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Review article

Primed for global coronavirus pandemic: Emerging research and clinical outcome

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Abstract

The global effort to combat and contain the coronavirus disease 2019 (COVID-19) caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now proceeding on a war footing. The world was slow to react to the developing crisis, but once the contours of the impending calamity became evident, the different state and non-state actors have raced to put their act together. The COVID-19 pandemic has blatantly exposed the shortcomings of our healthcare system and the limitations of medical science, despite considerable advances in recent years. To effectively tackle the current pandemic, almost unprecedented in the modern age, there is an urgent need for a concerted, sustained, and coordinated effort towards the development of new diagnostics, therapeutic and vaccines, and the ramping up of the healthcare infrastructure, especially in the poorer underprivileged nations. Towards this end, researchers around the world are working tirelessly to develop new diagnostics, vaccines, and therapeutics. Efforts to develop a vaccine against COVID-19 are presently underway in several countries around the world, but a new vaccine is expected only by the end of the year-at the earliest. New drug development against COVID-19 and its approval may take even longer. Under such circumstances, drug repurposing has emerged as a realistic and effective strategy to counter the current menace, and several antiviral and antimalarial medicines are currently in different stages of clinical trials. Researchers are also experimenting with nutrients, vitamins, monoclonal antibodies, and convalescent plasma as immunity boosters against the SARS-CoV-2. This report presents a critical analysis of the global clinical trial landscape for COVID-19 with an emphasis on the therapeutic agents and vaccines currently being tested at pandemic speed.

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Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CoV, coronaviruses; MERS-CoV, middle east respiratory syndrome virus; ACE2, angiotensin-converting enzyme-2; RdRP, RNA-dependent RNA polymerase.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious malady caused by recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has rapidly transformed into a deadly pandemic, almost unprecedented in the annals of the modern age [1,2]. The world faced a similar crisis in 1918 when the Spanish flu pandemic broke out [3]. Recent reports suggest that COVID-19 originated in the city of Wuhan, in the Hubei province of China, on December 12, 2019, from where it quickly spread around the globe [4]. World Health Organization (WHO) declared it a public health emergency of international concern (PHEIC) on January 30, 2020, and a pandemic on March 11, 2020. As of July 8, 2020, 11,863,477 cases and 544,949 deaths had been reported in 188 countries [5].

Coronaviruses (CoV) belong to the subfamily Orthocoronavirinae of the family Coronaviridae, order Nidovirales and realm Riboviria. These zoonotic viruses are composed of a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry enclosed in a lipid envelope. Coronaviridae family can be further divided into four genera: α-coronavirus (α-CoV), β-coronavirus (β-CoV), γ-coronavirus (γ-CoV), and δ-coronavirus (δ-CoV), based on the variation in protein sequences. Amongst these, β-CoV is the most dangerous and poses a significant threat to human health. However, the β-CoV virus is non-pathogenic in animals, and reported from bats, mice and domesticated animals like camels. These animals serve as a reservoir but are generally immune to coronavirus-induced diseases [6].

Studies focused on the source of β-CoV revealed inter-species transmission of the virus from animals to humans in the recent past, as in the case of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 [7]. Scientists believe that the SARS-CoV2 virus was probably transmitted to humans from bats through an intermediary animal, in the Wuhan seafood market, in the same way as the other coronaviruses [5,8,9]. The infected patient manifested flu-like symptoms (infection in the lower respiratory system, fever, dry cough, and sore throat), but SARS-CoV2 appears much more transmissible and dangerous than flu [10]. This highly contagious and virulent virus forced approximately one-third of the world’s population under a complete lockdown. However, the situation is slowly improving in many countries across the globe [11].

These crown-like viruses contain 27–34 kilobase (kb) single-stranded positive-sense RNA (ss-RNA) genome surrounded by a membrane studded with glycoprotein spikes. These spikes interact with the angiotensin-converting enzyme-2 (ACE2) receptors to gain entry into the host cell. The virus is internalized by endocytosis, and viral RNA is released from the endosome by acidification or action of intracellular protease (Fig. 1) [12].

Subsequently, viral RNA translation generates the RNA-dependent RNA polymerase, a critical step in the formation of the replication-transcription complex to generate genomic RNA by replication, and sub-genomic RNA (sgRNA) by transcription [13]. Sub-genomic RNA is translated to the structural viral proteins and subsequently transported to the endoplasmic reticulum, where these proteins move along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment, and combine with the nucleocapsids. After the final step of the virus assembly within the Golgi vesicles the new virus particles are released out of the cell by exocytosis, and the host cell dies by necrosis (Fig. 1) [14].

Currently, no FDA approved vaccine to prevent, or drug to treat, COVID-19 or diseases caused by other coronaviruses are available [15]. Academic and research institutions, pharmaceutical firms, and government and non-government organizations around the world are currently working in tandem towards the speedy development of vaccines, drugs and other therapies for prevention and treatment of COVID-19. Fortunately, the fact that SARS-CoV-2 shares 82% nucleotide identity with SARS-CoV-1 (GenBank ID: NC_004718.3), and more than 90% nucleotide identity with MERS-CoV, has greatly assisted scientists in their efforts at designing vaccines and therapies for COVID-19 (Fig. 2) [16].

Currently, numerous clinical trials are underway for the development of vaccines and repurposing of existing therapeutics. Besides, many monoclonal antibodies and several novel small molecule inhibitors are also being tested for the treatment of COVID-19 infection [17,18]. Although a few reports summarising the development of vaccines and therapeutics against COVID-19 have been published in the last 2–3 months, these articles generally focus on specific topics such as the development of vaccines or repurposing of existing drugs [19–25]. Consequently, a comprehensive review which captures a broader panorama of the current efforts directed towards the development of various prophylactic and therapeutic agents against COVID-19 is urgently needed. In this review article, we exhaustively discuss the current status of various
preventive and therapeutic agents in various stages of preclinical and clinical development against COVID-19, including vaccines, repurposed drugs, monoclonal antibodies, plasma therapy, and other miscellaneous therapies.

2. Clinical trials on vaccines

A vaccine is a preventive or preemptive approach against a disease that provides long-term protection. It is a biological preparation in which an attenuated form of the microbe, its toxins or one of its surface proteins provides active acquired immunity against specific infectious diseases. However, despite all-out global efforts, a vaccine against COVID-19 is not expected to be available before the end of 2020. Several clinical trials are currently ongoing in a number of countries around the world to develop a vaccine against SARS-CoV-2. Kaiser Permanente Washington Health Research Institute (KPWHRI) in Seattle, United States of America (USA), is presently carrying out a National Institute of Allergy and Infectious Diseases (NIAID, NIH), supported Phase-1 clinical trial on an investigational vaccine, mRNA-1273, against SARS-CoV-2. NIAID scientists in collaboration with the biotechnology company, Moderna Inc. based in Cambridge, USA, designed and developed this vaccine to target the Spike protein of the SARS-CoV-2 [26]. Coalition for Epidemic Preparedness Innovations (CEPI) supported the manufacturing of this vaccine for clinical trial studies [27]. The interim data from the Phase-I trial of this vaccine has shown positive results for efficacy and safety. On May 06, 2020, the FDA, after reviewing the investigational new drug (IND) application permitted a Phase-II study. On May 12, 2020, Moderna Inc. received FDA fast track designation for this vaccine. Subsequently, on May 29, 2020, the dosing of the first set of participants in all age cohorts was initiated. Meanwhile, the Phase-III study protocol has also been approved, and the trial is expected to start in July 2020 (Table 1, Entry 1) [28–30].

A Hong Kong-based biotech firm, CanSino Biologics Inc., together with the Academy of Military Medical Sciences (AMMS), China, has developed a novel recombinant coronavirus vaccine (adenovirus type 5 vectors) which encodes for a full-length Spike
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Table 1

| S.N. | Vaccine                                          | Company/Developer                          | Current stage of clinical evaluation | Comment                                  |
|------|-------------------------------------------------|--------------------------------------------|-------------------------------------|------------------------------------------|
| 1    | mRNA-1273                                       | Moderna Inc., USA                          | Phase-I, NCT04283461 (ClinicalTrials.gov) | Spike protein                            |
| 2    | Non-Replicating Viral Vector, Ad5-nCoV           | CanSino Biologics Inc. and Beijing Institute of Biotechnology, China | Phase-I, NCT04312117 (ClinicalTrials.gov) ChCTR20000169050 (ICTRP) Phase II, NCT04314389 (ClinicalTrials.gov) | Adenovirus type 5 vector (Ad5) |
| 3    | ChAdOx1                                         | University of Oxford, UK                   | Phase-I, NCT04324606 Phase II, NCT04341389 (ClinicalTrials.gov) | Chimpanzee adenovirus vector |
| 4    | INO-4800                                        | Inovio Pharmaceuticals, USA                | Phase-I, NCT04336410 (ClinicalTrials.gov) | DNA plasmid vaccine electroporation device |
| 5    | BacilleCalmette-Guérin (BCG) vaccine            | Institute of Biotechnology, Academy of Military Medical Sciences, China | Phase-II, ChCTR2000031781 (ICTRP) | Adenovirus vector |
| 6    | Recombinant new coronavirus (2019-nCoV) vaccine (adenovirus vector) | Insti-ute of Biotechnology, Academy of Military Medical Sciences, China | Phase-I, NCT04348370 (ClinicalTrials.gov) | Tuberculosis vaccine |
| 7    | NVX-CoV2373                                     | Novavax Inc., USA                          | Phase-I, NCT043418988 | 1) Nucleoside modified mRNA (modRNA) 2) Uridine containing mRNA (uRNA) 3) Self-amplifying mRNA (saRNA) 4) Engineered genetic sequence of SARS-CoV-2 |
| 8    | CIGB 2020                                       | Centre for Genetic Engineering and Biotechnology (CIGB), Havana, Cuba. | Phase-I, NCT043418988 | Activates the innate immune system |
| 9    | Recombinant chimeric COVID-19 epitope DC        | Shenzhen Third People's Hospital, China | Phase-I, ChCTR20000030750 (ICTRP) | Epitope gene recombinant chimeric DC vaccine |
| 10   | BacTRL-Spike                                    | Synmivio Corporation, Canada               | Phase-I, NCT04334980 (ClinicalTrials.gov) | Engineered *Bifidobacterium longum* which delivers plasmids containing synthetic DNA encoding spike protein from SARS-CoV-2 |
| 11   | Inactivated novel coronavirus                    | Sinovac Biotech Ltd., China               | Phase-I-III, ChCTR20000031809 (ICTRP) NCT04352608 (ClinicalTrials.gov) | Inactivated virus |

(5) protein of SARS-CoV-2. A Phase-I vaccine trial was conducted on the residents of Wuhan, the city where the virus originated to check whether this vaccine could stimulate antibody production and boost immunity against SARS-CoV-2. In preclinical studies, Ad5-nCoV showed an acceptable safety profile and generated a robust immune response in animal models. Currently, a randomized, double-blinded, and placebo-controlled Phase-II clinical study with Ad5-nCoV (registered on April 10, 2020) is ongoing. This trial will evaluate the immunogenicity and safety of Ad5-nCoV in 500 healthy adults over 18 years of age (Table 1, Entry 2) [31–33].

