Recent Updates in Experimental Research and Clinical Evaluation on Drugs for COVID-19 Treatment

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Since the outbreak of corona virus disease 2019 (COVID-19) in Wuhan (China) in December 2019, the epidemic has rapidly spread to many countries around the world, posing a huge threat to global public health. In response to the pandemic, a number of clinical studies have been initiated to evaluate the effect of various treatments against COVID-19, combining medical strategies and clinical trial data from around the globe. Herein, we summarize the clinical evaluation about the drugs mentioned in this review for COVID-19 treatment. This review discusses the recent data regarding the efficacy of various treatments in COVID-19 patients, to control and prevent the outbreak.

Keywords: corona virus disease 2019, corona virus disease 2019 treatment, severe acute respiratory syndrome corona virus 2 variants, antimicrobials, immunotherapy, traditional Chinese medicine

INTRODUCTION

The outbreak of corona virus disease 2019 (COVID-19), from Wuhan, Hubei Province, China, in December 2019, has now become the first global pandemic caused by the spread of coronavirus. On February 11, 2020, the World Health Organization (WHO) gave a name for the novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease of 2019 (COVID-19) caused by SARS-CoV-2 (Bevova et al., 2020). Most recently, several predominate SARS-CoV-2 variants, including, but not limited to, B.1.1.7 (alpha) variant, B.1.351 (beta) variant, P.1 (gamma), and B.1.617.2 (delta) variant, were first detected in the United Kingdom, South Africa, Brazil, and India, and became a novel global concern (Ong et al., 2021; Sanches et al., 2021). The SARS-CoV-2 variants have greater ability of virus infectivity and immune escape, suggesting that the SARS-CoV-2 variants may result in poor treatment efficacy and prognosis for COVID-19 patients. In the past few months, many research teams from around the world have been conducting in vitro and in vivo studies of the virus, seeking effective prevention and control measures to prevent its spread. China is relatively fast and effective in the control of epidemic. We are, therefore, able to comprehensively analyze common domestic treatment methods and combined domestic and foreign research to jointly explore effective treatment programs for COVID-19, to provide guidance for the second wave of the epidemic.

Many products including, but not limited to, traditional Chinese medicines (TCMs), antiviral drugs (e.g., chloroquine phosphate and alpha-interferon) (Wang and Zhu, 2020), monoclonal antibodies (e.g., tozumab combined with adamumab) (Sarkar et al., 2020), convalescence plasma, and mesenchymal stem cells (MSCs) (Peng et al., 2020) have become the focus of our communication for COVID-19 treatment. The Chinese Clinical Trial Registry (ChiCTR) shows a large number of TCM-related drugs studied for the treatment and prevention of COVID-19 (e.g., Lianhuaqingwen...
capsule, Shuanghuanglian oral liquid, Xuebijing injection, etc.) (Li H. et al., 2020), while Western drugs focus on antiviral drugs and immunotherapy (e.g., stem cell-based therapy, antibodies, etc.) (Ni et al., 2020a; Gulati et al., 2021). In the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), it mentioned several antiviral drugs such as chloroquine (CQ), alpha-interferon (IFN-α), lopinavir/ritonavir, and umifenovir, and also mentioned immunotherapy, such as tocilizumab (Wei, 2020a; Zhao et al., 2020a; Wei, 2020b). Notably, as the adage, “old drug, new trick,” most of the antiviral drugs used for COVID-19 treatment are existing compounds screened for potential use based on mechanistic similarities to other viruses.

Herein, we summarize the clinical evaluation for COVID-19 treatment about the drugs mentioned in this review. Figure 1 depicts the overview of the organization of this review. Furthermore, we discuss recent representative progresses and considerations in the treatment for COVID-19, especially antimicrobials (antivirals and antibiotics/antibacterial), immunotherapy, and TCMs.

**ANTIMICROBIALS**

**Chloroquine and hydroxychloroquine**

As a widely used antimalarial and immunomodulatory drug, chloroquine (CQ) shows a broad-spectrum antiviral activity. Table 1 summarizes the clinical trials of CQ and HCQ for the treatment of COVID-19. Some researchers indicated that CQ is effective against SARS-CoV-2 virus in early clinical studies (Huang et al., 2020c). Of note, chloroquine phosphate is undergoing some clinical trials regarding prophylactic use in health personnel (Clinicaltrials.gov, NCT04443270) and against infection by SARS-CoV-2 (Clinicaltrials.gov, NCT04344951). Evidence from a multicenter prospective observational study indicated that patients in CQ treatment group have shorter median time to achieve an undetectable viral RNA and shorter duration of fever; also, more importantly, no severe side effects were found during CQ treatment (Huang et al., 2020b). Hydroxychloroquine (HCQ) is an analog of CQ by replacing an ethyl group in CQ with a hydroxyethyl group (Zhou et al., 1878). Nowadays, ChiCTR conducts many clinical trials in China to examine the effectiveness and safety of CQ or HCQ against COVID-19 (Gao et al., 2020). A team from Renmin Hospital of Wuhan University investigated the effects of HCQ among 62 patients suffering from COVID-19 (www.chictr.org.cn, ChiCTR2000029559). As a result, Chen et al. found that HCQ could significantly shorten time to clinical recovery (TTCR) and improve pneumonia.

However, the high-quality clinical data showing a clear and reliable benefit of CQ or HCQ remains limited. Also, the CQ or HCQ treatment could induce severe cardiac side effects, impede innate and adaptive antiviral immune responses, and cause some uncertain effects (Meyerowitz et al., 2020). Commonly, QT prolongation and torsade de Pointes (TdP) occur on patients who are administered with CQ or HCQ (Blignaut et al., 2019). Hence, before CQ and HCQ treatment, an initial cardiac evaluation is necessary for COVID-19 patients (Zhou W. et al., 2020). Also, several follow-up evaluations, such as regular ophthalmological examination and cardiac monitor, are suggested for patients with short- or long-term treatment (Knox and Owens, 1966). Thus, using CQ or HCQ as a
### TABLE 1 | Summary of clinical trials of chloroquine (CQ) and hydroxychloroquine (HCQ) on COVID-19 treatment.

| Trial title                                                                                   | Sponsor                                                | Trial phase | Primary intervention                     | Secondary intervention                        | Status                                   | Identifier       |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------|------------------------------------------|-----------------------------------------------|------------------------------------------|------------------|
| Efficacy of Chloroquine or Hydroxychloroquine in COVID-19 Treatment                           | Tanta University                                      | II/III      | Chloroquine or hydroxychloroquine       | N/A                                           | Recruiting                         | NCT04353336     |
| Chloroquine for Mild Symptomatic and Asymptomatic COVID-19                                    | HaEmek Medical Center, Israel                          | II/III      | Chloroquine                              | Standard care                                 | Terminated (Terminated due to changes in treatment guidelines.) | NCT04333628     |
| Zinc With Chloroquine/ Hydroxychloroquine in Treatment of COVID-19                            | Tanta University                                      | III         | Chloroquine                              | Chloroquine + zinc tablets                    | Recruiting                         | NCT04447534     |
| The Vietnam Chloroquine Treatment on COVID-19 (VCC)                                          | Oxford University Clinical Research Unit, Vietnam      | II          | Chloroquine phosphate                    | N/A                                           | Recruiting                         | NCT04328493     |
| Chloroquine + Losartan Compared to Chloroquine Alone for the Treatment of COVID-19 Pneumonia | Hospital Universario Dr. Jose E. Gonzalez              | II          | Chloroquine phosphate                    | Chloroquine + losartan                        | Withdrawn (Evidence showed chloroquine is not effective against COVID-19.) | NCT04428268     |
| Chloroquine Phosphate Prophylactic Use in Health Personnel Exposed to COVID-19 Patients     | CMN "20 de Noviembre"                                 | I           | Chloroquine phosphate                    | N/A                                           | Not yet recruiting                  | NCT04443270     |
| Prevention with Chloroquine in Health Personnel Exposed to Infection with Coronavirus Disease 2019 (TS-COVID) | Fundacion Clinica Valle del Lili                      | II          | Chloroquine                              | N/A                                           | Active, not recruiting               | NCT04627467     |
| Chloroquine Phosphate Against Infection by the Novel Coronavirus SARS-CoV-2 (COVID-19): The HOPE Open-Label, Non-Randomized Clinical Trial (HOPE) | Uni-Pharma Kleon Tsets Pharmaceutical Laboratories S.A. | II          | Chloroquine                              | N/A                                           | Recruiting                         | NCT04344951     |
| Chloroquine Outpatient Treatment Evaluation for HIV-COVID-19 (CQUOTE)                         | University of Cape Town                               | III         | Chloroquine or hydroxychloroquine       | Standard care                                 | Withdrawn (Equipoise for hydroxychloroquine was lost.) | NCT04360759     |
| Chloroquine as Antiviral Treatment in Coronavirus Infection 2020                             | Wroclaw Medical University                            | IV          | Chloroquine phosphate                    | Telemedicine                                   | Completed                           | NCT04331600     |
| Chloroquine, Hydroxychloroquine or Only Supportive Care in Patients Admitted With Moderate to Severe COVID-19 (ARCHAIC) | UMC Utrecht                                           | IV          | Chloroquine sulfate or hydroxychloroquine | Supportive care only                          | Terminated (Currently, almost no patients are admitted to Dutch hospitals. If any effect of HCQ is to be expected, we need more than 1,000 inclusions.) | NCT04362332     |
| Chloroquine Diphosphate in the Prevention of SARS in COVID-19 Infection (CloroCOVID19II)     | Fundação de Medicina Tropical Dr. Heitor Vieira Dourado | II          | Chloroquine diphosphate                  | Placebo oral tablet                           | Completed                           | NCT04342650     |
| Efficacy of Chloroquine or Hydroxychloroquine in Treating Pneumonia Caused by SARS-CoV-2- COVID-19 | Centro de Estudos e Pesquisa em Emergencias medicase Terapia Intensiva | III | Chloroquine or hydroxychloroquine       | Standard care                                 | Completed                           | NCT04420247     |
| Saved From COVID-19                                                                            | Columbia University                                   | II          | Chloroquine                              | Placebo oral tablet                           | Terminated (Low enrollment.)          | NCT04349371     |
| Prophylaxis of Exposed COVID-19 Individuals With Mild Symptoms Using Chloroquine Compounds (PRECISE) | Government of Punjab, Specialized Healthcare and Medical Education Department | IV          | Chloroquine or hydroxychloroquine       | Standard of care + placebo                   | Terminated (Poor accrual.)           | NCT04351191     |

(Continued on following page)
| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|----------------------|------------------------|--------|------------|
| The Clinical Study of Carrimycin on Treatment Patients With COVID-19 | Beijing YouAn Hospital | IV | Carrimycin | Chloroquine phosphate or lopinavir/ritonavir tablets or arbidol | Not yet recruiting | NCT04286503 |
| Post-Exposure Prophylaxis for Asymptomatic SARS-CoV-2 COVID-19 Patients With Chloroquine Compounds (PEACE) | Government of Punjab, Specialized Healthcare and Medical Education Department | IV | Chloroquine or hydroxychloroquine | Standard of care + placebo | Terminated (Poor accrual.) | NCT04346667 |
| Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19 (Chloroquine UN) | Universidad Nacional de Colombia | III | Hydroxychloroquine | Placebo oral tablet | Withdrawn (The study did not get financed. Never got started.) | NCT04346329 |
| Angiotensin Converting Enzyme Inhibitors in Treatment of Covid 19 | Tanta University | III | Captopril or enalapril | Chloroquine | Not yet recruiting | NCT04345406 |
| Evaluation of Efficacy of Levamisole and Formoterol + Budesonide in Treatment of COVID-19 | Fasa University of Medical Sciences | II/III | Levamisole pill + budesonide + formoterol inhaler | Hydroxychloroquine + lopinavir/ritonavir | Recruiting | NCT04331470 |
| Austrian Coronavirus Adaptive Clinical Trial (COVID-19) (ACOVACT) | Medical University of Vienna | II/III | Chloroquine or hydroxychloroquine | Lopinavir/ritonavir; Standard care | Recruiting | NCT04351724 |
| An Adaptive Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19 | Chromis LLC | II/III | Favipiravir | Chloroquine, hydroxychloroquine, lopinavir/ritonavir, etc. | Active, not recruiting | NCT04432448 |
| Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus | Misr University for Science and Technology | III | Natural honey | Chloroquine phosphate or hydroxychloroquine or lopinavir/ritonavir tablets or arbidol or oseltamivir with or without azithromycin | Recruiting | NCT04323345 |
| Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19 | Promomed, LLC | III | Favipiravir | Chloroquine, hydroxychloroquine, lopinavir/ritonavir, etc. | Completed | NCT04542694 |
| Hydroxychloroquine for Treatment of Non-Severe COVID-19 (HONEST) | Makerere University | II | Hydroxychloroquine tablets | Standard care only | Active, not recruiting | NCT04860284 |
| Efficacy and Safety of Anti-HCV Drugs in the Treatment of COVID-19 | Cairo University | II/III | Hydroxychloroquine + sofosbuvir/daclatasvir | Hydroxychloroquine | Not yet recruiting | NCT04443725 |
| Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2 (HOPE Trial) | Gangnam Severance Hospital | III | Hydroxychloroquine | N/A | Not yet recruiting | NCT04330144 |
| PATCH 2 and 3: Prevention and Treatment of COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2) With Hydroxychloroquine | United Health Group | II | Hydroxychloroquine | Placebo drug | Terminated (As enrollment began, external studies called into question the safety and efficacy of hydroxychloroquine as a treatment, which resulted in controversy. The timing of the controversy significantly impacted our ability to enroll and retain participants.) | NCT04353037 |
| Efficacy of Azithromycin-Associated Hydroxychloroquine Therapy Given in General | Assistance Publique—Hôpitaux de Paris | III | Hydroxychloroquine + azithromycin | Dietary supplement: Azinc | Withdrawn (Regulatory approvals have not been obtained.) | NCT04371406 |

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COVID-19 treatment was controversial, which results from their ocular, cardiac, and neuro toxicities (Oren et al., 2020; Zou et al., 2020). Additionally, the certainty of evidence is low.

