactivated SARS-CoV-2	Phase III randomized, double blind, parallel placebo controlled, phase III clinical trial	ChiCTR2000034780	United Arab Emirates
mRNA-1273	Novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine. It encodes for spike (S) protein of SARS-CoV-2.	Phase III, randomized, stratified, observer-blind, placebo-controlled Study	NCT04470427	United States
BNT162b1 and BNT162b2	Nucleoside modified mRNA formulated in lipid nanoparticles	Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study	NCT04368728	United States, Argentina, Brazil

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Marzuq A. Ungogo: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision. **Mustapha Mohammed:** Conceptualization, Data Curation, Writing - Original Draft. **Bala N. Umar:** Investigation, Data Curation, Writing - Original Draft. **Auwal A. Bala:** Investigation, Writing - Original Draft. **Garba M. Khalid:** Visualization, Resources, Writing - Original Draft.

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