The University of Oxford's Jenner Institute, along with the Oxford vaccine group, has also developed a single-dose vaccine, ChAdOx1-nCoV-19, from a non-replicating adenovirus vaccine vector (ChAdOx1), that generates a robust immune response. Phase-I clinical trial with this vaccine is ongoing while recruitment for the Phase-II clinical trial is currently in progress (Table 1, Entry 3) [34].

On April 06, 2020, Inovio Pharmaceuticals, an American biotechnology company, announced an open-label Phase-I clinical trial with the INO-4800 vaccine in 40 healthy adults to evaluate its safety. INO-4800 is a DNA vaccine that translates into proteins within the cell and initiates an intense, targeted antibody and T-cell response by activating the immune system. The clinical trial are presently underway at the University of Pennsylvania, Philadelphia and the Centre for Pharmaceutical Research, Kansas City, and preliminary results are expected by the end of June 2020. The International Vaccine Institute (VI), Seoul, South Korea, in collaboration with Seoul National University Hospital has also started a Phase-I clinical trial on the INO-4800 vaccine in South Korea. The Phase–II–III efficacy trial for INO-4800 is slated to begin in the summer of 2020, upon regulatory approval (Table 1, Entry 4) [35,36]. In this endeavor, two Phase-III clinical trials with Bacillus Calmette-Guérin (BCG) vaccine to protect people against COVID-19 are also advancing in six countries (Table 1, Entry 5).

The Institute of Biotechnology, AMMS, China, registered a randomized, double-blind, placebo-controlled Phase-II clinical trial of recombinant novel coronavirus (2019-nCoV) vaccine (adenovirus vector) in healthy adults aged 18 and above on April 10, 2020, (Table 1, Entry 6). The same day BioNTech, a German biotechnology company, and the American pharmaceutical company Pfizer secured an approval from the German regulatory authority to conduct a Phase-I–II clinical trial for BioNTech’s BNT162 vaccine against COVID-19 infection. An initial vaccine trial would start in Germany and after regulatory approval clinical trials would also begin in USA and China. This project includes four COVID-19 vaccine candidates, two of which utilize a modified nucleoside mRNA (modRNA), one candidate utilizes self-amplifying mRNA (saRNA), and the fourth one is based on uridine containing mRNA (uRNA) (Table 1, Entry 7).

On May 25, 2020, Novavax Inc., Rockville, USA, enrolled the first participants in a Phase-I–II clinical trial for NVX-CoV2373, a COVID-19 vaccine candidate. NVX-CoV2373 is a stable, prefusion engineered protein made from the genomic sequence of SARS-CoV-2, and is anticipated to work by stimulating the production of neutralizing antibodies. Phase-I–II clinical trial will be conducted in two parts. Phase-I trial would involve approximately 130 healthy participants at two sites in Australia in a randomized, observer-blinded, placebo-controlled study for the evaluation of the
vaccine immunogenicity and safety while the Phase-II trial would assess immunity, safety, and COVID-19 disease reduction at multiple locations across the globe (Table 1, Entry 8) [37]. Additional vaccine candidates currently undergoing clinical trials are CIGB 2020, recombinant chimeric COVID-19 epitope dendritic cell vaccine, and BactRIL-Spike (Table 1, Entries 9–11). On June 13, 2020, Sinovac Biotech Ltd. announced positive results from its ongoing Phase I-II clinical trial on the CoronaVac vaccine against COVID-19, conducted on 743 healthy participants (143 for Phase-I and 600 for Phase-II, aged 18 to 59) in China. No adverse effects were observed in these randomized, double-blind, placebo-controlled trials. Furthermore, the Phase-II study showed that CoronaVac prompted positive immune response indicated by the production of neutralizing antibodies after 14 days of vaccine administration, with a 90% seroconversion rate. Now, the company is planning to carry out its Phase III study in Brazil [38]. Preclinical studies carried out earlier showed that the inactivated vaccine candidate provides protection and is entirely safe for rhesus macaques [39].

3. Clinical trials on existing drugs (Drug repurposing)

Drug repurposing, also known as drug repositioning, drug retasking or drug reprofiling, is a developmental strategy for establishing new uses for existing drugs, including approved, investigational, or discontinued therapeutics. As compared to the new drug development process, drug repurposing is a highly efficient and relatively riskless process, as prior knowledge and literature regarding the existing drug such as pharmacokinetics, pharmacology, formulation, potential toxicity, and manufacturing data are already available. Reduced number of required steps for FDA approval further reduces the time and costs for the medicine to reach the market. Although this strategy has been known for quite some time now, its importance has only been recognized in the last decade or so. Currently, repurposing of drugs constitutes about one-third of the total drug approvals and around 25% of the annual revenue from the pharmaceutical industry [40]. Consequently, when the goal is the development of an effective drug against a disease in a limited time-frame, like in the case of COVID-19, drug repurposing stands out as a promising strategy. Notable efforts towards the repurposing of drugs for developing an effective therapeutic for COVID-19 are discussed below.

3.1. Small molecule drugs

The use of an effective vaccine to prevent COVID-19 infections could be a potentially fool-proof strategy for controlling this epidemic. However, vaccine development for clinical use is projected to take a minimum of 6–8 months, a significant drawback in this time of crisis. Similarly, the development of a new drug against COVID-19 would take even longer. Under such circumstances, drug repurposing has emerged as an attractive approach to combat COVID-19, primarily because of the relatively low investment costs, shorter development timelines, and faster approval rates [41–43]. Various existing drugs are now under investigation as potential treatment of COVID-19. Clinical trials on truvada [emtricitabine (1) and tenofovir (2)], azvudine, a reverse transcriptase inhibitor used for the treatment of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) (3), and ruxolitinib, a Janus kinase (JAK) inhibitor (4), are currently in progress (Table 2, Entries 1–3). Likewise the first affiliated hospital of Zhejiang University, China, is conducting a trial to evaluate and compare the safety and efficacy of a combination of TMC-310911 (ASC09) (5) and ritonavir (6) against COVID-19 (Table 2, Entry 4) [44].

A combination of lopinavir (7) and ritonavir (6), developed by Abbott Laboratories, Chicago, USA, and sold under the brand name kaletra, was approved to treat HIV-AIDS. Kaletra inhibits chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), viral protease enzymes responsible for the cleavage of viral protein into short peptides during the assembly of new virus particles within the host cells. A clinical study conducted with lopinavir-ritonavir on 199 hospitalized adults with severe COVID-19 (99 patients in the lopinavir-ritonavir group and 100 patient in the placebo group) in China-Japan Friendship Hospital, Beijing, China, showed no benefit with lopinavir-ritonavir treatment beyond standard care (ChiCTR2000029308) (Table 2, Entry 5) [45]. However, another open-label, randomized, multi-center, Phase-II trial, testing the efficacy and safety of a combination of lopinavir-ritonavir, ribavirin, and β-interferon in adult patients with mild to moderate COVID-19 symptoms revealed promising results. This University of Hong Kong sponsored triple combination therapy (lopinavir-ritonavir, ribavirin, and β-interferon) trial involved 127 COVID-19 patients (86 patients in the combination therapy group and 41 patients assigned to the control group). Study results showed that triple-drug combination was safe and more effective at reducing the duration of viral shedding as compared to lopinavir-ritonavir alone in patients with mild to moderate symptoms [46].

Umifenovir (arbidol) (8), a broad-spectrum antiviral compound used to treat influenza infection in China and Russia, is currently under investigation for the treatment of COVID-19. Arbidol interferes with the binding of viral spike glycoprotein to the mammalian cell receptor ACE2, and thus prevents the virus entry into the host cells through endocytosis [47–49]. Guangzhou Eighth People’s Hospital in Guangzhou, China, conducted a randomized controlled study on COVID-19 patients to evaluate the efficacy and safety of arbidol or lopinavir/ritonavir (LPV/r) in clinical settings. Of the 44 mild to moderately ill adult COVID-19 patients enrolled in the trial, 21 patients were randomly assigned to receive LPV/r, 16 to receive arbidol, and 7 to the control group with no antiviral medication. The results indicated little benefit for LPV/r or arbidol monotherapy. On the contrary, LPV/r treatment resulted in more adverse events. However, additional studies with larger sample size are required to reach more definitive conclusions (NCT04252885) (Table 2, Entry 6) [50].

Prezcofib is a two-drug combination of darunavir (9), an HIV-1 protease inhibitor, and cobicistat (10), a CYP3A inhibitor used for the treatment of HIV-1 infection. Prezcofib is currently in Phase-III clinical trial at the Shanghai Public Health Clinical Center in China, and in Spain (Table 2, Entry 7). However, in vitro testing of darunavir, a key component of prezcofib, against SARS-CoV-2, revealed no antiviral activity at clinically relevant concentrations [51]. Johnson & Johnson (J&J) in a statement have stated that they have no evidence to support the use of darunavir against SARS-CoV-2, and that the company is screening additional antiviral compounds, including darunavir, for potential activity against SARS-CoV-2 in collaboration with different organizations [52]. Clinical trials on the therapeutic agents, triazavirin (11), baricitinib (12), thalidomide (13), fingolimod (14), ganovo (danoprevir, 15), galidesivir (BCX4430) (16), mefloquine (17), celecoxib (18), oseltamivir (19), pipenfendone (20), and camostat mesylate (foypan, 21) are also underway, either as a single agent or as a combination of two or more drugs (Table 2, Entries 8–18). On April 16, 2020, Karlypharm Therapeutics Inc., Newton, USA, initiated a global, randomized clinical trial with selinexor (22) in severely ill COVID-19 patients. Selinexor, an FDA approved drug for relapsed refractory multiple myeloma, blocks the transport of several viral proteins from the nucleus to the cytoplasm of the host cells by inhibiting the cellular protein XP01 (Table 2, Entry 19).