Together, we would like to recommend monitoring the accumulative effect of long-term and/or high-dose CQ or HCQ in clinical settings. Also, researchers are not supposed

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|---------------------|------------------------|--------|------------|
| Practice in Early-Stage Disease in COVID-19 Patients (MG-COVID) | University Hospital, Strasbourg, France | III | Hydroxychloroquine and azithromycin | Hydroxychloroquine; IV antibiotics and standard of care | Withdrawn (In view of the notices concerning hydroxychloroquine issued by the regulatory authorities, we withdraw the protocol.) | NCT04347512 |
| Evaluation of the Efficacy of the Hydroxychloroquine-Azithromycin Combination in the Prevention of COVID-19 Related Sdri (Teachcovid) | Hospital Israelta Albert Einstein | III | Hydroxychloroquine + azithromycin | Hydroxychloroquine | Completed | NCT04321278 |
| Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition COVID-19 Brasil II) | University Hospital Tuebingen | II | Hydroxychloroquine | Placebo capsules | Terminated (It appeared to be impossible for the study lefts to recruit the targeted number of patients, due to reduced incidence and reduced acceptance to IMP.) | NCT04340544 |
| Hydroxychloroquine for the Treatment of Mild COVID-19 Disease (CMTHY) | University Hospital Tuebingen | III | Hydroxychloroquine | Placebo capsules | Terminated (Reduced acceptance of IMP.) | NCT04322221 |
| Hydroxychloroquine for COVID-19 (COV-HCQ) | University Hospital Tuebingen | III | Hydroxychloroquine sulfate | Placebo | Terminated (Decrease in number of eligible patients.) | NCT04325893 |
| Hydroxychloroquine and Azithromycin for the Treatment of COVID-19 Infection Assessing | Centenario Hospital Miguel Hidalgo | III | Hydroxychloroquine | Ivermectin; placebo | Completed | NCT04391127 |
| Hydroxychloroquine in Patients With SARS-CoV-2 (COVID-19) Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HERO-HCQ) | Oregon Health and Science University | III | Hydroxychloroquine | Placebo | Withdrawn (Discontinued in favor of more promising directions that may benefit patients.) | NCT04363866 |
| Hydroxychloroquine and lopinavir/ritonavir to Improve the Health of People With COVID-19: “The Hope Coalition - 1” | Shahid Beheshti University of Medical Sciences | IV | Favipiravir | Hydroxychloroquine | Not yet recruiting | NCT04359615 |
| Hydroxychloroquine and lopinavir/ritonavir to Improve the Health of People With COVID-19: “The Hope Coalition - 1” | Cardresearch | III | Hydroxychloroquine sulfate tablets | Lopinavir/ritonavir oral tablet; placebo | Recruiting | NCT04403100 |
| Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAIXS) | Centre Hospitalier Universitaire de Saint Etienne | III | Hydroxychloroquine oral tablet | Lopinavir/ritonavir oral tablet; placebo | Active, not recruiting | NCT04328285 |
| Azithromycin in Hospitalized COVID-19 Patients (ACI) | Shahid Beheshti University of Medical Sciences | IV | Hydroxychloroquine | Azithromycin | Not yet recruiting | NCT04359316 |

(All information in the table are collected from https://clinicaltrials.gov).
### TABLE 2 | Summary of clinical trials of lopinavir/ritonavir on COVID-19 treatment.

| Trial title                                                                 | Sponsor                                           | Trial phase | Primary intervention       | Secondary intervention                                                                 | Status                                                                 | Identifier    |
|-----------------------------------------------------------------------------|---------------------------------------------------|-------------|---------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------|
| Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19) | Asan Medical Center                               | II          | Lopinavir/ritonavir tablet | Hydroxychloroquine sulfate tablet                                                      | Terminated (Terminated early because no patients were further enrolled since mid-Apr 2020.) | NCT04307693  |
| COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir (CORIPREV-LR) | Darrell Tan                                      | III         | Lopinavir/ritonavir       | N/A                                                                                    | Recruiting                                                             | NCT04321174  |
| Lopinavir/Ritonavir for the Treatment of COVID-19 Positive Patients With Cancer and Immune Suppression in the Last Year | OHSU Knight Cancer Institute                      | II          | Lopinavir/ritonavir       | Placebo                                                                               | Withdrawn (Limited resources.)                                        | NCT04455958  |
| FLARE: Favipiravir ± Lopinavir: A RCT of Early Antivirals (FLARE)           | University College, London                        | II          | Favipiravir               | Lopinavir/ritonavir; placebo                                                          | Recruiting                                                             | NCT04499677  |
| Trial of Early Therapies During Non-Hospitalized Outpatient Window for COVID-19 (TREATNOW) | Vanderbilt University Medical Center               | II          | Lopinavir/ritonavir tablets | Placebo                                                                               | Recruiting                                                             | NCT04372628  |
| Combination Therapies to Reduce Carriage of SARS-CoV-2 and Improve Outcome of COVID-19 in Ivory Coast: A phase Randomized IIb Trial (INTENSE-COV) | ANRS, Emerging Infectious Diseases                | III/IV      | Lopinavir/ritonavir       | Lopinavir/ritonavir ± telmisartan; lopinavir/ritonavir ± atorvastatin                 | Recruiting                                                             | NCT04466241  |
| Comparative Therapeutic Efficacy of Pragmatic Same-Day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP) | October 6 University                              | IV          | Remdesivir + tocilizumab + lopinavir/ritonavir | Hydroxychloroquine + tocilizumab + ivermectin                                         | Recruiting                                                             | NCT04779047  |
| Evaluation of Additional Treatments for COVID-19: A Randomized Trial in Niger (TRASCOV) | Epicentre                                         | III         | Standard care + lopinavir/ritonavir | Standard care                                                                        | Withdrawn (Epidemic dynamics.)                                        | NCT04490483  |
| Baricitinib Therapy in COVID-19 | Fabrizio Cantini                                  | II/III      | Lopinavir/ritonavir tablets | N/A                                                                                    | Completed                                                               | NCT04358614  |
| Efficacy of Pragmatic Same-Day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP) | Calmy Alexandra                                  | III         | Lopinavir/ritonavir       | N/A                                                                                    | Completed                                                               | NCT04364022  |
| Preventing Pulmonary Complications in Surgical Patients at Risk of COVID-19 (PROTECT-Surg) | University of Birmingham                         | III         | Lopinavir/ritonavir       | Hydroxychloroquine; lopinavir/ritonavir + hydroxychloroquine                           | Not yet recruiting                                                      | NCT04320277  |
| Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVePy)         | Institut National de la Santé Et de la Recherche Médicale, France | III         | Lopinavir/ritonavir       | Lopinavir/ritonavir + interferon β-1a; remdesivir; hydroxychloroquine; standard care; placebo | Active, not recruiting                                                | NCT04315948  |
| Treatment for COVID-19 in High-Risk Adult Outpatients                      | University of Washington                         | II/III      | Lopinavir/ritonavir       | Hydroxychloroquine + folic acid; hydroxychloroquine + azithromycin Corticosteroid; hydroxychloroquine; azithromycin; convalescent plasma; tocilizumab; immunoglobulin; synthetic neutralizing antibodies; aspirin; colchicine; baricitinib; anakinra; dimethyl fumarate; rituximab | Active, not recruiting                                                | NCT04354428  |
| Randomized Evaluation of COVID-19 Therapy (RECOVERY)                        | University of Oxford                             | II/III      | Lopinavir/ritonavir       | Hydroxychloroquine; lopinavir/ritonavir + hydroxychloroquine                           | Recruiting                                                             | NCT04366089  |

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to overstate or understate the clinical efficacy of CQ and HCQ on COVID-19 treatment.

**Lopinavir/ritonavir**

Lopinavir/ritonavir tablets (brand name: Kaletra) are two structurally related protease inhibitors and works as antiretroviral agents (Cvetkovic and Goa, 2003). Table 2 summarizes the clinical trials of lopinavir/ritonavir on COVID-19 treatment. The mechanism of action of protease inhibitors is block cleavage in Gag and Gag-Pol, and result in producing immature and noninfectious virus particles (Adamson, 2012). Similar to CQ, lopinavir/ritonavir could act as potential antiviral agents against SARS in vitro and in patients with SARS infection (Chu et al., 2004). Also, lopinavir/ritonavir has favorable clinical outcome with the Middle East respiratory syndrome coronavirus (MERS-CoV) after MERS reported in 2012 (Mo and Fisher, 2016; Arabi et al., 2018). Evidence from randomized trials indicated that lopinavir/ritonavir might improve outcomes in severe and critical COVID-19 patients, but it may induce mortality (Verdugo-Paiva et al., 2020). Moreover, it is reported that lopinavir/ritonavir could only improve a minority of throat-swab nucleic acid results in hospitals (Liu et al., 2020). Also, Cao et al. revealed that no beneficial response or clinical improvement was observed after treatment with lopinavir/ritonavir in a randomized, controlled, open-label trial with 199 in hospital patients suffering from severe SARS-CoV-2 infection, even though improvement was found for some secondary endpoints (Cao et al., 2020; Stower, 2020). Together, the response of COVID-19 patients with lopinavir/ritonavir is not ideal and unfavorable. As the previous study showed, CQ had more potent effects to patients with COVID-19 than the use of lopinavir/ritonavir; hence, an ongoing clinical trial in China would like to access the effectiveness and safety of CQ and lopinavir/ritonavir for patients suffering from mild or general SARS-CoV-2 infection (www.chictr.org.cn, ChiCTR2000029741). Overall, available data on the anti-SARS-CoV-2 activity of lopinavir/ritonavir are still limited and investigational, thereby the clinical application of lopinavir/ritonavir should be considered and monitored carefully.

**Remdesivir**

Remdesivir (GS-5734, brand name: Veklury), as a nucleotide analog prodrug, is a broad-spectrum antiviral drug that acts on RNA-dependent RNA polymerase (RdRp) and results in premature termination (Tchesnokov et al., 2019; Lamb, 2020). Table 3 shows the summary of clinical trials of remdesivir on COVID-19 treatment. As previously mentioned, Wang et al. showed that the EC_{50} value of remdesivir is 1.76 μM in Vero E6 cells, which suggests that remdesivir has high effectiveness in the control of SARS-CoV-2 infection in vitro (Wang M. et al., 2020). More importantly, the intravenous remdesivir was administrated to the patient who was the first case diagnosed as SARS-CoV-2 infection in the United States (Holshue et al., 2020). No adverse effects were observed in association with the infusion; also, clinical benefits were found in patients. Another case demonstrated that remdesivir could accelerate recovery time by 4 days, which is a meaningful and optimistic progress for patients and medical systems (Jorgensen et al., 2020). Notably, remdesivir is FDA approved specifically for the treatment of COVID-19. However, as more and more clinical cases were reported, the outcome of remdesivir treatment sometimes cannot achieve the expected effects on COVID-19 patients. Many researchers (Wang Y. et al., 2020) carried out a randomized, double-blind, placebo-controlled, multicenter trial; as a result, Wang et al. found that remdesivir is not associated with statistically significant clinical improvement, even though some patients in the remdesivir treatment group had numerically faster time to improve than those in the placebo group. More importantly, remdesivir treatment was discontinued early due to the adverse events, including, but not limited to, nausea, constipation, and respiratory failure or acute respiratory distress. Overall, the certainty of evidence remains less. Since

### Table 2 | Continued Summary of clinical trials of lopinavir/ritonavir on COVID-19 treatment.

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|----------------------|-----------------------|--------|------------|
| A Study of Combination Therapies to Treat COVID-19 Infection Isotretinoin in Treatment of COVID-19 (Randomized) | ProgenaBiome | II | Hydroxychloroquine + lopinavir/ritonavir, + azithromycin | Hydroxychloroquine + azithromycin | Withdrawn (Was never started.) | NCT04469702 |
| P2Et Extract in the Symptomatic Treatment of Subjects With COVID-19 | Hospital Universitario San Ignacio | II/III | Lopinavir/ritonavir, hydroxychloroquine, Caesalpinia spinosa extract capsule | Placebo | Recruiting | NCT04410510 |
| | | | | | | |

(All information in the table are collected from https://clinicaltrials.gov).
| Trial title                                                                                       | Sponsor                      | Trial phase | Primary intervention | Secondary intervention      | Status                        | Identifier        |
|-------------------------------------------------------------------------------------------------|------------------------------|-------------|----------------------|-----------------------------|-------------------------------|------------------|
| Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to <18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN) | Gilead Sciences               | II/III      | Remdesivir           | N/A                         | Recruiting                    | NCT04431453      |
| Remdesivir Efficacy in Coronavirus Disease                                                      | Tanta University             | II/III      | Remdesivir           | Standard of care            | Recruiting                    | NCT04345419      |
| Study in Participants With Early-Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation | Gilead Sciences               | I/II        | Remdesivir           | Placebo                     | Completed                      | NCT04539262      |
| A Trial of Remdesivir in Adults With Severe COVID-19                                              | Capital Medical University   | III         | Remdesivir           | Placebo                     | Suspended (The epidemic of COVID-19 has been controlled well at present; no eligible patients can be recruited.) | NCT04252664      |
| A Trial of Remdesivir in Adults With Mild and Moderate COVID-19                                   | Capital Medical University   | III         | Remdesivir           | Placebo                     | Terminated (The epidemic of COVID-19 has been controlled well in China; no eligible patients can be enrolled at present.) | NCT04257656      |
| Comparison of Remdesivir Versus Lopinavir/Ritonavir and Remdesivir Combination in COVID-19 Patients | Ahmed Essam                  | IV          | Remdesivir           | Lopinavir/ritonavir + remdesivir | Recruiting                    | NCT04738045      |
| Efficacy and Safety of DWU124/8 With remdesivir in Severe COVID-19 Patients                       | Daewoong Pharmaceutical Co., LTD. | III      | DWU124/8 + remdesivir | Placebo + remdesivir        | Recruiting                    | NCT04713176      |
| Efficacy and Safety of Remdesivir and Tocilizumab for the Management of Severe COVID-19: A Randomized Controlled Trial | M Abdur Rahim Medical College and Hospital | III | Remdesivir + tocilizumab | N/A                    | Completed                      | NCT04678739      |
| REMdesivir-HU Clinical Study and Severe Covid-19 Patients                                         | University of Pecs           | III         | Remdesivir-HU        | N/A                         | Active, not recruiting         | NCT04610541      |
| Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) | Gilead Sciences               | III         | Remdesivir           | N/A                         | Completed                      | NCT04292899      |
| Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment | Gilead Sciences               | III         | Remdesivir           | Standard of care            | Completed                      | NCT04292730      |
| Study to Evaluate the Efficacy and Safety of remdesivir in Participants With Severely Reduced Kidney Function Who Are Hospitalized for Coronavirus Disease 2019 (COVID-19) (REDPINE) | Gilead Sciences               | III         | Remdesivir           | Placebo                     | Recruiting                    | NCT04745351      |
| Study of Merimepodib in Combination With Remdesivir                                               | ViralClear Pharmaceuticals, Inc | II | Merimepodib + remdesivir | Placebo + remdesivir        | Terminated (Failure to meet primary endpoint) | NCT04410354      |

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TABLE 3 | (Continued) Summary of clinical trials of remdesivir on COVID-19 treatment.

| Trial title                                                                 | Sponsor                        | Trial phase | Primary intervention | Secondary intervention | Status                  | Identifier     |
|-----------------------------------------------------------------------------|--------------------------------|-------------|----------------------|------------------------|-------------------------|----------------|
| in Adult Patients With Advanced COVID-19                                   | Ain Shams University           | III         | Remdesivir           | Standard of care       | Completed               | NCT04853901   |
| Remdesivir Efficacy in Management of COVID-19 Patients                     | Hoffmann-La Roche              | III         | Remdesivir + tocilizumab | Remdesivir + placebo   | Completed               | NCT04409262   |
| A Study to Evaluate the Efficacy and Safety of Remdesivir Plus tocilizumab | Gilead Sciences                | III         | Remdesivir           | Placebo                | Active, not recruiting  | NCT04501962   |
| Compared With remdesivir Plus Placebo in Hospitalized Patients With Severe| National Institute of Allergy  | II          | Remdesivir           | Placebo                | Completed               | NCT02818582   |
| COVID-19 Pneumonia (REMDACTA)                                              | and Infectious Diseases (NAID) |             |                      |                        |                         |                |
| Study to Evaluate the Efficacy and Safety of remdesivir (GS-5734™) Treatment | ASST Fatebenefratelli Sacco     | III         | Remdesivir + dexamethasone | Baricitinib + dexamethasone; remdesivir + baricitinib + dexamethasone | Not yet recruiting | NCT04832880   |
| of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting              |                                |             |                      |                        |                         |                |
| Safety, Tolerability and Pharmacokinetics of Inhaled Nanoparticle Formulation | NeuroActiva, Inc               | I           | Remdesivir           | NA-831; NA-831 + remdesivir | Recruiting             | NCT04480333   |
| of Remdesivir (GS-5734™) and NA-831 (Neuroviral)                          | National Institute of Allergy and Infectious Diseases (NAID) | II          | Remdesivir           | Placebo                | Completed               | NCT04401579   |
| GS-5734 to Assess the Antiviral Activity, Longer-Term Clearance of Ebola Virus, and Safety in Male Ebola Survivors With Evidence of Ebola Virus Persistence in Somen | M Abdur Rahim Medical College and Hospital | III         | Remdesivir + tocilizumab | Remdesivir + placebo | Completed               | NCT04683026   |
| Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial) (AMMURAVID) | ASST Fatebenefratelli Sacco     | III         | Remdesivir + dexamethasone | Baricitinib + dexamethasone; remdesivir + baricitinib + dexamethasone | Not yet recruiting | NCT04832880   |
| for COVID-19 (the AMMURAVID Trial) (AMMURAVID)                              | Sunnybrook Health Sciences Centre | II          | Remdesivir + standard supportive care | Interferon β-1a + standard supportive care | Recruiting             | NCT04330690   |
| Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO)      | M Abdur Rahim Medical College and Hospital | III         | Remdesivir + baricitinib | Remdesivir + tocilizumab | Recruiting             | NCT04683026   |
| Efficacy of Ramdicivir and Baricitinib for the Treatment of Severe COVID-19 Patients | National Institute of Allergy and Infectious Diseases (NAID) | III         | Remdesivir + baricitinib | Remdesivir + placebo | Completed               | NCT04401579   |
| Adaptive COVID-19 TreatmentTrial 2 (ACTT-2)                                | Oslo University Hospital        | II/III      | Remdesivir           | Hydroxychloroquine     | Recruiting             | NCT04321616   |
| The Efficacy of Different Anti-Viral Drugs in COVID 19 Infected Patients    | The University of The West Indies | III         | Remdesivir           | Acalabrutinib; interferon β-1a | Not yet recruiting | NCT04647669   |
| World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments (SOLIDARITY) | National Institute of Allergy and Infectious Diseases (NAID) | II          | Remdesivir + risankizumab | Remdesivir + placebo | Recruiting             | NCT04583956   |
| ACTIV-5/Big Effect Trial (BET-A) for the Treatment of COVID-19              | National Institute of Allergy and Infectious Diseases (NAID) | II          | Remdesivir + risankizumab | Remdesivir + placebo | Recruiting             | NCT04583969   |
| ACTIV-5/Big Effect Trial (BET-B) for the Treatment of COVID-19              | National Institute of Allergy and Infectious Diseases (NAID) | II          | Remdesivir + lenzilumab | Remdesivir + placebo | Recruiting             | NCT04583969   |
| Adaptive COVID-19 Treatment Trial 4 (ACTT-4)                               | National Institute of Allergy and Infectious Diseases (NAID) | III         | Remdesivir + baricitinib | Remdesivir + dexamethasone | Active, not recruiting | NCT04640168   |
| National Institute of Allergy and Infectious Diseases (NAID)               | Adaptive COVID-19 Treatment Trial (ACTT) | III         | Remdesivir           | Placebo                | Completed               | NCT04280705   |

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Nov. 2020, the WHO has issued a conditional recommendation against the use of remdesivir in COVID-19 patients.

### Interferons

The interferons (IFNs) as glycoproteins have broad-spectrum antiviral effects (Lin and Young, 2014). The IFNs can be divided into three types based on the differences in the structures of their respective receptors. In detail, the IFNs are classified into type I IFNs (IFN-α/β), type II IFNs (IFN-γ), and type III IFNs (IFN-λ). Table 4 shows the summary of clinical trials of IFNs on COVID-19 treatment. Mantlo et al. (2020) demonstrated that IFN-α (EC_{50} = 1.35 IU/ml) and IFN-β (EC_{50} = 0.76 IU/ml) at clinically achievable concentrations could suppress the replication of SARC-CoV-2 in Vero cells. These findings provide a valuable fundamental for the potential use of IFN-α/β to against COVID-19. Zhou et al. accessed the efficacy of IFN-α2b and arbidol involving 77 hospitalized patients; as a result, researchers revealed that IFN-α2b with or without arbidol could significantly reduce the duration for detectable virus as well as the inflammatory markers (Zhou Q. et al., 2020). Usually, the IFNs are used in combination with other...
| Trial title                                                                 | Sponsor                               | Trial phase | Primary intervention                                           | Secondary intervention                           | Status                     | Identifier     |
|---------------------------------------------------------------------------|---------------------------------------|-------------|---------------------------------------------------------------|--------------------------------------------------|----------------------------|-----------------|
| Double Therapy With IFN-beta 1b and Hydroxychloroquine                    | The University of Hong Kong            | II          | Interferon β-1b + hydroxychloroquine                          | Hydroxychloroquine                               | Completed                 | NCT04350281    |
| Pegylated Interferon Lambda Treatment for COVID-19                         | Raymond Chung                         | II          | Interferon λ                                                 | Placebo                                          | Enrolling by invitation   | NCT04343976    |
| Pegylated Interferon - α2b With SARS-CoV-2 (COVID-19)                     | Cadila Healthcare Limited             | II          | Interferon α-2b                                              | Standard of Care                                 | Recruiting                | NCT04480138    |
| Interferon Beta 1a in Hospitalized COVID-19 Patients (IB1aC)               | University of Medical Sciences         | IV          | Interferon β-1a + lopinavir/ritonavir + single dose of hydroxychloroquine | Lopinavir/ritonavir + single dose of hydroxychloroquine | Enrolling by invitation   | NCT04350671    |
| Dual Therapy With Interferon Beta-1b and Clofazimine for COVID-19          | The University of Hong Kong            | II          | Interferon β-1b + clofazimine                                | Clofazimine                                      | Recruiting                | NCT04465695    |
| The Investigation Into Beneficial Effects of High-Dose Interferon Beta 1-a, Compared to Low-dose Interferon Beta 1-a in Moderate to Severe Covid-19 | Shahid Beheshti University of Medical Sciences | II          | Lopinavir/ritonavir + high dose interferon β-1a              | Lopinavir/ritonavir + low dose interferon β-1a    | Not yet recruiting        | NCT04521400    |
| An Investigation into Beneficial Effects of Interferon Beta 1a, Compared to Interferon Beta 1b and the base Therapeutic Regimen in Moderate to Severe COVID-19: A Randomized Clinical Trial (COVIFERON) | Shahid Beheshti University of Medical Sciences | II          | Hydroxychloroquine + lopinavir/ritonavir + interferon β-1a   | Hydroxychloroquine + lopinavir/ritonavir + interferon β-1b; hydroxychloroquine + lopinavir/ritonavir | Completed                 | NCT04343768    |
| Clinical Study for the Treatment With Interferon-β-1a (IFN8-1a) of COVID-19 Patients (INTERCOP) | Emanuele Bosi                         | II          | Interferon β-1a                                             | Standard care                                    | Terminated (Futility.)    | NCT04449380    |
| Treatment of COVID-19 by Nebulization of Interferon Beta 1b Efficiency and Safety Study (COV-NI) | Centre Hospitalier Universitaire, Amiens | II          | Type 1 interferon + routine care                             | Routine care                                      | Recruiting                | NCT04469491    |
| Interferon Lambda for Immediate Antiviral Therapy at Diagnosis in COVID-19 (ILIAD) | University Health Network, Toronto    | II          | Interferon λ-1a                                            | Placebo                                          | Recruiting                | NCT04354259    |
| Pegylated Interferon Lambda for Treatment of COVID-19 Infection            | Soroka University Medical Center       | II          | Interferon λ + standard of care treatment                    | Standard of care treatment                       | Recruiting                | NCT04534673    |
| IFN-Beta 1b and Remdesivir for COVID-19                                   | The University of Hong Kong           | II          | Interferon β-1b + remdesivir                                | Remdesivir                                       | Recruiting                | NCT04647695    |
| The Containing Coronavirus Disease 19 (COVID-19) Trial (ConCorD-19)        | Pontificia Universidad Catolica de Chile | III         | Interferon β-1a                                             | Standard of care                                 | Recruiting                | NCT04552379    |
| Human Intravenous Interferon Beta-1a Safety and Preliminary Efficacy in Hospitalized Subjects With Coronavirus (HBISCUS) | Faron Pharmaceuticals Ltd.            | II          | Interferon β-1a                                            | Placebo                                          | Not yet recruiting        | NCT04860518    |
| Rintatolimod and IFN Alpha-2b for the Treatment of Mild or Moderate COVID-19 Infection in Cancer Patients | Roswell Park Cancer Institute         | I/II        | Recombinant interferon α-2b + rintatolimod                 | Rintatolimod                                     | Recruiting                | NCT04379518    |
| IFN Beta-1b and Ribavirin for Covid-19                                     | The University of Hong Kong           | II          | Interferon β-1b + ribavirin + standard care                  | Standard care                                     | Recruiting                | NCT04494399    |
| Adaptive COVID-19 Treatment Trial 3 (ACTT-3)                              | National Institute of Allergy and Infectious Diseases (NAID) | III         | Remdesivir + interferon β-1a                                | Remdesivir + placebo                             | Completed                 | NCT04492475    |
| Interferon Lambda Therapy for COVID-19                                     | Icahn School of Medicine at Mount Sinai | II          | Interferon λ-1a                                            | Supportive care                                   | withdrawn (Due to the number of competing trials at their site, the study team has closed enrollment and withdrawn this trial.) | NCT04388709    |
antiviral therapies (Mantlo et al., 2020). Of note, a group from China examined the effectiveness and safety profile of a triple antiviral therapy including IFN-β1b, lopinavir/ritonavir, and ribavirin with 86 patients suffering from mild to moderate SARS-CoV-2 infection (Hung et al., 2020). Their results showed that the triple combination treatment is superior to lopinavir/ritonavir treatment alone with shorter viral shedding duration and hospital stay period.