Another class of drugs, potentially effective against COVID-19, is glucocorticoid based medications. Glucocorticoids are known to decrease inflammation by suppressing the immune system, and
| S.N. | Drug | Institute/Country | Clinical Trials | Mechanism |
|------|------|-------------------|-----------------|-----------|
| 1    | Truvada (emtricitabine and tenofovir) | Plan Nacional de el Sida (PNS) and Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, China | Phase II, NCT04343928 (ClinicalTrials.gov), ChiCTR2000029468 (ICTRP) | Reverse transcriptase inhibitor |
| 2    | Azathymine | The First Affiliated Hospital of HeNan University of CM, China | Phase-0, ChiCTR2000030487, ChiCTR2000030424, ChiCTR2000030404 | Reverse transcriptase inhibitor |
| 3    | Ruxolitinib (Jakafi, Jakavi) | Tongji Hospital, Hubei, China, University of Jena, Germany, Grupo Cooperativo de Hemopatias Malignas, Mexico, and Fundación de investigación HM, Spain | Phase II, NCT04338958, Phase III, NCT04334044, Phasell, NCT04348695 (In combination with Simvastatin) | JAK inhibitor |
| 4    | TMC-310911 (ASC-09) | Ascleisis, First Affiliated Hospital of Zhejiang University, Tongji Hospital, China | Clinical Studies of Combinational Therapies NCT04261907, NCT04261270 (ClinicalTrials.gov) | Novel investigational protease inhibitor |
| 5    | Kaletra (lopinavir/ritonavir) | AbbVie Inc., USA. Included in WHO SOLIDARITY Trial | >10 latest stages clinical studies and included in WHO NCT04252885, NCT04321174, NCT04255017, NCT04307693 (ClinicalTrials.gov), ChiCTR2000029308 (ICTRP) | 3CL protease inhibitor |
| 6    | Umifenovir (Arbidol) | Ruijin Hospital, China | Clinical studies in China ChiCTR2000029621 (ICTRP), NCT04260594 | ACE2 inhibitor |
| 7    | Prezista/Prezobix (darunavir/ritonavir) | Janssen Pharmaceuticals, Belgium, Fundacio Lluita Contra la SIDA, Spain, and Medical Institutions in China | Phase-3 Clinical Studies in Spain NCT04304053, 3 clinical Studies in China NCT04252274 (ClinicalTrials.gov), ChiCTR2000030259, ChiCTR2000029541 (ICTRP) | Protease inhibitor |
| 8    | Triazavirin | Health commission of Heilongjiang province, China | Phase-3 Clinical Study in China ChiCTR2000030001 (ICTRP) | Inhibits RNA synthesis |
| 9    | Baricitinib | Hospital of Prato and University of Colorado, Denver, USA | Phase-3 Clinical Study in Italy NCT043402277 | JAK/NAK inhibitor |
| 10   | Thalomidine | First Affiliated Hospital of Wenzhou Medical University, China | Phase 2 Clinical Study in China NCT04273581, NCT04273529 (ClinicalTrials.gov) | Mechanism of action is not fully understood |
| 11   | Fingolimod | First Affiliated Hospital of Fujian Medical University, China | Phase-II Clinical Study in China NCT04290598 (ClinicalTrials.gov) | Sphingosine 1 phosphate receptor modulator |
| 12   | Ganovo (Danoprevir) | Ascleisis Pharma Inc., and the Ninth Hospital of Nan Chang, China | Phase-IV Clinical Study (In Combinational Therapies) NCT04291729 (ClinicalTrials.gov) | Protease inhibitor (Hepatitis C) |
| 13   | Galidesivir (BCX4430) | BioCryst Pharmaceuticals, USA | Phase-I NCT03891420 (ClinicalTrials.gov) | Nucleoside RNA polymerase inhibitor |
| 14   | Melphostione | FISABIO, Spain | Phase-III 2020-001194-69 (EU-CTR) | Antimalarial drug |
| 15   | Celecoxib | Guangzhou Eighth People’s Hospital, China | Phase-0 IRCT20200317046797N1 (ICTRP) | COX-2 inhibitors |
| 16   | Oseltamivir (Tamiflu) | Tongji Hospital, China | Phase III, Alone and in combination with ASC09F or Ritonavir NCT04261270 (ClinicalTrials.gov) | Neuraminidase inhibitor (influenza). Prevents new viral particles from being released from cell |
| 17   | Pirfenidone | Huazhong University of Science and Technology and Guangzhou Medical University, China | Phase-III, NCT04282902 (ClinicalTrials.gov), ChiCTR2000030892, ChiCTR2000030333 (ICTRP) | Used for the treatment of idiopathic pulmonary fibrosis |
| 18   | Camostatmesilate (Foypan) | University of Aarhus, Denmark and Tabriz University of Medical Sciences, Iran | Phase 2 Clinical Study in Germany NCT04321096 (ClinicalTrials.gov), IRCT20200317046797N1 (ICTRP) | Spike protein |
| 19   | Selinexor (XPOVO) | Karyopharm Therapeutics Inc, USA | Phase-II, NCT04349098 (ClinicalTrials.gov) | XPO1 inhibitor |
| 20   | Ciclesonide | Korea University Guro Hospital, Korea | Phase-II Alone and in combination with hydroxycholoroquine NCT0430586 (ClinicalTrials.gov) | Glucocorticoid used to treat asthma and allergic rhinitis |
| 21   | Methylprednisolone | Various Institutes in China | Phase-II/III, NCT04273321, NCT04244591 (ClinicalTrials.gov), ChiCTR2000029566, ChiCTR2000029386 (ICTRP) | Glucocorticoid used to treat asthma and allergic rhinitis |
| 22   | Favipiravir (Favipiravir) | Zhejiang Hisun Pharmaceutical Co., and various research institutes in China | Approved in China ChiCTR2000029996, ChiCTR2000030894, ChiCTR2000029060, ChiCTR2000030254 (ICTRP) | RNA-dependent RNA polymerase inhibitor (RDRP) |
| 23   | Sovodak (sofosbuvir) | Tehran University of Medical Sciences, Iran | Phase-III IRCT20200128046294N2 (ICTRP) | RNA polymerase inhibitor |
### Table 2 (continued)

| S.N. | Drug | Institute/Country | Clinical Trials | Mechanism |
|------|------|-------------------|-----------------|-----------|
| 24   | Remdesivir (GS - 5734) (28) | Gilead Sciences, USA | > 10 Clinical studies worldwide and included in WHO SOLIDARITY Trial NCT04323761, NCT04257656 NCT04315948 (ClinicalTrials.gov) | RNA polymerase |
| 25   | Chloroquine (29) | Research Institutes Worldwide | > 10 Studies worldwide > 10 Clinical Studies in China and included in WHO SOLIDARITY Trial ChiCTR2000029609 (ICTPR) NCT04261517 (ClinicalTrials.gov) | Blocks viral entry by inhibiting glycosylation of host receptors, and endosomal acidification |
| 26   | Hydroxychloroquine (30) | Research Institutes Worldwide | > 10 Clinical Studies worldwide and included in WHO SOLIDARITY Trial NCT04321278, NCT04261517 (ClinicalTrials.gov) ChiCTR2000029868 ChiCTR2000029559 (ICTPR) EUCTR2020-000890-25 | Blocks viral entry by inhibiting glycosylation of host receptors, and endosomal acidification |
| 27   | Azithromycin (31) | Research Institutes Worldwide | >10 trials in combination with other drugs, NCT04322396, NCT04321278 NCT04322123 (ClinicalTrials.gov) | Antibiotic |
| 28   | Harvoni (sofosbuvir (26) ledipasvir (32)) | Tehran University of Medical Sciences, Iran | Phase II/III IRTC201002280003409N29 (ICTPR) | RNA polymerase inhibitor |
| 29   | Umifenovir (Arbidol) | Ruijin Hospital, China | Clinical studies in China ChiCTR2000029621 (ICTPR) NCT04260594 (ClinicalTrials.gov) | ACE2 inhibitor |
| 30   | Colchicine (33) | Montreal Heart Institute, Canada | Phase II NCT04322682 (ClinicalTrials.gov) | Multiple proinflammatory mechanisms |
| 31   | Farxiga (dapagliflozin) (34) | AstraZeneca and Saint Luke’s Mid America Heart Institute, USA | Phase II/III NCT04350593 (ClinicalTrials.gov) | Sodium-glucose transportpro-tein-2 (SGLT2) inhibitor |
| 32   | Tradiprant (ODYSEY Trial) (35) | Vanda Pharmaceuticals, USA with the Feinstein Institutes for Medical Research, USA | Phase II-III, NCT0426426 (ClinicalTrials.gov) | Neurokinin-1 receptor (NK-1R) antagonist |
| 33   | Calqueurine (acalabrutinib) (36) | AstraZeneca, UK | Phase II, NCT04346199 (ClinicalTrials.gov) | Bruton’s tyrosine kinase (BTK) |
| 34   | Tranilast (37) | The First Affiliated Hospital, USTC, China | Phase IV ChiCTR2000030002 (ICTPR) | Suppression of the expression and/or action of the TGF-β pathway |
| 35   | Tetradrine (38) | Henan Provincial People’s Hospital, China | Phase IV, NCT0438317 (ClinicalTrials.gov) | Calcium channel blocker |
| 36   | Suramin (39) | The First Affiliated Hospital of Zhejiang University, China | Phase 0, ChiCTR2000030029 (ICTPR) | Combines with trypanosomal glycolytic enzymes to inhibit energy metabolism |
| 37   | Sildenafil (40) | Tongji Hospital, China | Phase III, NCT04304131 (ClinicalTrials.gov) | Phosphodiesterase-5 inhibitor, and vasodilator agent |
| 38   | polyinosinic-polyctydilicacid (41) | The First Affiliated Hospital of Wenzhou Medical University, China | Phase IV ChiCTR2000029776 | Toll-like receptor 3 (TLR3) |
| 39   | Nintedanib (42) | Tongji Hospital, China | Phase II, NCT04338802 (ClinicalTrials.gov) | Used for the treatment of idiopathic pulmonary fibrosis |
| 40   | Linagliptin (43) | University of Miami, USA | Phase – IV, NCT04341935 | DPP4 inhibitor |
| 41   | Leflunomide (44) | Renmin Hospital of Wuhan University, China | Phase III, ChiCTR2000030058 (ICTPR) | Inhibits DHODH |
| 42   | Itraconazole (45) | Belgium - FFS Health-DGM | Phase II 2020-01243-15 (EU-CTR) 2020-01236-10 (EU-CTR) NL8491 (NTR) | P-glycoprotein inhibitor |
| 43   | Imatinib (Gleevec) (46) | Amsterdam UMC, Netherlands | Phase II 2020-01236-10 (EU-CTR) NL8491 (NTR) | Tyrosine kinase inhibitor |
| 44   | Losartan (47) | Various Research Institutes in USA and Iran | NCT04340057, NCT04311177 NCT04335123, NCT04312009 (ClinicalTrials.gov) IRTC20108020040678N4 (ICTPR) In combination with Simvastatin and Aspirin NCT04343001 (ClinicalTrials.gov) Phase – IV, NCT04348409 Phase – IV, NCT04341493 Phase III, NCT04343248 Combination with Ivermectin Phase – II NCT04360356 (ClinicalTrials.gov) | Angiotensin-II type 1 receptor blocker |
| 45   | Nitazoxanide (48) | Azidus Brazil, Romark Laboratories L.C., USA, and Tanta Faculty of Medicine, Egypt | Phase IV, NCT04341493 | Used for the treatment of various helminthic, protozoal, and viral infections |
| 46   | Tranexamic Acid (TXA) (49) | University of Alabama at Birmingham, USA | Phase II NCT04338126 NCT04338074 (ClinicalTrials.gov) | Reduces conversion of plasminogen to plasmin |
| 47   | Amiodarone (50) | Nicolaus Copernicus University, Poland | Phase II/III NCT04351763 (ClinicalTrials.gov) | KCNH2 and CACNA2D2 inhibitor |
| 48   | CM4620-Injectable Emulsion (IE) (52) | CalciMedica, Inc., US | Phase II, NCT04345614 (ClinicalTrials.gov) | CRAC channel inhibitor |
| 49   | Dalargin (53) | Burnasuy Federal Medical Biophysical Center, Russia | Phase II, NCT04346693 (ClinicalTrials.gov) | Antioxidant |
| 50   | Deferoxamine (Desferal) (54) | Kermanshah University of Medical Sciences, Iran | Phase II, NCT04333550 (ClinicalTrials.gov) | Chelating agent |
| 51   | Dexametadominide (55) | The Third Affiliated Hospital of Zunyi Medical University, China | Phase 0 ChiCTR2000030853 (ICTPR) | Selectively binds to presynaptic alpha-2 adrenoceptors |
| 52   | S.L.A. Pharma AG, Switzerland | | Phase III, NCT04335032 (ClinicalTrials.gov) | Omega-3 fatty acid |