However, some reports indicated that the application of IFN-λ has more advantages in COVID-19 treatment. The most outstanding profile of IFN-λ over IFN-α/β is the absence of pro-inflammatory effects (Prokunina-Olsson et al., 2020). This is because the response to IFN-λ administration localizes to epithelial cells, which could reduce side effects and inflammatory effects related to the systemic action from IFN-α/β treatment. Also, researchers showed that IFN-λ reduces the presence of virus in the lungs and prevents the induction of cytokine storm; hence, the application of IFN-λ could avoid pneumonia and acute respiratory distress syndrome (ARDS) (Andreakos and Tsiodras, 2020). Overall, IFN-λ is a promising and potential therapeutic agent for patients suffering from COVID-19. Notably, more clinical study is necessary in the future.

**Umifenovir**

Umifenovir (brand name: Arbidol, ARB) is an antiviral drug, which has the ability to inhibit the replication of influenza A and B virus through impeding the early membrane fusion event (Leneva et al., 2009). Table 5 indicates the summary of clinical trials of umifenovir for the treatment of COVID-19. Zhu et al. (2020) accessed the efficacy and safety of lopinavir/ritonavir and umifenovir involving 50 COVID-19 patients, 34 cases with lopinavir/ritonavir treatment, and 16 cases with umifenovir treatment. From the results, no side effects and developed pneumonia or ARDS were observed in both groups. More importantly, patients with umifenovir treatment have shorter duration of positive RNA test compared with those with lopinavir/ritonavir treatment; thus, the authors indicated that umifenovir may be superior to lopinavir/ritonavir against COVID-19. Similarly, Deng et al. (2020) demonstrated that lopinavir/ritonavir combined with umifenovir had more favorable clinical outcomes compared with lopinavir/ritonavir only in a retrospective cohort study. Furthermore, Nojomi et al. (2020) evaluated HCQ followed by lopinavir/ritonavir or HCQ followed by umifenovir among 100 patients with COVID-19. As a result, the researchers found that patients in the umifenovir group had shorter hospitalized duration and higher peripheral oxygen saturation rate, also had improvements in requiring ICU admissions, and chest CT involvement. Moreover, some studies showed that umifenovir was well-tolerated with mild gastrointestinal tract reaction and related to the lower mortality in COVID-19 cases (Jomah et al., 2020).

However, Lian et al. (2020) indicated that umifenovir is not effective in the improved response in non-ICU COVID-19 patients with more advanced disease as compared with lopinavir/ritonavir treatment. The researchers suggested that this may be due to the limited diffusion of umifenovir in the lungs, while lopinavir/ritonavir had more activity in the systemic circulation (Leneva et al., 2009). Therefore, umifenovir treatment may not be effective for patients with severe COVID-19 disease and those patients should be treated with a combination therapy of lopinavir/ritonavir and umifenovir.
patients in a retrospective study. In detail, the study included 81 patients suffering from COVID-19, and evaluated several baseline clinical and laboratory factors. Of note, the patients with umifenovir treatment even had longer hospital stay duration than those patients in the control group. Hence, the authors indicated that umifenovir might not improve prognosis or accelerate SARS-CoV-2 clearance in non-ICU patients with COVID-19.

**Azithromycin**

Azithromycin is a macrolide antibiotic medication. Azithromycin binds to the 50S subunit of ribosome, and thereby prevents the mRNA translation and interferes with protein synthesis (Bakheit et al., 2014). Table 6 summarizes the clinical trials of azithromycin on COVID-19 treatment. Gautret et al. (2020) showed that azithromycin could reinforce the effectiveness of HCQ to clear the COVID-19 virus. Of note, the sample size was small, which only involved 20 cases. Also, researchers revealed that azithromycin combined with HCQ, or with lopinavir/ritonavir, could improve the clinical response and accelerate the COVID-19 virus clearance (Purwati et al., 2021). By contrast, Cavalcanti et al. (2020) reported that no improved clinical outcomes were observed in COVID-19 patients, suffering from mild to moderate COVID-19, treated with HCQ alone or with azithromycin compared with those with standard care in a multicenter, randomized, open-label, three-group, controlled trial involving 667 patients. Also, evidence from retrospective observational studies demonstrated that azithromycin in combination with HCQ did not induce favorable clinical outcomes for COVID-19 patients (Echeverría-Esnal et al., 2021).

**Antibacterial/antibiotic drugs**

It has been reported that bacterial coinfection happened in 3.5% of COVID-19 patients (Sieswerda et al., 2021). In other words, the hospitalized patients with COVID-19 have risk of bacterial infections. Sieswerda et al. (2021) recommended that the 5-day antibiotic therapy is required for the COVID-19 patients suffering with suspected bacterial respiratory infection after clinical improvements. However, their recommendation needs to be confirmed because unnecessary antibiotic treatment should be prevented. Also, some studies revealed that bacterial and fungal coinfection would occur in patients with SARS-CoV-2 infection, thereby the antimicrobial treatment regimen and stewardship interventions are necessary to control the exacerbating COVID-19 pandemic (Rawson et al., 2020). More importantly, antimicrobial resistance should be considered as the collateral effect of SARS-CoV-2 infection, and thus, proper trend for antibiotic stewardship interventions should be analyzed and prescribed in the emergency department (Pulia et al., 2020).

**IMMUNOTHERAPY**

**Monoclonal antibody Tocilizumab**

Tocilizumab (TCZ, trade name: Actemra) is a recombinant humanized monoclonal antibody (Sheppard et al., 2017). TCZ is well-tolerated without significant abnormalities after long-term toxicity tests on animals (Gabay et al., 2013). For the mechanism of action, TCZ specially binds membrane-bound interleukin-6 receptor (mIL-6R) and soluble interleukin-6 receptor (sIL-6R) and inhibits signal transduction (Ibrahim et al., 2020). It has been reported that COVID-19 induces higher plasma levels of cytokines including, but not limited to, IL-6, IL-2, IL-7, IL-10, tumor necrosis factor-a (TNF-a), IFN-γ-inducible protein, etc., in ICU patients with SARS-CoV-2 infection (Chen N. et al., 2020; Huang C. et al., 2020), which refers to a cytokine storm in patients. Furthermore, several studies indicated that TCZ treatment could return the temperature to normal quickly and improve the respiratory function through blocking IL-6 receptors (Fu et al., 2020; Zhang et al., 2020). Table 7 shows the clinical trials of TCZ on COVID-19 treatment. Luo et al. (2020) examined the efficacy of TCZ, as a recombinant humanized antihuman IL-6 receptor monoclonal antibody, and found that the serum IL-6 level decreased in 10 patients, while the persistent and dramatic increase in IL-6 was found in four patients who failed in the treatment. In contrast, Xu et al. (2020) recorded the clinical manifestation, computerized tomography (CT) scan image, and laboratory examinations to assess the effectiveness of TCZ in severe COVID-19 patients. Their results showed that TCZ has critical roles in pathogenesis and clinical improvement in patients. Moreover, Klopfenstein et al. (2020) performed a retrospective case-control study involving 20 patients with severe SARS-CoV-2 infection and found that TCZ could reduce the number of ICU admissions and/or mortality.

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**TABLE 5** | Summary of clinical trials of umifenovir on COVID-19 treatment.

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|------------|----------------------|------------------------|--------|------------|
| Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients With Mild to Moderate COVID-19 | R-Pharm | III | Favipiravir + stand of care | Umifenovir + intranasal recombinant interferon α, or hydroxychloroquine, or chloroquine, or mefloquine in recommended regimen | Active, not recruiting | NCT04501783 |
| Umifenovir in Hospitalized COVID-19 Patients (UAIIC) | Shahid Beheshti University of Medical Sciences | IV | Umifenovir + interferon β-1a + lopinavir/ritonavir + single dose of hydroxychloroquine + standards of care | Interferon β-1a + lopinavir/ritonavir + single dose of hydroxychloroquine + standards of care | Enrolling by invitation | NCT04350684 |

(All information in the table are collected from https://clinicaltrials.gov).
| Trial title                                                                 | Sponsor                                                                 | Trial phase | Primary intervention                        | Secondary intervention | Status                                  | Identifier  |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|---------------------------------------------|------------------------|-----------------------------------------|-------------|
| Hydroxychloroquine Plus Azithromycin Versus Hydroxychloroquine for COVID-19 Pneumonia (COVIDOC Trial) (COVIDOC) | University Hospital, Montpellier                                        | II/III      | Hydroxychloroquine + azithromycin          | Azithromycin           | Terminated (Halted prematurely.)          | NCT04345861 |
| Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial—CORIMUNO-19-VIRO (CORIMUNO-VIRO) | Assistance Publique - Hôpitaux de Paris                                   | II/III      | Sarilumab + azithromycin + hydroxychloroquine | Sarilumab             | Suspended (DSMB recommendation (futility).) | NCT04341870 |
| A Multi-Step Open-Label Two-arm Randomized Superiority Clinical Trial of Azithromycin Versus Usual Care in Ambulatory COVID19 (ATOMIC2) (ATOMIC2) | University of Oxford                                                      | III         | Azithromycin                                | N/A                    | Completed                                | NCT04381962 |
| Hydroxychloroquine Azithromycin COVID-19 Pregnancy Trial (HASCOPT)         | Hospital St. Joseph, Marseille, France                                    | III         | Hydroxychloroquine + azithromycin          | Conventional management | Withdrawn (No authorization obtained.)    | NCT04365231 |
| HOPE: A Trial of Hydroxychloroquine Plus Azithromycin in High Risk COVID-19 (HOPE_BRAZIL) | Latin American Cooperative Oncology Group                               | II          | Hydroxychloroquine + azithromycin          | Hydroxychloroquine + placebo | Withdrawn (Withdrawn due to lack of study lefts interested in participating.) | NCT04575558 |
| Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION)    | Thomas M. Lietman                                                        | III         | Azithromycin                                | Placebo                | Active, not recruiting                    | NCT04332107 |
| Atovaquone and Azithromycin Combination for Confirmed COVID-19 Infection   | HonorHealth Research Institute                                            | II          | Atovaquone/Azithromycin                     | N/A                    | Recruiting                               | NCT04339426 |
| Proactive Care of Ambulatory COVID19 Patients (AMBU-COVID)                 | Centre Hospitalier Universitaire, Amiens                                  | III         | Azithromycin                                | Symptomatic treatment  | Not yet recruiting                       | NCT04371107 |
| Hydroxychloroquine vs. Azithromycin for Outpatients in Utah With COVID-19 (HyAzOUT) | Intermountain Health Care, Inc                                            | III         | Hydroxychloroquine                          | Azithromycin           | Recruiting                               | NCT043334382 |
| Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19 (I-HAHPS) | Intermountain Health Care, Inc                                            | II          | Hydroxychloroquine                          | Azithromycin           | Active, not recruiting                    | NCT04329832 |
| Open Label Non-Comparative Trial of the Combination of Hydroxychloroquine and Azithromycin in the Treatment of Hospitalized Patients | University of New Mexico                                                 | II          | Hydroxychloroquine + azithromycin          | N/A                    | Active, not recruiting                    | NCT04458948 |
| Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19 | Rutgers, The State University of New Jersey                              | II          | Hydroxychloroquine sulfate + azithromycin  | Hydroxychloroquine sulfate | Active, not recruiting                    | NCT04336332 |
| Azithromycin + Amoxicillin/Clavulanate vs Amoxicillin/Clavulanate in COVID19 Patients with Pneumonia in Non-intensive Unit (AzA) | Nantes University Hospital                                               | III         | Azithromycin + amoxicillin/ clavulanate     | Amoxicillin/clavulanate | Not yet recruiting                        | NCT04363060 |
| Hospital do Coracao                                                        | III          | Hydroxychloroquine                          | N/A                    | Active, not recruiting (Continued on following page) | NCT04322123 |
| Trial title                                                                 | Sponsor                                                                 | Trial phase | Primary intervention                  | Secondary intervention          | Status                          | Identifier                  |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|---------------------------------------|---------------------------------|---------------------------------|-----------------------------|
| Safety and Efficacy of Hydroxychloroquine Associated with Azithromycin in SARS-CoV-2 Virus (COVID-19) (Coalition-I) | Centre Hôpital Universitaire Farhat Hached                              | III         | Hydroxychloroquine + azithromycin     | Hydroxychloroquine + placebo    | Not yet recruiting            | NCT04405921                |
| Hydroxychloroquine, Azithromycin in the Treatment of Covid-19 (PACTT)     | Gilberto Cruz arteaga                                                   | III         | Azithromycin + ivermectin + ribaroxaban + paracetamol | Azithromycin + ribaroxaban + paracetamol | Recruiting                     | NCT04673214                |
| Evaluation of Prognostic Modification in COVID-19 Patients in Early Intervention Treatment | National Institute of Allergy and Infectious Diseases (NIAD)            | II          | Hydroxychloroquine + azithromycin     | Placebo                         | Terminated (Slow enrollment and lack of community enthusiasm.) | NCT04358068                |
| Evaluating the Efficacy of Hydroxychloroquine and Azithromycin to Prevent Hospitalization or Death in Persons With COVID-19 | Novartis Pharmaceuticals                                                | III         | Hydroxychloroquine                    | Hydroxychloroquine + azithromycin | Completed                      | NCT04358081                |
| Hydroxychloroquine Monotherapy and in Combination with Azithromycin in Patients With Moderate and Severe COVID-19 Disease | Prof. Dr. Matthias Preusser                                              | II          | Azithromycin                          | Placebo                         | Recruiting                     | NCT04369365                |
| A Single-blinded, Randomized, Placebo Controlled phase II Trial of Prophylactic Treatment With Oral Azithromycin Versus Placebo in Cancer Patients Undergoing Antineoplastic Treatment During the Corona Virus Disease 19 (COVID-19) Pandemic | University Hospital, Strasbourg, France                                  | III         | Hydroxychloroquine                    | Azithromycin; telmisartan       | Recruiting                     | NCT04359953                |
| Efficacy of Hydroxychloroquine, Telmisartan and Azithromycin on the Survival of Hospitalized Elderly Patients With COVID-19 (COVID-Aging) | Chronic Obstructive Pulmonary Disease Trial Network, Denmark            | II          | Hydroxychloroquine + azithromycin     | Placebo                         | Completed                      | NCT04322396                |
| Proactive Protection With Azithromycin and Hydroxychloroquine in Hospitalized Patients With COVID-19 (ProPAC-COVID) | Frantisek Duska, MD, PhD                                                | III         | Hydroxychloroquine + azithromycin     | Hydroxychloroquine              | Terminated (Steering Committee decision in accordance with stopping rule 1: Emergence of new data.) | NCT04339816                |
| Azithromycin Added to Hydroxychloroquine in Patients Admitted to Intensive Care With COVID-19: Randomized Controlled Trial (AZIQUINE-ICU) | Sheba Medical Center                                                    | III         | Hydroxychloroquine + azithromycin     | Hydroxychloroquine + camostat mesylate | Recruiting                     | NCT04355052                |
| Open Label Study to Compare Efficacy, Safety and Tolerability of Hydroxychloroquine Combined With Azithromycin Compared to Hydroxychloroquine Combined With Camostat Mesylate and to "No Treatment" in SARS CoV 2 Virus (COSTA) | Sheba Medical Center                                                    | III         | Hydroxychloroquine + azithromycin     | Hydroxychloroquine + camostat mesylate |                               |                             |