(continued on next page)
| S.N. | Drug | Institute/Country | Clinical Trials | Mechanism |
|------|------|------------------|-----------------|-----------|
| 53   | Fluvoxamine (57) | Washington University School of Medicine, USA | Phase-II, NCT04342663 (ClinicalTrials.gov) | Selective serotonin reuptake inhibitor (SSRI) |
| 54   | Ibuprofen (58) | King’s College London, UK | Phase-IV, NCT04334629 (ClinicalTrials.gov) | NSAID |
| 55   | Valsalvart (59) | Radboud University, Netherland | Phase-IV, NCT04335786 (ClinicalTrials.gov) | Angiotensin II inhibitor |
| 56   | Telmisartan (60) | Laboratorio Elea Phoenix S.A., Argentina | Phase-II, NCT04355936 (ClinicalTrials.gov) | Non-peptide angiotensin II receptor antagonist |
| 57   | Tolacitinib (61) | Universita Politecnica Delle Marche (UNIVPM), Italy | Phase-II, NCT04332042 (ClinicalTrials.gov) | Janus kinase (JAK) inhibitor |
| 58   | Spironolactone (62) | Istanbul University-Cerrahpasa, Turkey | Phase-II, NCT04345887 (ClinicalTrials.gov) | Aldosterone antagonist |
| 59   | Sirolimus (63) | University of Cincinnati, USA | Phase II, NCT04341675 (ClinicalTrials.gov) | Immuno-suppressive and antineoplastic agent |
| 60   | Methotrexate (64) | Azidus, Brazil | Phase-II, NCT04352465 (ClinicalTrials.gov) | Inhibits the enzyme dihydrofolate reductase |
| 61   | Naproxen (65) | Assistance Publique – Hôpitaux de Paris (AP-HP), France | Phase-III, NCT04325633 (ClinicalTrials.gov) | NSAID |
| 62   | Piclidenoson (66) | Can-Fite Bio Pharma, Israel | Phase-II, NCT04333472 (ClinicalTrials.gov) | Antagonist of adenosine A3 receptors |
| 63   | Pyridostigmine bromide (67) | Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico | Phase-II, NCT04343963 (ClinicalTrials.gov) | Acetylcholinesterase inhibitor |
| 64   | Captoril (ACEIs) (68) | Tanta University, Egypt | Phase-III, NCT04345406 (ClinicalTrials.gov) | Angiotensin-converting-enzyme inhibitors |
| 65   | BLD2660 | Blade Therapeutics, USA | Phase-II, NCT04334460 (ClinicalTrials.gov) | Calpain inhibitor |
| 66   | Vazegepant (69) | Biohaven Pharmaceuticals, Inc. USA | Phase-II, NCT04346615 (ClinicalTrials.gov) | CGRP receptor antagonist |
| 67   | Valsartan (70) | Oryzon Genomics S. A. Spain | Phase-II 2020-001618-39(EU-CTR) | LSD1 inhibitor |
| 68   | Triiodothyronine (71) | Uni-pharma Kleon Tseits Pharmaceutical Laboratories S.A., Greece | Phase-II, NCT04348513 (ClinicalTrials.gov) | Thyroid hormone |
| 69   | Sitagliptin (72) | Shahid Beheshti University of Medical Sciences, Iran | Phase-II/III | Dipetidyl peptidase-4 (DPP-4) inhibitor |
| 70   | Ribavirin (trabivirin or VIRAZONE) (73) | Bausch Health Americas Inc., USA | Phase-I, NCT04356677 (ClinicalTrials.gov) | Induces mutations in RNA-dependent replication in RNA viruses |
| 71   | Noscapine (74) | Qazvin University of Medical Sciences, Iran | Phase-II | α-receptor agonist |
| 72   | Nafamostat mesylate (75) | University Hospital Padova, Italy | Phase-II, NCT04352400 (ClinicalTrials.gov) | Serine protease inhibitor |
| 73   | Melatonin (76) | Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Bolivia, and Semnan University of Medical Sciences, Iran | Phase-II, NCT04353128 (ClinicalTrials.gov) | Hormone that regulates the sleep–wake cycle |
| 74   | Isotretinoin (77) | Kafrelsheikh University, Egypt | Phase-III | Amplifies production of neutrophil gelatinase-associated lipocalin (NGAL) in the skin |
| 75   | Formoterol (78) | Mashal Daneshvari Hospital, Iran | Phase-III, NCT043426114 (ClinicalTrials.gov) | Long acting β₂ agonist used as a bronchodilator |
| 76   | Etoposide (79) | Boston Medical Center, USA | Phase-II, NCT04356690 (ClinicalTrials.gov) | Prevents cytokine storm |
| 77   | Estradiol (80) | Stony Brook University, USA | Phase-II, NCT04359329 (ClinicalTrials.gov) | Estrogen steroid hormone |
| 78   | Doxycycline (81) | Nantes University Hospital, France | Phase-III | Antibiotic |
| 79   | Crocin (82) | Mashhad University of Medical Sciences, Iran | Phase-II, NCT043535190 (ClinicalTrials.gov) | NMDA receptor antagonist |
| 80   | Chlorpromazine (83) and Chlorpromazine injection | Centre Hospitalier St Anne and Cairo University, Egypt | Phase-II, NCT043466739 (ClinicalTrials.gov) | D2 dopamine antagonist |
| 81   | Bromhexine (84) | Tabriz University of Medical Sciences, Iran | Phase-III, NCT04354805 (ClinicalTrials.gov) | |
| 82   | Bemcentinib (85) | University Hospital Southampton NHS Foundation Trust, UK | Phase-II IRT20200317046797N4 (ICTPR) | Enhances mucus production in the respiratory tract |
| 83   | Alovastatine (86) | Mazandaran University of Medical Sciences, Iran | Phase-II | Inhibitor of AXL kinase |
| 84   | Almitrine (87) | Assistance Publique–Hôpitaux de Paris (AP-HP), France | Phase-II | Used to prevent cardiovascular disease |
| 85   | Ramipril (88) | University of California, San Diego, USA | Phase-II, NCT04366050 (ClinicalTrials.gov) | Agonist of peripheral chemoreceptors present on the carotid bodies |
| 86   | Progesterone (89) | Cedars-Sinai Medical Center, USA | Phase-I, NCT04365127 (ClinicalTrials.gov) | Non-sulfhydryl ACE inhibitor |
| 87   | Prazosin (90) | Johns Hopkins University, USA | Phase-II, NCT04365257 (ClinicalTrials.gov) | Competitive alpha-1 adrenergic receptor blocker |
| 88   | N-acetylcysteine (91) | Memorial Sloan Kettering Cancer Centre, USA | Phase-II, NCT04374461 (ClinicalTrials.gov) | Mucoytic |
| 89   | Levamisole (92) | Ain Shams University, Egypt | Phase-III, NCT04360122 (ClinicalTrials.gov) | Modifiers or stimulaties cell-mediated immune processes |
| 90   | Lenfunomide (94) | The Third Hospital of Wuhan City, China | Phase-III, ChiCTR2000030058 | Inhibits dihydroorotate dehydrogenase |
| 91   | Hospital Universitario de Getafe, Spain | Phase-IV, NCT04361643 (ClinicalTrials.gov) | | |
therefore, can be good candidates for managing the symptoms of COVID-19 patients with severe pneumonia. A Phase-II trial, investigating whether the ciclesonide (23), a glucocorticoid, alone or in combination with hydroxychloroquine (HCQ) could eliminate SARS-CoV-2 from the respiratory tract of patients with mild COVID-19 symptoms (Table 2 Entry 24), a combination of chloroquine/hydroxychloroquine (Table 2 Entry 25 and 26), lopinavir/ritonavir (Table 2 Entry 27), and favipiravir, which reported a reduction in the disease duration from 11 days to 4–5 days and a faster recovery from COVID-19 disease [57].

Recently, another Phase-III clinical trial with sovodka (sofosbuvir 400 mg/daclatasvir 80 mg), and harvoni (sofosbuvir 400 mg/ledipasvir 90 mg) on COVID-19 patients began in different hospitals in Tehran, Iran (Registered on March 14, 2020). Sovodka and harvoni are Iranian antiviral drugs approved for the treatment of Hepatitis C. This study is not aimed as a cure for COVID-19 but rather testing the drugs as a supportive medicine to hasten the healing of COVID-19 patients (Table 2, Entry 23). There are several additional small molecules listed in Figs. 3–6, which are currently undergoing clinical validation (Table 2, Entries 24–103).

### 3.2. Important clinical trials

#### 3.2.1. SOLIDARITY trial

To address the unprecedented medical emergency due to COVID-19, WHO recently announced the launch of an exclusive and expansive, 4-arm pragmatic clinical trial, called SOLIDARITY TRIAL. This promising multinational trial is currently investigating four promising therapeutics/therapeutic combinations: viz. remdesivir (Table 2 Entry 24), a combination of chloroquine/hydroxychloroquine (Table 2 Entries 25 and 26), lopinavir/ritonavir (Table 2 Entry 5), and lopinavir/ritonavir/interferon-beta (Fig. 7) [58]. Despite the failure of lopinavir/ritonavir in initial studies, WHO is very optimistic about the potential efficacy of this drug combination against COVID-19, and has included it in SOLIDARITY trials [59,60]. As of June 03, 2020, 83 clinical trials on this combination therapy are active across the world [61].
and blocking endosomes acidification [62–65]. An open-label, non-randomized clinical trial at Institut Hospitalo-Universitaire (IHU) of the Fondation Méditerranéenne Infection (FMI), Marseille, France, in early March 2020, with a combination of the HCQ and azithromycin in 20 COVID-19 patients demonstrated significant viral load reduction. Although the results of this small size study were promising, further validation using a large sample size is needed for definitive conclusions [EUCTR2020-000890-25] [64]. Another clinical study at Shanghai Public Health Clinical Centre (SPHCC), China, investigated the therapeutic efficacy of HCQ in 30 patients with COVID-19 disease (15 each for the HCQ and the control group), and reported a good prognosis in the HCQ group. The research team, however, expressed the need for a larger sample size to further validate the findings [66].
In February 2020, Renmin Hospital, Wuhan University, China, carried out another study on 62 patients to evaluate the efficacy of HCQ in the treatment of COVID-19 disease. This study partially confirmed the therapeutic potential of HCQ in the treatment of COVID-19 as the HCQ treatment significantly shortened the time to clinical recovery (TTCR) and promoted the resolution of pneumonia. Nevertheless, more expansive clinical studies are required to confirm the utility of HCQ in COVID-19 patients (ChiCTR2000029559) [67]. However, two HCQ clinical trials conducted by the US Department of Veterans Affairs, and Columbia University Irving Medical Centre (CUIMC), New York, NY, USA, respectively, showed early negative results for efficacy and safety.
The US Department of Veterans Affairs study conducted on 368 COVID-19 patients found no evidence to demonstrate that the use of HCQ, either with or without azithromycin, reduced the risk of death or mechanical ventilation over supportive care. Moreover, HCQ treatment alone increased the overall mortality [68].

CUIMC conducted another large-scale clinical study with HCQ on 1376 participants with moderate to severe COVID-19 disease. Eight hundred eleven patients received HCQ, while 565 patients did not receive any drug (placebo). Remarkably, HCQ treated COVID-19 patients reported a similar level of risk from intubation or death as the placebo group [69]. As of June 04, 2020, as many as 398 clinical trials using HCQ and/or CQ were active worldwide [61]. Nonetheless, on June 17, WHO announced the suspension of the HCQ arm of the SOLIDARITY trial [70]. Earlier on June 15, 2020, FDA revoked the emergency authorization for HCQ and CQ as a treatment for COVID-19 after determining that the efficacy of these drugs against COVID-19 is questionable. Moreover, the use of HCQ and CQ for COVID-19 treatment is associated with severe side-effects [71].

Many nucleoside and nucleotide analogs are well-known antiviral agents and useful for the treatment of HIV, hepatitis B, cytomegalovirus, and herpes simplex virus infections. The nucleoside and nucleotide analogs get incorporated into the DNA and RNA, as they resemble the naturally occurring nucleic acid monomers leading to faulty viral RNA or DNA synthesis. These agents inhibit various enzymes such as DNA-dependent DNA polymerases (DdDP), RNA-dependent RNA polymerases (RdDP), RNA-dependent DNA polymerases (RdRP), ribonucleotide reductase, kinases, and nucleoside phosphorylase [72]. Consequently, nucleoside and nucleotide analogs are the most preferred candidates for the design and development of new antiviral drugs. Remdesivir, an RNA-dependent RNA polymerase based inhibitor drug initially developed by Gilead Sciences to combat Hepatitis C (Patent US20170071964), has shown appreciable efficacy against SARS-CoV-2, and is presently undergoing Phase-III clinical trial in China since February 06, 2020. Recently, the University Hospitals, Cleveland, USA, disclosed that they would conduct a couple of clinical trials with remdesivir [65]. Currently, remdesivir is a part of the WHO’s SOLIDARITY trial. Likewise, the University of Chicago, Chicago, USA, is presently evaluating the efficacy of remdesivir in a Phase-III clinical trial involving severally ill COVID-19 patients. On April 16, 2020, the medical news website, STAT, published a report on early results from a remdesivir clinical trial which revealed significant improvement in the fever and respiratory symptoms in COVID-19 patients receiving remdesivir, with nearly all remdesivir treated patients getting discharged from the hospital in less than a week [73].

On April 29, 2020, Gilead Inc. reported the results from another ongoing Phase-III trial (Adaptive COVID-19 Treatment Trial 1 (ACTT1), NCT04280705) with remdesivir, in patients with severe COVID-19. The results revealed that patients receiving drug
remdesivir recovered in 11 days as compared to the recovery time of 15 days for the placebo group. Furthermore, remdesivir showed the same clinical improvement in patients receiving a five-day treatment as those receiving a 10-day treatment. The drug candidate was well-tolerated and safe, and more than half of the patients were discharged by day 14 in both subject groups, with 31% faster recovery time as compared to placebo [74,75]. Additionally, Monroe Health System, New York, USA, and Albert Einstein College of Medicine, New York, USA, have started the ACTT2 study (next stage of ACTT trial) with remdesivir plus baricitinib on severely ill COVID-19 patients in USA [76]. According to information listed on the ClinicalTrials.gov website, Gilead terminated its trials with remdesivir on moderate and severe COVID-19 patients in China in April 2020. The primary reason for the abrupt termination of the remdesivir trial was the difficulty in recruiting enough infected patients for trials as the COVID-19 outbreak in China has mostly been contained [77]. As of June 29, 2020, about 19 clinical trials with remdesivir are registered and active [78]. Moreover, the results from remdesivir clinical trials have been extensively discussed and disseminated [79].

3.3. RECOVERY trail

Another notable large multi-arm RECOVERY trial began on March 19, 2020, in UK for developing potential coronavirus treatment (EudraCT 2020-001113-21, ISRCTN50189673 and NCT04381936). The primary objective of this Phase II-III clinical trial is the randomised evaluation of COVID-19 therapy (RECOVERY) by assessing the effects of different treatments. The RECOVERY trial continually reviews the latest reports on new drugs being repurposed as a potential treatment for COVID-19 and incorporates the most promising of these drugs in the clinical trials. Currently, drugs included in the RECOVERY trials are azithromycin, hydroxychloroquine, low-dose dexamethasone, lopinavir/ritonavir combination, and tocilizumab [80,81].

On June 16, 2020, a preliminary study on the Dexamethasone arm of the RECOVERY trial showed promising results in reducing mortality in critically ill COVID-19 patients. It was observed that mortality in patients on ventilators was reduced by one-third, and in patients who required oxygen support by one-fifth, compared to patients receiving standard care. However, no such reduction in mortality was observed in patients with milder illness not requiring respiratory support [82,83]. This report is the first proven instance of any drug improving survival in critically ill COVID-19 patients. However, although the study was useful and based on high-quality evidence, some experts have called for further research to conclusively establish the reported benefits [84]. Consequent to these findings dexamethasone has already been approved for critically ill COVID-19 patients requiring oxygen support or on the ventilator, in the UK and India [85,86].

Fig. 6. Known drugs undergoing clinical trials for COVID-19 (Drug repurposing).
3.3.1. ACCORD (accelerating COVID-19 research & development) trial

ACCORD is a fast-track clinical trial program launched by the UK government, which involves the government, academia and industry, for the development of new drug candidates to treat COVID-19 patients. The current program includes six different drugs and drug combinations. Initially two drugs would be investigated in Phase-II trials in various hospitals across the UK to assess their safety and efficacy. Bemcentinib, an AXL kinase inhibitor manufactured by the Norwegian pharma company BerGenBio, is the first candidate to enter the ACCORD program and is presently undergoing a Phase II clinical study to evaluate its safety and efficacy on 120 participants (60 in the bemcentinib and 60 in the SoC group).

Two molecules developed by the London based British-Swedish multinational pharmaceutical AstraZeneca, a Bruton’s tyrosine kinase (BTK) inhibitor, and a Phase-II drug candidate targeting interleukin 33 (IL-33) are also part of this program. In addition to the six initial candidates, the ACCORD program would evaluate the effectiveness and safety of additional drugs and drug combinations. Successful candidates would then be moved ahead rapidly for further studies on large scale trial platforms such as the RECOVERY trial [87].

3.3.2. CATALYST trial

The University of Birmingham (UK) has launched the CATALYST trial to evaluate a series of drugs for the treatment of COVID-19 patients. The trial will test a series of drugs, including existing therapeutics for cancer and inflammatory diseases such as rheumatoid arthritis. Initially the trial will assess four drugs and cellular therapies under a new adaptive trial design intended for a rapid investigation of effectiveness [88]. The drugs, namilumab (IZN-101) and infliximab (CT-P13) would be initially evaluated in a study conducted by the University of Birmingham and University of Oxford in collaboration with Izana Bioscience, Oxford, UK, and Celltrion Healthcare, Incheon, South Korea [89].

3.3.3. CALVID-1 trial

Vidofofludimus calcium (IMU-838) (100, Fig. 6) is an orally available, next-generation dihydroorotate dehydrogenase (DHODH) inhibitor currently under investigation for the treatment of several chronic inflammatory diseases. Immunic Inc., a biopharmaceutical company, based in San Diego, USA, has secured regulatory approval from the Federal Institute for Drugs and Medical Devices (BfArM), the medical regulatory body in Germany, on May 13, 2020, to conduct a Phase-II clinical trial named CALVID-1 with IMU-838 in COVID-19 patients. The company had earlier reported that IMU-838 prevents the replication of SARS-CoV-2 clinical isolates, the causative agent of COVID-19 [90–92]. On June 15, 2020, Immunic, Inc. announced the initiation of the phase-II trial with IMU-838 [93].