(Continued on following page)
| Trial title                                                                 | Sponsor                                                                 | Trial phase | Primary intervention                     | Secondary intervention                      | Status                                      | Identifier       |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------|
| Asymptomatic COVID-19 Trial (ACT)                                          | Rutgers, The State University of New Jersey                            | II          | Hydroxychloroquine + azithromycin        | Placebo                                    | Withdrawn (The investigators have decided not to go forward with this protocol.) | NCT04374552     |
| Hydroxychloroquine and Zinc With Either Azithromycin or Doxycycline for Treatment of COVID-19 in Outpatient Setting | St. Francis Hospital, New York                                          | IV          | Hydroxychloroquine + azithromycin + zinc sulfate | Hydroxychloroquine + doxycycline + zinc sulfate | Completed         | NCT04370782     |
| Epidemiology of SARS-CoV-2 and Mortality to Covid19 Disease in French Cancer Patients (ONCOVID)       | Gustave Roussy, Cancer Campus, Grand Paris                           | II          | Hydroxychloroquine + azithromycin        | Hydroxychloroquine                          | Recruiting       | NCT04341207     |
| Use of Hydroxychloroquine Alone or Associated for Inpatients With SARS-CoV2 Virus (COVID-19)       | Apsen Farmaceutica S.A.                                                | III         | Hydroxychloroquine sulfate               | Hydroxychloroquine sulfate + azithromycin   | Withdrawn (This study was canceled before enrollment due to a decision by the Sponsor.) | NCT04361461     |
| Phytomedicines Versus Hydroxychloroquine as an Add On Therapy to Azithromycin in Asymptomatic Covid-19 Patients (PHYTCOVID-19) | Institute for Research and Development of Medicinal and Food Plants of Guinea | II          | Hydroxychloroquine + azithromycin        | Quinine + azithromycin                      | Enrolling by invitation | NCT04501965     |
| Study Evaluating the Efficacy of Hydroxychloroquine and Azithromycin in Patients With COVID-19 and Hematological Malignancies (HYACINTHE) | Institut de cancérologie Strasbourg Europe                            | II          | Hydroxychloroquine + azithromycin        | Placebo                                    | Withdrawn (Competent authority decision.) | NCT04392128     |
| Hydroxychloroquine, Oseltamivir and Azithromycin for the Treatment of COVID-19 Infection: An RCT (PROTECT) | Shehnoor Azhar                                                       | III         | Azithromycin                             | Hydroxychloroquine; oseltamivir; hydroxychloroquine + azithromycin; hydroxychloroquine + oseltamivir; oseltamivir + azithromycin; hydroxychloroquine + oseltamivir + azithromycin | Recruiting       | NCT04338698     |
| Efficacy of Sofosbuvir Plus Ledipasvir in Egyptian Patients With COVID-19 Compared to Standard Treatment | Almaza Military Fever Hospital                                         | III          | Sofosbuvir + ledipasvir                  | Oseltamivir + hydroxychloroquine and azithromycin | Completed         | NCT04530422     |
| International ALLIANCE Study of Therapies to Prevent Progression of COVID-19                           | National Institute of Integrative Medicine, Australia                 | II          | Vitamin C + hydroxychloroquine + azithromycin + zinc citrate + vitamin D3 + vitamin B12 | Hydroxychloroquine + azithromycin + zinc citrate + vitamin D3 + vitamin B12 | Recruiting       | NCT04396768     |
| VA Remote and Equitable Access to COVID-19 Healthcare Delivery (VA-REACH TRIAL) (VA-REACH)          | Salomeh Keyhani MD                                                    | III         | Hydroxychloroquine                       | Azithromycin                               | Suspended (Concerns related to study drug) | NCT04363203     |
| Evaluate the Efficacy and Safety of Oral Hydroxychloroquine, Indomethacin and Zithromax in Subjects With Mild Symptoms of COVID-19 (COVID-19) | Perseverance Research Center, LLC                                    | I/II        | Hydroxychloroquine                       | Azithromycin; indomethacin                 | Recruiting       | NCT04344457     |
| Effectiveness of Hydroxychloroquine in COVID-19 Patients (COVID)                                 | Prof. Dr. Umar Farooq                                                 | III         | Hydroxychloroquine                       | Azithromycin                               | Not yet recruiting | NCT04328272     |

(Continued on following page)
TABLE 6 (Continued) Summary of clinical trials of azithromycin on COVID-19 treatment.

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|-----------------------|------------------------|--------|------------|
| Levamisole and Isoprinosine in the Treatment of COVID19: A Proposed Therapeutic Trial Efficacy and Safety of Favipiravir in COVID-19 Patients in Indonesia (FVR) | Cairo University | III | Levamisole + isoprinosine | Azithromycin + hydroxychloroquine | Not yet recruiting | NCT04383717 |
| | Ina-Respond | III | Favipiravir + azithromycin | Favipiravir | Suspended (Study halted prematurely but potentially will resume, the protocol will be amended.) | NCT04613271 |
| Treatment in Patients With Suspected or Confirmed COVID-19 With Early Moderate or Severe Disease (RCT) Safety and Efficacy of Doxycycline and Rivaroxaban in COVID-19 (DOXYCOV) A Study of Quintuple Therapy to Treat COVID-19 Infection (HADZPaC) Safety and Efficacy of Hydroxychloroquine for the Treatment and Prevention of Coronavirus Disease 2019 (COVID-19) Caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Effectiveness of Ivermectin as Add-On Therapy in COVID-19 Management Ivermectin for Severe COVID-19 Management Assessment of Efficacy and Safety of HCQ and Antibiotics Administrated to Patients COVID19(+) (COVID + PA) Evaluation of the Efficacy and Safety of Treatments for Patients Hospitalized for COVID-19 Infection Without Signs of Acute Respiratory Failure, in Tunisia (THINC) Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically III COVID-19 Patients OUTpatient Treatment of COVID-19 in Patients With Risk Factor for Poor Outcome (OUTCOV) A Study of the Effectiveness of an Off Label Mefloquine Use for the Treatment of Patients With COVID19 Add on to Azithromycin, Phytomedicine and/or Antimalarial Drug vs Hydroxychloroquine in Uncomplicated COVID-19 Patients (CANCOCVID-19) | Yauonde Central Hospital | IV | Doxycycline + Rivaroxaban | Hydroxychloroquine + azithromycin | Recruiting | NCT04715295 |
| | ProgenaBiome | II | Hydroxychloroquine + azithromycin + vitamin C + vitamin D + zinc | Vitamin C + vitamin D + zinc | Recruiting | NCT04334512 |
| | International Brain Research Foundation | I | Hydroxychloroquine + azithromycin with vitamins and minerals | N/A | Not yet recruiting | NCT04590274 |
| | Abderrahmane Mami Hospital | IV | Hydroxychloroquine + azithromycin | N/A | Withdrawn (- Interest in the use of HCQ is controversial.) | NCT04351919 |
| | Abderrahmane Mami Hospital | III | Hydroxychloroquine + azithromycin | Hydroxychloroquine + azithromycin + zinc; azithromycin + doxycycline | Withdrawn (- Interest in the use of HCQ is controversial.) | NCT04528927 |
| | Indonesia University | I | Oseltamivir + azithromycin | Oseltamivir + azithromycin + umbilical-cord derived mesenchymal stem cells | Recruiting | NCT04457609 |
| | Groupe Hospitalier Paris Saint Joseph | III | Azithromycin | Hydroxychloroquine; lopinavir/ritonavir | Withdrawn (The PI decided.) | NCT04365582 |
| | Bumansay Federal Medical Biophysical Center | II/III | Mefloquine | Hydroxychloroquine; mefloquine + azithromycin ± tocilizumab; hydroxychloroquine + azithromycin ± tocilizumab | Completed | NCT04347031 |
| | Institute for Research and Development of Medicinal and Food Plants of Guinea | II | Hydroxychloroquine + azithromycin | Cospherunate + azithromycin; cospherunate + phytomedicine + azithromycin | Enrolling by invitation | NCT04502342 |

(Continued on following page)
TABLE 6 | (Continued) Summary of clinical trials of azithromycin on COVID-19 treatment.

| Trial title                                                                 | Sponsor                                      | Trial phase | Primary intervention                        | Secondary intervention                                      | Status            | Identifier          |
|-----------------------------------------------------------------------------|----------------------------------------------|-------------|---------------------------------------------|------------------------------------------------------------|-------------------|---------------------|
| Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-19 | Ministry of Health, Turkey                   | III         | Favipiravir                                  | Favipiravir + hydroxychloroquine; favipiravir + azithromycin; hydroxychloroquine + azithromycin | Active, not recruiting | NCT04411433       |
| Efficacy and Safety Evaluation of Treatment Regimens in Adult COVID-19 Patients in Senegal (SENCOV-Fadji) | Institut Pasteur de Dakar                    | III         | Hydroxychloroquine + azithromycin           | Hydroxychloroquine + azithromycin + nafamostat mesilate     | Recruiting        | NCT04390594        |

(All information in the table are collected from https://clinicaltrials.gov).

compared with the patients without TCZ therapy. It should be noticed that the study performed by Klopfenstein et al. has some limitations, such as the small sample size and the retrospective nature of their work.

Interestingly, Stone et al. (2020) conducted a randomized, double-blind, placebo-controlled study (ClinicalTrials.gov, NCT04356937) with a larger sample size (243 patients with severe SARS-CoV-2 infection). The results from the study of Stone et al. demonstrated that TCZ is not effective in preventing intubation or death. However, some benefits, such as fewer serious infections in patients receiving TCZ therapy, cannot be ignored. Most recently, Salama et al. (2021) performed a trial enrolled with 389 COVID-19 patients (ClinicalTrials.gov, NCT04372186). The results showed that TCZ cannot improve survival rate; it only reduced the possibility of progression to the composite outcome of mechanical ventilation or death for the patients who were not receiving mechanical ventilation. Currently, TCZ undergoes several phase III clinical trials (ClinicalTrials.gov, NCT04423042, NCT04356937, NCT04403685, etc.) to further understand the TCZ treatment as a supportive care option in alleviating the severe respiratory symptoms correlated with SARS-CoV-2 infection (Alzghari and Acuña, 2020). Overall, TCZ appears to be an effective treatment for COVID-19 patients to calm the inflammatory storm and to reduce mortality. Notably, the efficacy of TCZ is controversial and remains to be further determined.

Mepolizumab

Mepolizumab (brand name: Nucala) is a human monoclonal antibody medication used for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis, and hypereosinophilic syndrome (HES) (Mukherjee et al., 2014; Ennis et al., 2019). Mepolizumab binds to IL-5 and prevents it from binding to its receptor on the surface of eosinophil white blood cells. Notably, some experts recommended to continue the mepolizumab therapy in COVID-19 patients with severe eosinophilic asthma, but the concern is that eosinopenia, which may serve as a diagnostic indicator for COVID-19 disease, may be a risk factor for worse disease outcomes (Li Q. et al., 2020; Du et al., 2020; Bousquet et al., 2021). In other words, it is a challenge to manage patients with severe eosinophilic asthma infected by SARS-CoV-2. Aksu et al. (2021) reported that no evidence of loss of asthma control was observed during mepolizumab therapy in a woman patient with asthma infected by SARS-CoV-2. In addition, Azim et al. (2021) observed the outcomes from four patients receiving mepolizumab treatment. The researchers found that all four patients had a further reduction in their eosinophil counts within the reference range at the presentation with SARS-CoV-2 infection, but the underlying mechanism is not fully investigated, and subsequently recovered without any immediate evidence of long-term respiratory outcomes. Of note, one of four patients required hospitalization and ventilatory support. They thereby suggested that the mepolizumab therapy should be continued without any changed outcomes in the COVID-19 course. However, evidence from Eger et al. (2020) involved 634 severe asthma patients diagnosed with COVID-19 showed that patients with severe asthma receiving mepolizumab therapy have a more severe course of COVID-19 and an increasing risk of severity of COVID-19 compared with the general population. Overall, because the relevant data are limited, and the guideline is currently absent, maintaining or postponing mepolizumab treatment until the patient recovers from SARS-CoV-2 infection should be a case-by-case based decision for COVID-19 patients with severe asthma.