3.3.4. Austrian coronavirus adaptive clinical trial (ACOVACT)

To compare the various antiviral agents available for treatment of COVID-19, Medical University of Vienna, Austria, in collaboration with Kaiser Franz Josef Hospital, Vienna is conducting an open-label, randomized-controlled, multi-arm ACOVACT trial (NCT04351724). ACOVACT trial includes three primary study arms, and patients are randomly assigned to receive HCQ, lopinavir/ritonavir, or standard therapy. Interestingly, patients from these three arms may enroll in multiple sub-studies which includes sub-study A (randomized to rivaroxaban versus standard care), sub-
### Table 3
Potential therapeutics other than small molecule drugs undergoing clinical trials for COVID-19.

| S.N. | Drug Name                  | Company/Developer                      | Function                                      | Comment                                           |
|------|----------------------------|----------------------------------------|-----------------------------------------------|---------------------------------------------------|
| 1    | Actemra (tocilizumab)      | Roche, Switzerland                     | Interleukin-6 inhibitor                        | Recombinant humanized monoclonal antibody Phase-III NCT04320615, NCT04317902, (ClinicalTrials.gov) |
| 2    | Sarilumab (Kefzara)        | Feinstein Institute, New York, USA, Gilead Sciences Inc., USA and Regeneron Pharmaceuticals, USA | Interleukin-6 inhibitor                        | Recombinant humanized monoclonal antibody NCT04315298, (ClinicalTrials.gov) |
| 3    | Leronlimab                 | CytoDyn, Canada                        | CCR5 antagonist                                | Humanized IgG4 monoclonal antibody Phase-II, NCT04343651 NCT04347239, (ClinicalTrials.gov) |
| 4    | Ultomiris (raluizumab-cwvz)| Alexion Pharmaceuticals, USA           | Inhibits C5                                    | Recombinant humanized monoclonal antibody Phase-II, NCT04351243 (ClinicalTrials.gov) |
| 5    | Gimsilumab                 | Kinevant Sciences GmbH, Switzerland and Roivant Sciences, Switzerland | Acts on granulocyte-macrophage colony-stimulating factor (GM-CSF) | Fully humanized monoclonal antibody Phase-II, NCT04351243 (ClinicalTrials.gov) |
| 6    | Meplazumab                 | Tang-Du Hospital, China                | Blocks interleukin 5                          | Humanized monoclonal antibody, Phase-I/II NCT04275245 (ClinicalTrials.gov) |
| 7    | Lenzilumab                 | Humanigen Inc., USA                    | CSF2/GM-CSF                                    | Humanized monoclonal antibody, NCT04351152 (ClinicalTrials.gov) |
| 8    | Ikezumab                   | Xiangya Hospital of Central South University, Interleukin 17A inhibitor China | VEGF-A inhibitor                               | Humanized monoclonal antibody ChICTR2000030703 |
| 9    | Bevacizumab (Avastin)      | Various institutes in China, france and Italy | VEGF-A inhibitor                               | Recombinant humanized monoclonal antibody NCT04344782, NCT04275414 (ClinicalTrials.gov) |
| 10   | Adalimumab (Humira)        | Shanghai Changzheng Hospital, China    | TNF inhibitor                                  | Fully humanized monoclonal antibody Phase-IV, ChICTR2000030809, (ICTPR) |
| 11   | Clazakizumab               | NYU Langone Health and Cedars-Sinai Medical Center, USA | IL-6 inhibitor                                 | Phase-II, NCT04343989, NCT04348500 (ClinicalTrials.gov) |
| 12   | Siltuximab                 | Fundacion Clinic per a la Recerca Biomédica, IL-6 inhibitor Spain | PD-1                                          | Phase-II, NCT04329650 (ClinicalTrials.gov) |
| 13   | Nivolumab                  | Assistance Publique - Hôpitaux de Paris, France | Interleukin 6                                  | human IgG4 monoclonal antibody, phase II NCT04343144 (ClinicalTrials.gov) |
| 14   | IFX-1                      | Infliximab GmbH, Germany               | CSA                                            | Monoclonal antibody phase II, NCT04333420 2020-001335-28 (EU-CTR) |
| 15   | TJ003234                   | I-Mab Biopharma Co., Ltd., China       | Granulocyte-macrophage colony-stimulating factor (GM-CSF) | Humanized immunoglobulin G1 (IgG1) monoclonal antibody Phase-I, NCT04341116, (ClinicalTrials.gov) |
| 16   | LY3127804                  | Eli Lilly and Company, USA             | Angiopoietin 2 (Ang2)                         | Humanized and engineered IgG4 isotype antibody Phase-II, NCT04342897, (ClinicalTrials.gov) |
| 17   | sirukumab                  | Janssen Pharmaceutica N.V., Belgium    | Interleukin 6                                  | Human interleukin-1 receptor antagonist Phase-II, NCT04380961 (ClinicalTrials.gov) |
| 18   | Kineret (anakinra)         | University Hospital Ghent, Belgium     | Interleukin-1 receptor antagonist              | Human interleukin-1 receptor antagonist (IL-1Ra), 2020-001500-41 (EU-CTR) |
| 19   | Novaferonc Nova            | Hu'nan Haiyaohongxingtang Pharmaceutical Co., Ltd., China | Boosts immune system                           | Cytokine gene-derived recombinant protein ChICTR2000029496 (ICTPR) |
| 20   | ATYR1923                   | aTyr Pharma Inc., USA                  | Selective modulator of neuropilin-2           | A fusion protein comprised of the immuno-modulatory domain of histidylRNA synthetase fused to the FC region of a human antibody Type I interferons Phase-I, NCT04311697, (ClinicalTrials.gov) |
| 21   | IFN-α2b                    | Tongji Hospital, China                 | Interferes with viral replication             | A recombinant human angiotensin-converting enzyme 2 (rhACE2) Type I interferons Phase-I, NCT04311697, (ClinicalTrials.gov) |
| 22   | APN01                      | APEIRON Biologics, Austria             | Blocks virus entry through ACE2               | A recombinant fusion protein Phase-I, NCT04343651 (ClinicalTrials.gov) |
| 23   | Sargramostim (Leukine)     | University Hospital, Ghent, Belgium    | Immunostimulator                               | Recombinant humanized monoclonal antibody Phase-II, NCT04351152 (ClinicalTrials.gov) |
| 24   | CD24Fc                     | OncoImmune Inc., USA                   | Interleukin 1 beta inhibitor, interleukin 6 inhibitor, and tumour necrosis factor alpha inhibitor | Phase-III, NCT04317902 (ClinicalTrials.gov) |
| 25   | PD-1 mAB                   | Jianfeng Xie, Southeast University, China, and West China Hospital, Sichuan University, China | PD-1 blocking antibody                        | Antibody, Phase-II, NCT04268537 (ClinicalTrials.gov) ChICTR2000030828 (ICTPR) |
| 26   | Intravenous immunoglobulin (IVIG) | Peking Union Medical College Hospital, China, and Centre Hospitalier St Anne, France | Enhance passive immunity, and anti-inflammatory and immunomodulatory effect | Immunoglobulin NCT04261426, NCT04350580 (ClinicalTrials.gov) |
| 27   | Angiotensin (1−7)          | Hôpital Erasme, Belgium                | Antioxidant and anti-inflammatory              | Heptapeptide Phase-II, NCT04326666 (ClinicalTrials.gov) |
| 28   | Aviptadil (RLF-100)        | Relief Therapeutics, Switzerland in collaboration with NeuroRx, USA | Used in the treatment of ARDS                 | Analog of vasoactive intestinal polypeptide Phase-IIb/III, NCT04311697 (ClinicalTrials.gov) |
| 29   | Ulinastatin                | Shanghai Changzheng Hospital, China    | Trypsin inhibitor                              | (continued on next page) |
| S.N. | Drug Name | Company/Developer | Function | Comment |
|------|-----------|-------------------|----------|---------|
| 30   | Thymosin  | Wuhan Jinyintan Hospital, China | Biological response modifier | Glycoprotein Phase-IV ChCTR2000030779 (ICTPR) Small protein isolated from the thymus |
| 31   | Solnatide | Medical University of Vienna, Vienna Austria | Reduces pulmonary edema | Synthetic Peptide Phase-II 2020-001244-26 (EU-CTR) |
| 32   | Procalcitonin | Assistance Publique – Hopitaux de Paris (AP-HP), France | Precursor of the hormone calcitonin | Peptide, Phase-IV |
| 33   | Peginterferon Lambda-1A (Interferon Lambda) | University Health Network, Toronto, Canada | Activates a STAT phosphorylation-dependent signaling cascade | Glycoprotein Phase-II, NCT04354299 (ClinicalTrials.gov) |
| 34   | Alteplase (t-PA) (Activase or Actilyse) | Denver Health and Hospital Authority, USA, and University College, London, UK | Serine protease that facilitates conversion of plasmin to plasminogen | Soluble TNF (sTNF) inhibitor NCT04370236, (ClinicalTrials.gov) |
| 35   | XPro1595 | INmune Bio Inc., USA | Soluble TNF (sTNF) inhibitor | Protein, Phase-II |
| 36   | Metenkefalin + Tridecactide | Bosnaijek, Bosna Herzegovina | Immunomodulator | Opioid peptide Phase-II, NCT04374032 (ClinicalTrials.gov) |
| 37   | PUL-042 Inhalation Solution | Pulmotect Inc., USA | TLR 2/6/9 agonist | Mixture of oligodeoxynucleotide and lipopeptide Phase-II, NCT04313023 NCT04312997, (ClinicalTrials.gov) |
| 38   | Defibrotide | Research institutes in Italy and Spain | Increase t-PA function and decrease plasminogen activator inhibitor-1 activity | Mixture of single-stranded oligonucleotides NCT04335201 NCT04348383 (ClinicalTrials.gov) 2020-001409-21 (EU-CTR) |
| 39   | Enoxaparin | Tongji Medical College of Huazhong University of Science and Technology and The Third People’s Hospital of Shenzhen, China | Irreversibly inactivates clotting factor Xa | Heparin (Polysaccharide) Phase-0 ChCTR2000030700 ChCTR2000030701 (ICTPR) NCT04359277 (ClinicalTrials.gov) |
| 40   | Tinzaparin | Assistance Publique – Hopitaux de Paris, France | Accelerates the inhibition of factor Xa | Heparin Polysaccharide Phase-II NCT04344756 (ClinicalTrials.gov) NCT04313023 |
| 41   | Aescin or escin | University of Catanzaro, Italy | Mixture of saponins with anti-inflammatory, vasoconstrictor and vasoprotective effects, induces nitric oxide synthesis | Steroid tethered with trisaccharide Phase-II, NCT04322344 (ClinicalTrials.gov) |
| 42   | Kolimycin | The First Affiliated Hospital of Harbin Medical University, China | Binds to the 30S subunit of the bacterial ribosome | Amino oligo-sugar Phase-0 ChCTR2000032242, (ICTPR) |
| 43   | Dornase | University College, London, UK, and Fondation Ophtalmologique Adolphe de Rothschild, France | Highly purified solution of recombinant human deoxyribonuclease I | Phase-II, NCT04359654 (ClinicalTrials.gov) |
| 44   | Vitamin A | Mostafakhomeini Medical Centre, Saveh, Iran | Boosts immunity | Phase -- II IRCT20180520037382N2 (ICTPR) NCT04265453, NCT03680274 |
| 45   | Vitamin C (Ascorbic acid) | Zhongnan Hospital of Wuhan University and Universite de Sherbrooke, Canada | Antioxidant and cofactor; Boosts immunity | Phase-III, NCT04357782, NCT04344184 (ClinicalTrials.gov) |
| 46   | Vitamin D | University Hospital, Angers, France and Universidad de Granada, Spain | Boosts immunity | NCT04312997, (ClinicalTrials.gov) NCT04344041 (ClinicalTrials.gov) |
| 47   | Calcifediol | Tehran University of Medical Sciences, Iran | Boosts immunity | Phase-III IRCT20200401046909N1 IRCT20200401046909N2 (ICTPR) |
| 48   | Zinc | University of Melbourne, The Cleveland Clinic and University Hospital, Lille, France | Intravenous high dose zinc alone and in combination with vitamin C or vitamin D | Phase-I/II ACTRN12620000454976 NCT04342728, NCT04351490 (ClinicalTrials.gov) |
| 49   | Lipoic acid | Maoming People’s Hospital, Maoming, China | Antioxidant | Phase-IV ChCTR2000030471 |
| 50   | Vitamin A, B, C, D, and E | Imam Khomeini Hospital, Tehran, Iran | Boosts immunity | Phase-III IRCT20200319068189N1 (ICTPR) |
| 51   | Umbilical cord-derived stem cells | Huangshi Hospital of Traditional Chinese Medicine and Guangwu District of Hubei Maternal and Child Health Hospital, China | MSCs are known to possess immunomodulatory and regenerative properties | Fight the inflammation and lung degeneration ChCTR2000031494 |
| 52   | Adipose-derived mesenchymal stem cells (HB-adMSCs) | Hope Biosciences, Texas, USA | MSCs are known to possess immunomodulatory and regenerative properties | Phase-III NCT04349631, (ClinicalTrials.gov) |
| 53   | Nest Cell® | Azidus, Brazil | Mesenchymal stem cell therapy | Phase-I, NCT04315987 (ClinicalTrials.gov) |
| 54   | NK cells | Universidad Nacional de Colombia | Involved in the early defense against infectious pathogens and Allogeneic NK transfer | Phase-I/II |
through the receptor-binding domain (S1B domain), and host receptor, human angiotensin-converting enzyme 2 (ACE2) thus are structurally very similar. They predominantly bind to the Hu-1) show 77.5% identity in primary amino acid sequence and Urbani) and SARS-CoV-2 (SARS-S, 1273 residues, strain Wuhan-