Sarilumab

Sarilumab (brand name: Kevzara) is a humanized monoclonal antibody against IL-6 receptor. In 2017, FDA approved sarilumab for rheumatoid arthritis treatment (Khiali et al., 2021). It has reported that severe COVID-19 disease is characterized by elevated serum levels of C reactive protein (CRP) and cytokines, including, but not limited to, IFN-γ, IL-8, and IL-6 (Conti et al., 2020; Mo et al., 2020; Qin et al., 2020). Hence, this result provides a clue that anti-IL-6 agents have the possibility against SARS-CoV-2 infection. In a retrospective case report involving 15 COVID-19 patients, early intervention with sarilumab could have clinical improvement with decreased
| Trial title                                                                                     | Sponsor                                      | Trial phase | Primary intervention | Secondary intervention | Status                                | Identifier          |
|-----------------------------------------------------------------------------------------------|----------------------------------------------|-------------|----------------------|------------------------|---------------------------------------|---------------------|
| Tocilizumab in Coronavirus-19 Positive Patients                                               | University of Calgary                         | III         | Tocilizumab          | N/A                    | Not yet recruiting                    | NCT04423042        |
| Efficacy of Tocilizumab on Patients With COVID-19                                              | Massachusetts General Hospital                | III         | Tocilizumab          | Placebo                | Completed                            | NCT04356937        |
| Tocilizumab in COVID-19 Lahore General Hospital (TC19LGH)                                     | Lahore General Hospital                      | I           | Tocilizumab          | N/A                    | Recruiting                           | NCT04560205        |
| Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia | Fundacion SEIMC-GESIDA                       | II          | Tocilizumab          | N/A                    | Completed                            | NCT04445272        |
| Tocilizumab - An Option for Patients With COVID-19 Associated Cytokine Release Syndrome; A Single Center Experience | FMH College of Medicine and Dentistry        | IV          | Tocilizumab          | Methy/prednisolone     | Completed                            | NCT04730023        |
| Safety and Efficacy of tocilizumab in Moderate to Severe COVID-19 With Inflammatory Markers (TOCIRAS) | Beneficência Portuguesa de São Paulo         | III         | Tocilizumab +        | Supportive care        | Terminated (Safety)                  | NCT04403685        |
| Low-Dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 (COVIDO2E-2) | University of Chicago                         | II          | Tocilizumab          | Standard of care       | Recruiting                           | NCT04479358        |
| Tocilizumab for SARS-CoV2 (COVID-19) Severe Pneumonitis                                        | Università Politecnica delle Marche          | II          | Tocilizumab          | N/A                    | Active, not recruiting               | NCT04315480        |
| Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01) (COVITOZ-01) | Hospital Universitario Ramon y Cajal         | II          | Tocilizumab          | Standard care          | Recruiting                           | NCT04435717        |
| Tocilizumab in the Treatment of Coronavirus Induced Disease (COVID-19) (CORON-ACT)             | University Hospital Inselspital, Berne        | II          | Tocilizumab          | Placebo                | Terminated (1.) Not possible to recruit the planned number of patients during the planned study period; 2.) “Dexamethasone” was included in the standard of care for the study population during the course of the study and inclusion criteria could no longer be met.) | NCT04335071        |
| Tocilizumab for Patients With Cancer and COVID-19 Disease                                       | National Cancer Institute (NCI)              | II          | Tocilizumab          | N/A                    | Terminated (Other - Randomized data no longer support continuation.) Recruiting | NCT04370834        |
| Evaluating Tocilizumab for Severe COVID-19 Infection in Breast Cancer vs. Non-Cancer Patients  | Beni-Suef University                          | II          | Tocilizumab          | N/A                    | Recruiting                           | NCT04871854        |
| Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)                                                 | National Cancer Institute, Naples            | II          | Tocilizumab          | N/A                    | Active, not recruiting               | NCT04317092        |
| Tocilizumab Treatment in Patients With COVID-19                                                 | Instituto Nacional de Cancrologia de Mexico  | II          | Tocilizumab          | N/A                    | Active, not recruiting               | NCT04363853        |
| Trial of Tocilizumab for Treatment of Severe COVID-19: ARCHITECTS (ARCHITECTS)                 | Queen’s Medical Centre                        | III         | Tocilizumab          | Placebo                | Recruiting                           | NCT04412772        |
| Tocilizumab to Prevent Clinical Decompensation in                                              | University of Chicago                         | II          | Tocilizumab          | N/A                    | Completed                            | NCT04331795        |

(Continued on following page)
### Summary of clinical trials of tocilizumab (TCZ) on COVID-19 treatment.

| Trial title                                                                 | Sponsor                                                                 | Phase | Primary intervention            | Secondary intervention              | Status                   | Identifier   |
|----------------------------------------------------------------------------|------------------------------------------------------------------------|-------|-------------------------------|-------------------------------------|--------------------------|--------------|
| Hospitalized, Non-Critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE) | Abderrahmane Mami Hospital                                               | III   | Tocilizumab                   | Deferoxamine                       | Not yet recruiting       | NCT04361032 |
| Assessment of Efficacy and Safety of Tocilizumab Compared to Deferoxamine, Associated With Standards Treatments in COVID-19 (+) Patients Hospitalized in Intensive Care in Tunisia (TRONCHER) | Assistance Publique - Hôpitaux de Paris                                 | II    | Dexamethasone + tocilizumab    | Dexamethasone                     | Recruiting              | NCT04476979 |
| Tocilizumab Versus Methylprednisolone in the Cytokine Release Syndrome of Patients With COVID-19 | Hospital Sao Domingos                                                   | II    | Tocilizumab                   | Methylprednisolone                 | Not yet recruiting       | NCT04377503 |
| Clinical Trial of the Use of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection (hepb) | University of Sao Paulo                                                | III   | Heparin + tocilizumab         | Heparin                            | Recruiting              | NCT04600141 |
| Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalized COVID-19 Patients With High Risk of Progression | University of Malaya                                                   | III   | Tocilizumab                   | Methylprednisolone                 | Not yet recruiting       | NCT04345445 |
| Efficacy of Early Administration of Tocilizumab in COVID-19 Patients | Azienda Unità Sanitaria Locale Reggio Emilia                            | II    | Tocilizumab                   | Standard of care                   | Terminated (Based on interim analysis for futility and given an enrollment rate almost nil.) | NCT04346355 |
| The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation | Hadassah Medical Organization                                           | IV    | Tocilizumab                   | Placebo                            | Recruiting              | NCT04377750 |
| A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation, to Compare Standard-of-Care Treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study | Karolinska University Hospital                                         | II    | Tocilizumab + standard of care | Anakinra + standard of care        | Recruiting              | NCT04412291 |
| A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) | Hoffmann-La Roche                                                      | III   | Tocilizumab                   | Placebo                            | Completed               | NCT04320615 |
| A Study to Investigate Intravenous Tocilizumab in Participants With Moderate to Severe COVID-19 Pneumonia (MARIPOSA) | Hoffmann-La Roche                                                      | II    | Tocilizumab                   | N/A                                | Completed               | NCT04363736 |

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CRP level to patients with COVID-19 disease. More importantly, serum levels of CRP could be a potential biomarker for treatment response (Montesarchio et al., 2020). An open-label cohort study assessed the clinical outcome of sarilumab among 28 patients infected by SARS-CoV-2 compared with 28 contemporary patients receiving standard of care alone (Della-Torre et al., 2020). The results indicated that no significant difference was observed between sarilumab and standard of care. Of note, the clinical improvement suggested that sarilumab is relative to faster recovery in a subset of patients showing minor lung consolidation at baseline. In addition, there are several ongoing clinical trials to evaluate the effectiveness of sarilumab either plus standard of care (Caballero Bermejo et al., 2020) or combined with corticosteroids (ClinicalTrials.gov, NCT04357808) (Garcia-Vicuña et al., 2020) on COVID-19 disease. To date, the overall evaluation toward sarilumab on COVID-19 disease is much positive, which needs further tracking in the future.

### Stem cell-based therapy

To date, most studies regarding stem-based therapy to SARS-CoV-2 infection have focused on mesenchymal stem cells (MSCs) (Choudhery and Harris, 2020). MSC-based therapy has the ability to suppress the cytokine storm by secreting anti-inflammatory, anti-apoptosis, and antifibrosis cytokines. Also, MSCs contribute to antibacterial activity, as well as tissue repair and regeneration (Sadeghi et al., 2020). Table 8 shows clinical trials of MSCs on COVID-19 treatment. For patients suffering from COVID-19, MSCs would repair damaged alveolar epithelial cells and blood vessels, and also prevent pulmonary fibrosis (Chen et al., 2018; Leeman et al., 2019; Zanoni et al., 2019; Afra and Matin, 2020; Li Z. et al., 2020; Golchin et al., 2020). Seven COVID-19 patients who received intravenous transplantation of MSCs had significantly improved pulmonary function in 2 days after transplantation (Leng et al., 2020). Notably, the increased peripheral lymphocytes and IL-10 level, decreased C-reactive protein (CRP) and TNF-α level, and disappeared overactivated cytokine-secreting immune cells were observed within 14 days after MSC injection. Interestingly, Jayaramayya et al. reported that MSC-derived exosomes (MSC-Exo) may be an option to improve the clinical response to COVID-19 patients (Jayaramayya et al., 2020). A phase I clinical trial investigated the use of MSC-Exo inhalation to alleviate COVID-19-induced symptoms (clinicaltrials.gov, NCT04276987). Moreover, MSC-like derivatives have acceptable safety and efficacy for COVID-19 treatment in preclinical and clinical studies (Li Z. et al., 2020). However, some limitations remain to be considered (Sadeghi et al., 2020). First, some patients with, including, but not limited to, a history of malignant tumor, coinfections of other respiratory viruses, and pregnant woman are not eligible to evolve in clinical trials. Most clinical trials worldwide remain in phase I and II, and

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|------------|----------------------|------------------------|--------|------------|
| A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA) | Genentech, Inc | III | Tocilizumab | Placebo | Recruiting | NCT04372186 |
| COVID-19: Salvage Tocilizumab as a Rescue Measure (COVIDSTORM) | Jarmo Oksi | III | Tocilizumab | Standard of care | Recruiting | NCT04577534 |
| A Trial Using Anakinra, Tocilizumab Alone or in Association With Ruxolitinib in Severe Stage 2b and 3 of COVID-19-Associated Disease (INFLAMMACOV) | Assistance Publique Hopitaux De Marseille | III | Tocilizumab ± ruxolitinib | Anakinra ± ruxolitinib | Not yet recruiting | NCT04424056 |
| Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-19 (SARS-CoV-2 Infection) | Emory University | III | Tocilizumab + standard of care | Standard of care | Withdrawn (Study abandoned due to drug billing issues.) | NCT04361552 |
| Checkpoint Blockade in COVID-19 Pandemic (COPERNICO) | MedSiR | II | Tocilizumab + pembrolizumab | Standard of care | Recruiting | NCT04335305 |
| Personalized Immunotherapy for SARS-CoV-2 (COVID-19) Associated With Organ Dysfunction (ESCAPE) | Hellenic Institute for the Study of Sepsis | II | Tocilizumab | Anakinra | Completed | NCT04339712 |
| Treatment of COVID-19 Patients With Anti-Interleukin Drugs (COV-AID) | University Hospital, Ghent | III | Tocilizumab | Anakinra + tocilizumab; anakinra; anakinra + siltuximab; usual care | Active, not recruiting | NCT04330638 |

(All information in the table are collected from https://clinicaltrials.gov).
| Trial title                                                                 | Sponsor                                                                 | Trial phase | Primary intervention                      | Secondary intervention                                      | Status               | Identifier          |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------|-------------------------------------------|-------------------------------------------------------------|----------------------|---------------------|
| Mesenchymal Stem Cell Infusion for COVID-19 Infection Treatment of COVID-19 | Dr. Zaineb Akram                                                        | II          | Mesenchymal stem cells                    | Placebo                                                     | Recruiting           | NCT04444271        |
| Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-Derived Mesenchymal Stem Cells | Institute of Biophysics and Cell Engineering of National Academy of Sciences of Belarus | I/II        | Allogenic pooled olfactory mucosa-derived mesenchymal stem cells | Standard treatment                                          | Enrolling by invitation | NCT04382547        |
| Safety and Efficacy of Intravenous Wharton’s Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID-19 | BioXcellerator                                                           | I/II        | Wharton’s Jelly derived mesenchymal stem cells | Hydroxychloroquine, lopinavir/ritonavir or azithromycin and placebo | Recruiting           | NCT04390152        |
| Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome | M.D. Anderson Cancer Center                                               | I/II        | Mesenchymal stem cells                    | Standard of care                                            | Recruiting           | NCT04565665        |
| Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19) | Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubran       | II          | Mesenchymal stem cells                    | N/A                                                         | Recruiting           | NCT04416139        |
| Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19) | Guangzhou Institute of Respiratory Disease                               | II          | Bone marrow-derived mesenchymal stem cells | Placebo                                                     | Not yet recruiting   | NCT04346368        |
| Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMMA) | Trustern                                                                 | II          | Umbilical cord derived mesenchymal stem cells | Placebo                                                     | Not yet recruiting   | NCT04429763        |
| NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE) | Azidus Brasil                                                            | II          | NestaCell® mesenchymal stem cells          | Placebo                                                     | Not yet recruiting   | NCT04315987        |
| Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients | Renmin Hospital of Wuhan University                                      | I/II        | Allogeneic human dental pulp stem cells   | Placebo                                                     | Recruiting           | NCT04336254        |
| Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 (MESCEL-COVID19) | Hospital Infantil Universitario Nino Jesus, Madrid, Spain                | II          | Undifferentiated allogeneic mesenchymal cells derived from umbilical cord tissue | Standard of care | Recruiting           | NCT04366271        |
| Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSGs) (RECOVER) (RECOVER) | Longeveron LLC                                                           | I           | Longeveron mesenchymal stem cells          | Placebo                                                     | Recruiting           | NCT04629105        |
| Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome (MSC- COVID19) | Central Hospital, Nancy, France                                           | II          | Ex vivo expanded Wharton’s Jelly mesenchymal stem cells | Placebo                                                     | Not yet recruiting   | NCT04625738        |
| Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia | Nature Cell Co. Ltd                                                      | II          | Allogenic adipose tissue-derived mesenchymal stem cells | N/A                                                         | Not yet recruiting   | NCT04527224        |
| Treatment With Human Umbilical Cord-Derived | Beijing 302 Hospital                                                     | II          | Human umbilical cord-mesenchymal stem cells | Placebo                                                     | Completed            | NCT04288102        |