Table 3 (continued)

| S.N. | Drug Name                                      | Company/Developer                                                                 | Function                                                                 | Comment                                                                 |
|------|-----------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|
| 55   | NK cells, IL15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells, NKG2D-AECD CAR-NK cells | Chongqing Public Health Medical Center, China                                     | Middle East Gene Therapy corporation                                    | NCT04344548 [ClinicalTrials.gov]                                        |
|      |                                               |                                                                                  | Boost innate immunity and adaptive immunity                               | IRCT20200417047113N1 [ICTPR]                                           |
| 56   | TAK-88B (Plasma-derived antibodies)           | Takeda Pharmaceutical Co., Japan                                                 | Plasma which contains antibodies against the virus                        | Phase-I/II                                                              |
| 57   | Amniotic fluid                                | University of Utah, USA                                                          | Protective liquid contained in the amniotic sac of a gravid amniote        | Polyclonal hyperimmune globulin (H-IG)                                   |
| 58   | Heat-killed Mycobacterium w                   | CSIR, India and Cadila Pharmaceuticals, India                                   | Interferon (IFN) mediated inhibition manifested by activated              | Phase-I, NCT04353518                                                   |
|      |                                               |                                                                                  | macrophage                                                                | NCT04347174 [ClinicalTrials.gov]                                       |
| 59   | Nitric oxide                                  | Sanovitze Research & Development Corp., University of British Columbia, Canada and Massachusetts General Hospital, USA | Interferon (IFN) mediated inhibition manifested by activated              | Phase-II, NCT04337918                                                  |
| 60   | Sevoflurane                                   | University of Zurich                                                           | NMDA receptor antagonist. Inhibits nAChR and 5-H3 receptor currents       | NCT03331445                                                           |
| 61   | Stannous Protoporphyrin (RBT-9)               | Renibus Therapeutics Inc., USA                                                   | Coordination compound                                                      | Phase-II, NCT04364763 [ClinicalTrials.gov]                              |
| 62   | Sodium Bicarbonate                            | Mansoura University, Egypyp                                                      | Inhalable sodium bicarbonate immunomodulator                              | Phase-I, NCT04374591 [ClinicalTrials.gov]                               |
| 63   | MBt-x-4DP0004                                 | 4DF Pharma plc, UK                                                              | It breaks down excess DNA in the pulmonary secretions of people            | Phase-II, NCT04363372 [ClinicalTrials.gov]                              |
| 64   | Pulmozyme/Dornase alpha aerosol               | Hopital Fondation Adolphe de Rothschild, France                                 | Synthetic protein                                                         | Phaseli                                                                |
| 65   | Rintatolimod in combination with IFN Alpha-2b | Roswell Park Cancer Institute, USA                                               | TLR3 agonist                                                              | Double-stranded RNA molecule                                            |
|      |                                               |                                                                                  | Phase/I/II                                                                | NCT04379518 [ClinicalTrials.gov]                                       |

study B (renin-angiotensin (RAS) blockade versus no RAS blockade), and sub-study C (clazakizumab versus standard care) [94].

3.4. Monoclonal antibodies

Antibodies are a promising new class of therapeutics that have shown good efficacy against many viruses. Monoclonal antibodies (mAB) are man-made synthetic antibodies that mimic natural antibodies and primarily target susceptible sites on viral surface proteins. In coronaviruses they act by targeting the trimeric spike (S) glycoproteins on the viral surface that mediates the entry of the virus into the host cells. Monoclonal antibody-based therapeutics could be used not only as a prophylactic treatment for individuals exposed to the virus but also to prevent disease progression in patients already infected by the virus [95].

The spike proteins of SARS-CoV (SARS-S, 1255 residues, strain Urbani) and SARS-CoV-2 (SARS2-S,1273 residues, strain Wuhan-Hu-1) show 77.5% identity in primary amino acid sequence and thus are structurally very similar. They predominantly bind to the host receptor, human angiotensin-converting enzyme 2 (ACE2) protein, through the receptor-binding domain (S1g domain), and trigger irreversible conformational changes in the coronavirus spike proteins leading to membrane fusion [96–98].

Actemra (tocilizumab), a humanized monoclonal antibody that suppresses the immune system by inhibiting interleukin-6 (IL-6), is used for the treatment of rheumatoid arthritis. It is manufactured by the pharmaceutical giant Roche under the brand name actemra. FDA has recently approved actemra for a double-blind, placebo-controlled, randomized Phase-I COVACTA trial (registered on May 25, 2020) to treat severely ill COVID-19 patients with high IL-6 levels in the blood. COVACTA trial will be useful for assessing the safety and efficacy of intravenous actemra plus standard of care (SOC), versus placebo plus SOC 450 patients have been enrolled for this trial). On May 28, 2020, Roche and Gilead Sciences announced the initiation of another global, multi-center, double-blind, randomized Phase-III REMDACoTA trial to evaluate the safety and efficacy of actemra in combination with remdesivir versus placebo plus remdesivir in hospitalized COVID-19 patients with severe pneumonia (Table 3, Entry 1). The data obtained in the REMDACoTA trial will supplement the COVACTA study [99–102]. Likewise, Feinstein Institutes for Medical Research, New York, USA, in collaboration with Gilead Sciences and Regeneron Pharmaceuticals, New York, USA, are launching clinical trials with sarilumab, another humanized monoclonal antibody and effective inhibitor of IL-6 receptor (Table 3, Entry 2). A Phase Ib/III clinical trial with lenonlimab, a humanized Ig4 monoclonal antibody, and a CCR5 antagonist, is being carried out by CytoDyn Inc. on critically ill COVID-19 patients. In this study patients will receive lenonlimab for two weeks (Table 3, Entry 1). Alexion Pharmaceuticals, Boston, USA, announced another global Phase-I/II clinical trial to investigate ultomiris (ravulizumab)-cwvz as a treatment for adult COVID-19 patients with severe pneumonia or acute respiratory distress syndrome (ARDS) (Table 3, Entry 4). Kinevant Sciences GmbH, and Roivant Sciences, both based in Basel, Switzerland, are independently conducting Phase-II clinical trial with gimsilumn, a fully humanized monoclonal antibody (Table 3, Entry 5).

Another open-label, Phase-I-II clinical trial (NCT04275245) conducted by Tang-Du Hospital, China, with meplazumab on 17 patients (assigned to meplazumab group) between February 03 and February 10, 2020, found that meplazumab improved the recovery of patients with SARS-CoV-2 induced pneumonia. However, the study investigators have recommended the need for a more comprehensive clinical investigation of meplazumab for the treatment of COVID-19 (Table 3, Entry 6) [103].

A study evaluating lenzilumab (anti-human GM-CSF monoclonal antibody) on hospitalized COVID-19 patients with pneumonia showed 92% recovery (11 out of 12 patients), and significant improvement in oxygenation with a median time to discharge of 5 days. No adverse events were reported. In fact, after two days of treatment with lenzilumab, a significant reduction in inflammatory myeloid cells was observed [104]. Additionally, a large number of monoclonal antibody (mAB)-based drugs such as ixekizumab, bevacizumab (avastin), adalimumab (humira), clazakizumab,
siltuximab, nivolumab, IFX-1, TJ003234, LY3127804 and sirukumab are currently undergoing trials for COVID-19 treatment at different institutions around the world (Table 3, Entries 8–17).

3.5. Other recombinant proteins and peptides

On April 10, 2020, University Hospital, Ghent, Belgium, registered a Phase-III clinical trial with the drug anakinra, a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). The trial goal is to compare the safety and efficacy of the simultaneous blockade of the interleukin-6 pathway and interleukin-1 pathway in improving oxygenation and short- and long-term prognosis of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome (Table 3, Entry 18).

Hunan Haiyai Hongxingtang Pharmaceutical Company, China, carried out an open-label, randomized, parallel-controlled trial for evaluating the efficacy of novaferon as a single agent, and in combination with lopinavir/ritonavir. They also tested the anti-SARS-CoV-2 effects of novaferon in cell-based assays. Study results confirmed the anti-SARS-CoV-2 effects of novaferon in vitro, and in COVID-19 patients (Table 3, Entry 19) [105].