(Continued on following page)
| Trial title                                                                 | Sponsor                                      | Trial phase | Primary intervention                                                                                                                                             | Secondary intervention                                                                 | Status                  | Identifier           |
|---------------------------------------------------------------------------|----------------------------------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------|-----------------------|
| Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia | Stem Cell and Cancer Research Indonesia      | II          | Secretome-mesenchymal stem cells + standard care                                                                                                               | Standard treatment                                                                   | Recruiting             | NCT04753476          |
| Mesenchymal Stem Cells in Patients Diagnosed With COVID-19                | Hospital Reg. Lic. Adolfo Lopez Mateos        | I           | Mesenchymal stem cells                                                                                                                                          | N/A                                                                                 | Recruiting             | NCT04611256          |
| Use of UC-MSCs for COVID-19 Patients                                     | Camillo Ricord                              | I/II        | Umbilical cord mesenchymal stem cells + heparin along with best supportive care Wharton’s Jelly derived mesenchymal stem cells | Vehicle + heparin along with best supportive care                                  | Completed               | NCT04355728          |
| Treatment of COVID-19 Patients Using Wharton’s Jelly-Mesenchymal Stem Cells | Stem Cells Arabia                           | I           | Wharton’s Jelly derived mesenchymal stem cells                                                                                                               | N/A                                                                                 | Recruiting             | NCT04313322          |
| Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 | Beijing 302 Hospital                        | I           | Mesenchymal stem cells + conventional treatment                                                                                                               | Conventional treatment                                                              | Recruiting             | NCT04252118          |
| A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19 | Hope Biosciences                           | II          | Autologous adipose-derived mesenchymal stem cells                                                                                                               | N/A                                                                                 | Active, not recruiting | NCT04349631          |
| Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 (COVID-19) | Joshua M Hare                                    | I           | Umbilical cord tissue-derived mesenchymal stem cells                                                                                                               | Placebo                                                                             | Not yet recruiting     | NCT04490486          |
| Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia | Puren Hospital Affiliated to Wuhan University of Science and Technology | I/II        | Umbilical cord tissue-derived mesenchymal stem cells                                                                                                               | Placebo                                                                             | Recruiting             | NCT04339660          |
| Study of Intravenous Administration of Allogeneic Adipose-Derived Mesenchymal Stem Cells for COVID-19-Induced Acute Respiratory Distress | Sorrento Therapeutics, Inc                   | II          | Allogeneic adipose-derived mesenchymal stem cells                                                                                                               | Placebo                                                                             | Not yet recruiting     | NCT04728698          |
| Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19 Disease | Regeneris Medical                            | I           | Autologous adipose-derived mesenchymal stem cells                                                                                                               | N/A                                                                                 | Not yet recruiting     | NCT04352803          |
| A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19 | Hope Biosciences                           | II          | Allogeneic adipose-derived mesenchymal stem cells                                                                                                               | Placebo                                                                             | Active, not recruiting | NCT04348435          |
| Mesenchymal Stem Cells for the Treatment of COVID-19 Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19 | Thomas Advanced Medical LLC Celltex Therapeutics Corporation | I           | PrimePro™ mesenchymal stem cells                                                                                                                                   | Placebo                                                                             | Completed              | NCT04573270          |
| Mesenchymal Stem Cells for the Treatment of COVID-19 Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19 | Instituto de Investigación Sanitaria         | II          | Autologous adipose-derived stem cells                                                                                                                            | Placebo                                                                             | Not yet recruiting     | NCT04428801          |
| Mesenchymal Stem Cells for the Treatment of COVID-19 Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19 | Instituto de Investigación Sanitaria         | II          | Regular treatment                                                                                                                                             | (Continued on following page)                                                      | Suspended              | NCT04348461          |
| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|------------|-----------------------|------------------------|--------|------------|
| BATLe Against COVID-19 Using Mesenchymal Stromal Cells | de la Fundación Jiménez Díaz | | Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells | Antibacterial (ceftriaxone, azithromycin), anticoagulants, hormones, oxygen therapy | financial support | |
| Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs | Institute of Cell Therapy | I/II | Placenta-derived multipotent mesenchymal stromal cells + antibacterial (ceftriaxone, azithromycin), anticoagulants, hormones, oxygen therapy | | Recruiting | NCT04461925 |
| A Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection (COVID-19) | Rohto Pharmaceutical Co., Ltd | II | Mesenchymal stem cells | Placebo | Not yet recruiting | NCT04888949 |
| Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS (ULSC) | Restem, LLC. | I/II | Umbilical cord lining stem cells | Placebo | Recruiting | NCT04494386 |
| Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients (DW-MSC) | Ina-Respond | I | Allogeneic mesenchymal stem cells | Placebo | Completed | NCT04535856 |
| Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS | Bayix Inc | I/II | Human umbilical cord mesenchymal stem cells + supportive care | Placebo control + supportive care | Not yet recruiting | NCT04452097 |
| Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19 | Hope Biosciences | II | Allogeneic adipose-derived mesenchymal stem cells | Placebo | Active, not recruiting | NCT04362189 |
| Clinical Use of Stem Cells for the Treatment of COVID-19 | SBÜ Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi | I | Mesenchymal stem cells | Placebo | Recruiting | NCT04392778 |
| Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) | Baylor College of Medicine | I/II | Mesenchymal stem cells | Supportive care | Recruiting | NCT04345601 |
| Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients with Respiratory Distress Due to COVID-19 (COVIDMES) | Banc de Sang i Teixits | I/II | Wharton’s Jelly derived mesenchymal stem cells | Placebo | Recruiting | NCT04390139 |
| Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS) | University Hospital Tuebingen | II | Mesenchymal stem cells | N/A | Not yet recruiting | NCT04377334 |
| Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation | ImmunityBio, Inc | I | Immunomodulatory mesenchymal stem cells | Placebo | Recruiting | NCT04397796 |
| The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19 (ARDOSXO) | AVEM HealthCare | I/II | Mesenchymal stem cell—exosomes | N/A | Not yet recruiting | NCT04798716 |
| A phase II Study in Patients With Moderate to Severe ARDS Due to COVID-19 | Stemedica Cell Technologies, Inc | II | Allogeneic mesenchymal stem cells | | Recruiting | NCT04780685 |
| Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) (REALIST) | Belfast Health and Social Care Trust | I/II | Human umbilical cord-derived CD362-enriched mesenchymal stem cells | Placebo | Recruiting | NCT03042143 |

(Continued on following page)
TABLE 8 (Continued) Summary of clinical trials of mesenchymal stem cells (MSCs) on COVID-19 treatment.

| Trial title                                                                 | Sponsor                                      | Trial phase | Primary intervention                        | Secondary intervention | Status             | Identifier     |
|----------------------------------------------------------------------------|----------------------------------------------|-------------|---------------------------------------------|------------------------|--------------------|----------------|
| Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19 (COVID-19) | Hospital de Clinicas de Porto Alegre         | I           | Mesenchymal stem cells                      | N/A                    | Not yet recruiting | NCT04467047    |
| Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients | Jinnah Hospital                              | II          | Umbilical cord-derived mesenchymal stem cells + standard care | Standard care          | Recruiting        | NCT04437823    |
| Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (COVID-19) | Red de Terapia Cellular                       | II          | Mesenchymal stromal cells                   | Placebo               | Recruiting        | NCT04361942    |
| Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19) | Masonic Cancer Center, University of Minnesota | II          | Mesenchymal stromal cells                   | Placebo               | Active, not recruiting | NCT04466098   |
| Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome (CIRCA-19) | Ottawa Hospital Research Institute           | I/I         | Mesenchymal Stromal Cells                   | N/A                   | Completed          | NCT04400032    |

(All information in the table are collected from https://clinicaltrials.gov).

comprehensive results are not clear. Furthermore, it is difficult to evaluate the effectiveness of MSC therapy alone when coadministration with other conventional drugs, such as remdesivir or dexamethasone, in many cases. Importantly, the standard therapeutic protocol, such as administration route, dosage, and transplantation frequency, needs to be determined. Nevertheless, the MSC profile on the immune system provides researchers evidence that it may be a good candidate as a combination therapy of infectious diseases such as COVID-19. Overall, MSC-based therapy appears to be a potential and promising therapeutic method to overcome SARS-CoV-2 infection.

**Convalescence plasma transfusion**

Convalescent plasma treatment provides immediate immunity by passive polyclonal antibody administration (Mair-Jenkins et al., 2015). The efficacy of convalescent plasma transfusion may result from viremia suppression (Chen L. et al., 2020). It has reported that convalescent plasma treatment can be used to improve the survival rate on patients with severe acute respiratory syndromes of viral etiology (Mair-Jenkins et al., 2015). Several studies indicated that SARS patients who were treated with convalescent plasma had a shorter hospital stay and lower mortality than those who were not treated with convalescent plasma (Soo et al., 2004; Cheng et al., 2005; Lai, 2005). Table 9 shows the clinical trials of convalescent plasma transfusion on COVID-19 treatment. Based on the findings from recent studies, initiating treatment no later than 5 days may be the most appropriate (Woelfel et al., 2020; Zhao et al., 2020b). Tiberghien et al. (2020) recommend that convalescent plasma administration at the early phases of the disease in patients at high risk of deleterious evolution may reduce the frequency of patient deterioration and, thereby, COVID-19 mortality. Also, close monitoring is necessary to detect any unintended side effects. However, a randomized trial (clinicaltrials.gov, NCT04383535) evolved in 228 COVID-19 patients to evaluate the clinical status after convalescent plasma intervention was added to standard treatment (Simonovich et al., 2021). Unfortunately, no significant differences were found in clinical outcomes or overall mortality between patients infused with convalescent plasma added to standard treatment and those who received standard treatment alone within 30 days. Similarly, an open-label, multicenter, randomized clinical trial (www.chictr.org.cn, ChiCTR2000029757) was performed in seven medical centers with 103 COVID-19 patients (Li L. et al., 2020). The results showed that convalescent plasma therapy in addition to standard treatment, compared with standard treatment alone, did not result in a significant improvement in time to clinical improvement within 28 days. Of note, it is known that other treatments, including antiviral drugs, steroids, and intravenous immunoglobulin, have the possibility to affect the relationship between convalescent plasma and antibody level (Luke et al., 2006). Thus, it is controversial whether it is worthwhile to examine the safety and efficacy of convalescent plasma intervention against SARS-CoV-2 infection in further randomized clinical trials.

**Vaccines**

An efficacious vaccine is critical to prevent morbidity and mortality caused by COVID-19. There are four categories of COVID-19 vaccines under clinical evaluation, including whole-pathogen vaccines (inactivated vaccines), subunit vaccines, and nucleic acid (DNA and mRNA) vaccines. However, defining and assessing an efficacious vaccine is complex. In the case of SARS-CoV-2 infection, an efficacious vaccine could reduce the likelihood of an infection in an individual, severity of a disease
in an individual, or the degree of transmission within a population (Hodgson et al., 2021). The comprehensive understanding of SARS-CoV-2 is unclear and evolving, thereby the outcomes for a COVID-19 vaccine are critically appraised with scientific rigor to understand their generalizability and clinical significance.

Currently, three vaccines are authorized in the United States: Pfizer-BioNTech (Name: BNT162b2), Moderna (Name: mRNA-1273), and Johnson and Johnson/Janssen (Name: INJ-78436735). Tables 10–12 summarize the clinical trials of these vaccines for the treatment of COVID-19. Of note, people under 12 years old are not eligible to receive vaccine produced by Pfizer-BioNTech, and people under 18 years old are not eligible to receive vaccines produced by Moderna and Johnson and Johnson/Janssen. Kamidani et al. (2021) indicated that children are supposed to have the opportunity to be included in clinical trials in parallel to ongoing adult phase III clinical trials. It is because the development of a pediatric COVID-19 vaccine could prevent disease and alleviate downstream effects including social isolation and interruption in education, thereby enabling children to re-engage in their world. Considering the SARS-CoV-2 variants, evidence from Polack et al. (2020) proved that BNT162b2 is 95% effective against SARS-CoV-2 infection. A 6 months of follow-up evaluation from Thomas et al. (2021) indicated that BNT162b2 has a favorable safety profile and effectively prevents COVID-19 for up to 6 months including the beta variant even though there is a gradual decline in effectiveness. Bernal et al. (Lopez Bernal et al., 2021) reported that the efficacy of the one-shot BNT162b2 vaccine is 30.7% among individuals with the delta variant, while the efficacy is 48.7% among individuals with the alpha variant. The efficacy of two shots of BNT162b2 vaccine is 88.0% among individuals with the delta variant, while the efficacy is 93.7% among individuals with the alpha variant. In other words, as CDC recommendation, vaccination against COVID-19 is the best way to stop the spread of these predominate COVID-19 strains.