Additionally, the Food and Drug Administration (FDA) has accepted ATyr Pharma’s Investigational New Drug (IND) application for the Phase-II clinical investigation of ATYR1923 in COVID-19 patients with severe respiratory complications. ATYR1923, a fusion protein comprising of the immuno-modulatory domain of histidyl t-RNA synthetase fused to the fragment crystallization (Fc) region of a human antibody, directly binds to the neuropilin-2 (Nrp2) to modulate Nrp2 signaling and downregulate the innate and adaptive immune response in inflammatory conditions. Currently, ATyr Pharma is conducting a Phase-Ib-Ila clinical trial with ATYR1923 on patients with pulmonary sarcoidosis (Table 3, Entry 20) [106]. Likewise, several other proteins and peptide-based agents such as IFNα2b, humin recombinant ACE2 (APN01), saragrostim (leukine), CD24Fc, anti-programmed cell death-1 mAb, angiotensin (1–7), aviptadil, intravenous immunoglobulin, ulinastatin, thymosin, solnatide, procalcitonin, interferon lambda, alteplase, XPro1595, and metenkefalin in combination with tridecactide are currently registered for clinical trials and are being actively tested (Table 3, Entries 21–36).

3.6. Oligonucleotides and polysugars

Oligonucleotide and polysaccharide based therapeutic agents such as PUL-042AD, defibrotide, enoxaparin, tinzaparin, aescin, kolimycin, and dornase are also being actively pursued in multiple clinical trials for the treatment of COVID-19 (Table 3 Entry 37–43).

3.7. Vitamins and cofactors

Vitamins and other cofactors play a significant role in boosting the immune system. Therefore, clinical trials with vitamins A, B, C, D and E, and cofactor lipoic acid, calcifediol, and zinc are currently underway for the treatment of COVID-19 (Table 3 Entries 38–50).

3.8. Stem cells, plasma and, other body fluids-based therapy

To stimulate a robust host immune response against SARS-CoV-2, FDA has permitted the emergency use of antibody-laden blood plasma collected from the people who recovered from COVID-19 infection [107,108]. Towards this end, Takeda Pharmaceuticals Company, Tokyo, Japan, has started clinical trials with plasma-derived therapy called TAK-888, which involves isolation of coronavirus-specific antibodies from COVID-19 survivors and its administration to infected patients. The development of drugs and vaccines against COVID-19 is a time-consuming process, whereas blood plasma is readily accessible and relatively safe. Mayo Clinic recently conducted studies with convalescent plasma on 5000 hospitalized COVID-19 patients under the FDA’s Expanded Access Program (EAP). The study found transfusion of convalescent plasma to be safe for the treatment of severely ill COVID-19 patients [109]. Currently, a large number of clinical trials based on convalescent plasma, amniotic fluid stem cells, and NK cells have been initiated worldwide (Table 3 Entries 51–57).

3.9. Miscellaneous

Heat-killed mycobacterium based vaccine against leprosy activates the toll-like receptor (TLR) pathway, modulates immune response, and explicitly enhances host-T cell functions [110]. Mycobacterium w vaccine is registered as an ‘Mw vaccine’ in India, and is currently undergoing clinical trial for the treatment of COVID-19 patients. Mw vaccine potentially mitigates the cytokine storm responsible for the severity of the symptoms, and fatality, in the majority of the COVID-19 patients (Table 3 Entry 58). In addition, clinical studies to evaluate the efficacy of nitric oxide inhalation, sevoflurane, stannous protoporphyrin (RBT-9), sodium bicarbonate, and MRx-4DP0004 in COVID-19 patients are also being carried out by several healthcare institutions (Table 3, Entries 59–65).

4. Preclinical research

For the development of a therapeutic agent for COVID-19 treatment, a variety of small molecules drugs, antibodies, cell-based or RNA-based compounds are undergoing preclinical studies. Besides, screening and reinvestigation of many existing drugs, especially antivirals and antibiotics, are ongoing as a post-infection treatment option against COVID-19 [43].

4.1. Antiviral drugs

As COVID-19 is a viral disease, considerable scientific attention has been focused on repurposing approved antiviral drugs (Fig. 8) [111]. In preclinical cell-based studies, ribavirin (a ribonucleoside analog) (73) showed activity against SARS-CoV-2 (EC50 = 109.50 μM, CC50 > 400 μM, selectivity index (SI) > 3.65) [65]. Molecular docking studies suggest that ribavirin, sofosbuvir (26), galidesivir (16), setrobuvir (109), IDX-184 (110), and tenofovir (2) tightly bind to the SARS-CoV-2 RdRp and can thus serve as potential candidates for drug repurposing studies against COVID-19 [112]. Another promising candidate is β-D-N4-hydroxyxyctydine (NHC, EIDD-1931) (111). This orally bioavailable ribonucleoside analog exhibits broad-spectrum antiviral activity against several unrelated RNA viruses, such as influenza virus, coronavirus, Ebola virus, and Venezuelan equine encephalitis virus (VEEV). The University of North Carolina (UNC) led team recently reported promising antiviral activity of NHC against SARS-CoV-2, MERS-CoV, SARS-CoV, and related CoVs in vitro. NHC prodrug, β-D-N4-hydroxyxyctydine-5′-isopropyl ester (EIDD-2801) (112), also yielded excellent results in the form of improved lung function, reduced virus load, and weight loss in mice infected with SARS-CoV or MERS-CoV [113].

Another antiviral drug, nicosamide (113), an FDA-approved anti-helmintic drug, is effective against the SARS-CoV-2 family of viruses such as SARS-CoV, MERS-CoV. Nicosamide exhibits activity in nanomolar to the micromolar range, highlighting its potential use as a suitable drug repurposing candidate for SARS-CoV-2 [114–116]. Koet et al. recently carried out a study wherein they
evaluated the in vivo inhibitory activity of 50 FDA approved drugs in Vero cells to identify potential drug candidates against SARS-CoV-2. The screening led to the identification of two drugs, i.e., niclosamide, an anti-helminthic drug, and tilorone, an antiviral drug. Both these drugs showed encouraging results [117]. Niclosamide inhibited SARS-CoV-2 activity at IC50 = 0.28 μM. In contrast, while tilorone (114) exhibited an IC50 value of 4.09 μM. Recently, N. C. Gassen and co-workers have shown that niclosamide blocks SKP2 activity, enhances autophagy and inhibits MERS-CoV replication [116,118]. A similar mechanism might be attributable to the inhibition of SARS-CoV-2 infection by niclosamide. Likewise, human clinical studies of tilorone as a treatment for acute respiratory viral infections (ARVIs) have demonstrated 72% prophylactic efficacy in respiratory tract infections in humans [119].

4.2. Other miscellaneous drugs and drug like molecules

A recent study by researchers at Nanjing University, China, demonstrated that N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) possesses very good inhibitory activity against SARS-CoV-2 in vitro (CC50 = 158.0 μg/ml, IC50 12.5 μg/ml, SI 12.6) and MERS-CoV (CC50 = 161.0 μg/ml, IC50 = 62.8 μg/ml, SI 2.6). These results suggest that HTCC can be a potential drug candidate for the treatment of COVID-19. However, HTCC drug is yet to be registered and approved for clinical use [120].

A team of researchers at the University of Frankfurt, Germany, reported that inhibition of glycolysis with low concentrations of 2-deoxy-D-glucose (2-DG, 115) entirely blocked the replication of SARS-CoV-2 in Caco-2 cells, in vitro. The study found that infected host cells are manipulated by the virus to increase their dependence on glycolysis dramatically. However, the presence of 2-DG inhibits glycolysis as the decoy glucose, 2-DG, cannot be converted into energy. Thus the presence of low concentrations of 2-DG prevents the replication of SARS-CoV-2 [121].

Brilacidin (116) is an antibiotic currently being investigated for the treatment of inflammation of the oral mucosa (Phase-II clinical study) and inflammatory bowel disease. Brilacidin blocks VERO cells infection by the SARS-CoV-2 virus in a dose-dependent
manner relative to the control (DMSO) group. Brilicadin's ability to attack the outer envelope of the SARS-CoV2 appears to be the underlyng mechanism by which it acts against SARS-CoV-2 [122,123].

Recently, another drug teicoplanin (117), a glycopeptide antibiotic, showed excellent in vitro inhibitory activity against SARS-CoV-2. Although the bactericidal activity of teicoplanin against gram-positive bacterial infections, especially staphylococcal infections is well-known, it has also shown efficacy against a variety of viruses such as Ebola virus, influenza virus, flavivirus, hepatitis C virus, HIV, and coronaviruses such as MERS-CoV and SARS-CoV. Teicoplanin showed a promising IC50 value of 1.66 μM against SARS-CoV-2, which is much lower than the concentration reached in vitro through inhibition of importin (IMP) Imp receptor, which reduces in viral RNA at 48 h. Antiviral activity of ivermectin is present at 1 hour post-SARS-CoV-2 infection was able to induce ~5000-fold reduction in viral RNA at 48 h. Antiviral activity of ivermectin is through inhibition of importin (IMP) Imps/β1 heterodimer mediated nuclear import of viral proteins [127].

Auranofin (118), an FDA-approved drug for the treatment of rheumatoid arthritis, has been investigated as a potential therapeutic agent for several diseases such as cancer, neurodegenerative disorders, HIV/AIDS, parasitic infections and bacterial infections. Recently, auranofin was approved by the FDA for Phase-II clinical trials in cancer patients [128]. In light of these developments, researchers studied the antiviral activity of auranofin against SARS-CoV-2 and analysed its potential effect on virus-induced inflammation in human cells. Interestingly, the treatment of SARS-CoV-2 infected human cells with auranofin resulted in a 95% reduction in the viral RNA load at 48 h. Auranofin treatment also attenuated the expression of SARS-CoV-2-induced cytokines in human cells [129].

Apilimod (LAM-002) (119), an inhibitor of the interleukins IL-12 and IL-23 production, was developed for the treatment of autoimmune conditions such as Crohn's disease and rheumatoid arthritis. However, apilimod gave disappointing results in clinical studies, and consequently further drug development was stopped. Apilimod is a phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) lipid kinase inhibitor, and recent data suggests that inhibition of PIKfyve by apilimod significantly reduces SARS-CoV-2 pseudovirions entry into 293/hACE2 cells in a dose-dependent manner. Although apilimod exhibits activity as a single agent, it is more effective when used in combination with remdesivir [130,131].

5. Conclusion

This report provides a comprehensive review of the urgent global efforts, currently underway, towards the discovery and development of vaccines and therapeutic agents for the prevention and treatment of COVID-19. This review is specifically focused on the ongoing clinical and preclinical studies on the various vaccines, repurposed drugs, and other therapeutic agents being investigated as part of the urgent global response to control and combat the COVID-19 pandemic. The development of a vaccine seems to be the most promising approach in this respect. Drug repurposing is another important strategy for the development of an effective therapeutic against COVID-19 in a limited time-frame, and several known drugs, primarily antivirals, are currently undergoing clinical trials. Besides, researchers are also directing their efforts towards the identification of new targets for the discovery and development of vaccines and therapeutics against COVID-19. However, an effective vaccine or therapeutic is not expected anytime soon. We anticipate that in the coming months, biologists will identify new targets, and medicinal chemists will screen more drugs and molecular libraries against novel and existing targets in their efforts to find a cure for COVID-19.

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