Most recently, a COVID-19 vaccine booster emerged to help individuals build enough protection after vaccination. According to the information from Centers for Disease Control and Prevention (CDC, https://www.cdc.gov), individuals who have received their second dose of an mRNA COVID-19 vaccine (produced by either Pfizer-BioNTech or Moderna) for 8 months are eligible to get a booster shot. Currently, for individuals who got Johnson and Johnson/Janssen vaccine, there is not enough data to support getting an mRNA vaccine dose.

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**TABLE 9 | Summary of clinical trials of convalescence plasma on COVID-19 treatment.**

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|----------------------|------------------------|--------|------------|
| Safety in Convalescent Plasma Transfusion to COVID-19 | Hospital San Jose Tec de Monterrey | I | Convalescent plasma | N/A | Terminated (Other clinical trials proved that the use of convalescent plasma for patients with COVID-19 is safe.) | NCT04333355 |
| Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19 | Lifefactores Zona Franca, SAS | II/III | Convalescent plasma | Anti-COVID-19 human immunoglobulin; standard therapy (remdesivir, chloroquine, hydroxychloroquine, azithromycin) | Not yet recruiting | NCT04395170 |
| Convalescent Plasma of COVID-19 to Treat SARS-CoV-2, a Randomized Doble Blind 2 Center Trial (CPC-SARS) | Grupo Mexicano para el Estudio de la Medicina Intensiva | II | Convalescent plasma + conventional therapy (azithromycin and hydroxychloroquine) | Conventional therapy (azithromycin and hydroxychloroquine) and 20% albumin | Completed | NCT04405310 |
| Convalescent Plasma Therapy in Severe COVID-19 Infection | Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh | II | Standard supportive treatment | Standard treatment + convalescent plasma | Recruiting | NCT04403477 |
| Convalescent Plasma Therapy in Patients With COVID-19 | Biotarma | I | Convalescent plasma | N/A | Completed | NCT04407208 |
| Convalescent Plasma for II Patients by COVID-19 (COPLASCOV19) | Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado | I/II | Convalescent plasma | N/A | Recruiting | NCT04356482 |
| COVID19-Convalescent Plasma for Treating Patients With Active Symptomatic COVID 19 Infection (FALP-COVID) | Fundacion Arturo Lopez Perez | I/II | Convalescent plasma | N/A | Recruiting | NCT04384588 |

(All information in the table are collected from https://clinicaltrials.gov).
| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|----------------------|------------------------|--------|------------|
| Safety and Immunogenicity Study of 20vPnC When Coadministered With a Booster Dose of BNT162b2 | Pfizer | III | An injection of pneumococcal vaccine (20vPnC) and of COVID-19 vaccine (BNT162b2) at the same visit | An injection of pneumococcal vaccine (20vPnC) alone; an injection of COVID-19 vaccine (BNT162b2) alone | Active, not recruiting | NCT04887948 |
| Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Formulations of BNT162b2 Against COVID-19 in Healthy Adults | BioNTech SE | III | BNT162b2 | N/A | Active, not recruiting | NCT04816669 |
| A Trial Investigating the Safety and Effects of One or Two Additional Doses of Comirnaty or One Dose of BNT162b2 (01 or BNT162-04) Trial Subjects | BioNTech SE | II | BNT162b2 | N/A | Recruiting | NCT04949490 |
| Study to Evaluate the Safety and Efficacy of a Booster Dose of BNT162b2 Against COVID-19 in Participants ≥16 Years of Age | BioNTech SE | III | BNT162b2 | Placebo | Recruiting | NCT04955626 |
| Study to Evaluate Safety, Tolerability and Immunogenicity of BNT162b2 in Immunocompromised Participants ≥2 Years | BioNTech SE | II | BNT162b2 | N/A | Not yet recruiting | NCT04895982 |
| Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older | BioNTech SE | III | BNT162b2 | Placebo | Recruiting | NCT04754594 |
| A phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of BNT162b2 RNA-Based COVID-19 Vaccines Against COVID-19 in Healthy Participants | BioNTech SE | III | BNT162b2 | Placebo | Completed | NCT04713553 |
| Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b2) in Chinese Healthy Population | BioNTech SE | II | BNT162b2 | Placebo | Active, not recruiting | NCT04649021 |
| Third Dose of mRNA Vaccination to Boost COVID-19 Immunity Impact of the Immune System on Response to Anti-Coronavirus Disease 19 (COVID-19) Vaccine in Allogeneic Stem Cell Recipients (Covid Vaccin Aki) | The University of Hong Kong University of Liege | IV III | BNT162b2 BNT162b2 | N/A N/A | Recruiting Recruiting | NCT05057182 NCT04951323 |
| Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Japanese Adults Booster Dose of COVID-19 Vaccine for Kidney Transplant Recipients Without Adequate Humoral Response (WHO) Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals Randomized Trial of COVID-19 Booster Vaccinations (Cobovax Study) | BioNTech SE Dafna Yahav The University of Hong Kong | IV II III IV | BNT162b2 BNT162b2 BNT162b2 BNT162b2 | N/A N/A N/A CoronaVac | Not yet recruiting Recruiting Recruiting Recruiting | NCT04961229 NCT04368728 NCT05057169 |

(Continued on following page)
TABLE 10 | (Continued) Summary of clinical trials of BNT162b2 vaccine (produced by Pfizer-BioNTech) on COVID-19 treatment.

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|------------|----------------------|------------------------|--------|------------|
| Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children <12 Years of Age | BioNTech SE | II/III | BNT162b2 | N/A | Recruiting | NCT04816643 |
| Safety and Immunogenicity of a SARS CoV-2 Multivalent RNA Vaccine in Healthy Participants | BioNTech SE | II | BNT162b2 | N/A | Recruiting | NCT05004181 |
| Third Dose Vaccination with AstraZeneca or Pfizer COVID-19 Vaccine Among Adults Received Sinovac COVID-19 Vaccine | Mahidol University | II | BNT162b2 | ChAdOx1 AZD1222 | Not yet recruiting | NCT06049226 |
| Vaccination for Recovered Inpatients With COVID-19 (VATICO) | International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) | IV | BNT162b2 | mRNA-1273 | Recruiting | NCT04969250 |
| Mix and Match of the Second COVID-19 Vaccine Dose for Safety and Immunogenicity (MOSAIC) | Canadian Immunization Research Network | II | BNT162b2 | mRNA-1273; ChAdOx1-S | Recruiting | NCT04894435 |
| COVID-19 Booster Vaccine in Autoimmune Disease Non-Responders | National Institute of Allergy and Infectious Diseases (NIAID) | II | BNT162b2 | mRNA-1273; Ad26.COVID.S | Recruiting | NCT05000216 |

(All information in the table are collected from https://clinicaltrials.gov).

TRADITIONAL CHINESE MEDICINE

Xuebijing injection (XBJ) consists of Carthamus tinctorius L., Paeonia lactiflora Pall, Ligusticum striatum DC, Salvia miltiorrhiza Bunge, and Angelica sinensis (Oliv.) Diels (Shi et al., 2017). XBJ constructs a “drug-ingredient-target-pathway” effector network to exert its therapeutic effects on COVID-19 prevention and treatment (Zheng et al., 2020). Guo et al. (2020) conducted a retrospective case-control study to determine the efficacy of XBJ on SARS-CoV-2 infection with 42 patients who received routine treatment combined with XBJ (observation group) and 16 patients who received routine treatment alone (control group). The results showed that patients in the observation group had a significant reduction in body temperature, improvement in CT imaging results, and shorter time in a negative nucleic acid test recovery relative to those in the control group. Also, improvement in IL-6 levels was found in the observation group compared with those in the control group, while TNF-α and IL-10 levels did not show significant differences between the two groups. In addition, 284 COVID-19 patients were enrolled in a multicenter, prospective, randomized controlled trial to assess the effectiveness of Lianhuaqingwen (LH) capsule (Hu et al., 2021). Compared with patients in the control group (received usual treatment alone), patients with usual treatment in combination with LH capsule treatment had higher recovery rate, shorter median time to symptom recovery, and higher rate of improvements in chest CT manifestations and clinical cure. Hence, both XBJ and LH capsules could be considered to ameliorate clinical symptoms of COVID-19. Moreover, Ni et al. reported that using Western medicine combined with Chinese traditional patent medicine Shuanghuanglian oral liquid (SHL) has expected therapeutic outcomes to COVID-19 patients, and thereby warrants further clinical trials (Ni et al., 2020b).

CONCLUDING REMARKS

For antimicrobial drugs, the acquired drug resistance should be considered and explored. The use of CQ and HCQ is controversial due to their toxicity and side effects. Moreover, lopinavir/ritonavir, umifenovir, and azithromycin appear to be promising therapeutic drugs even though some studies do not show ideal and unfavorable clinical outcomes on COVID-19 patients. The IFNs are usually used in addition to other antiviral drugs. Also, the application of IFN-λ have more advantages than other types of IFNs in COVID-19 treatment.

TCZ, an antibody, has the ability to improve clinical responses on COVID-19 patients by suppressing inflammatory storm and, thereby, reduces mortality cases. Mepolizumab, as an antibody medication for asthma, may increase the risk of severe COVID-19 and induce a more severe course of COVID-19, particularly for COVID-19 patients with severe asthma receiving mepolizumab therapy. Sarilumab, as an FDA-approved antibody medication for rheumatoid arthritis treatment, shows clinical improvement with decreased CRP level to patients with COVID-19 disease. Furthermore, stem cell-based therapy, especially MSCs, could improve clinical symptoms and repair tissue caused by SARS-CoV-2 infection. Of note, the standard protocol of MSCs therapy needs to be determined. Additionally, COVID-19 patients who received convalescent plasma transfusion in addition to standard treatment shows no clinical differences compared with those who...
received standard treatment alone. Therefore, it is controversial whether it is worthwhile to assess the safety and efficacy of convalescent plasma intervention against SARS-CoV-2 infection in further randomized clinical trials. In addition, TCMs play a critical role in ameliorating and alleviating clinical symptoms on COVID-19 patients. Also, it is known that TCMs in combination with Western medicine is a potential therapeutic strategy against SARS-CoV-2 infection.

### TABLE 11 | Summary of clinical trials of mRNA-1273 vaccine (produced by Moderna) on COVID-19 treatment.

| Trial title | Sponsor | Trial phase | Primary intervention | Secondary intervention | Status | Identifier |
|-------------|---------|-------------|----------------------|------------------------|--------|------------|
| A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove) | ModernaTX, Inc | II/III | mRNA-1273 | Placebo | Active, not recruiting | NCT04649151 |
| A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age | ModernaTX, Inc | II/III | mRNA-1273 | Placebo | Recruiting | NCT04796896 |
| A Study to Evaluate Safety and Immuneogenicity of mRNA-1273 Vaccine to Prevent COVID-19 in Adult Organ Transplant Recipients and in Healthy Adult Participants | ModernaTX, Inc | III | mRNA-1273 | N/A | Recruiting | NCT04860297 |
| A Study to Evaluate Efficacy, Safety, and Immuneogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19 | ModernaTX, Inc | III | mRNA-1273 | Placebo | Active, not recruiting | NCT04470427 |
| Safety and Immuneogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis of SARS-CoV-2 Infection (COVID-19) | National Institute of Allergy and Infectious Diseases (NIAID) | I | mRNA-1273 | N/A | Active, not recruiting | NCT04283461 |
| Study About the Response to the Administration of a Third Dose of mRNA-1273 Vaccine (COVID-19 Vaccine Moderna) in Renal Transplants With Immunological Failure Initial to Vaccination (VAXTRES) | Maria Joyera Rodriguez | II | mRNA-1273 | N/A | Not yet recruiting | NCT04930770 |
| Third Dose of COVID-19 Vaccine in LTCF Residents | Mark Loeb | IV | mRNA-1273 | Prevnar13 | Not yet recruiting | NCT04978038 |
| Safety and Immunogenicity Study of a SARS-CoV-2 (COVID-19) Variant Vaccine (mRNA-1273.351) in Naïve and Previously Vaccinated Adults (CovCompareM) | Assistance Publique - Hôpitaux de Paris | II | mRNA-1273 | N/A | Not yet recruiting | NCT04748471 |
| A Study to Evaluate the Immunogenicity and Safety of mRNA-1273.211 Vaccine for COVID-19 Variants | ModernaTX, Inc | II/III | mRNA-1273 | mRNA-1273.211; mRNA-1273.617.2 | Active, not recruiting | NCT04927065 |
| Safety and Immunogenicity Study of a SARS-CoV-2 (COVID-19) Variant Vaccine (mRNA-1273.351) in Naïve and Previously Vaccinated Adults | National Institute of Allergy and Infectious Diseases (NIAID) | I | mRNA-1273 | mRNA-1273.351 | Active, not recruiting | NCT04785144 |
| RECOVAC Booster Vaccination Study | University Medical Center Groningen | IV | mRNA-1273 | Ad26.COV2.S vaccine | Not yet recruiting | NCT06030974 |
| Third Dose of Moderna COVID-19 Vaccine in Transplant Recipients | University Hospital, Toronto | IV | mRNA-1273 | Placebo | Not yet recruiting | NCT04858907 |
| Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines | National Institute of Allergy and Infectious Diseases (NIAID) | I/II | mRNA-1273 | mRNA-1273.211; Ad26.COV2.S; BNT162b2 | Recruiting | NCT0489209 |
| SARS-CoV-2 Immune Responses After COVID-19 Therapy and Subsequent Vaccine | National Institute of Allergy and Infectious Diseases (NIAID) | IV | mRNA-1273 | N/A | Recruiting | NCT04952402 |

(All information in the table are collected from https://clinicaltrials.gov).
To date, remdesivir is FDA approved specifically for the treatment of COVID-19. Also, several vaccines are authorized and recommended in the United States and other countries. Most treatment regimens against the COVID-19 pandemic are controversial and remain under preclinical and clinical trials. Overall, more comprehensive information regarding each treatment regimen is uncertain and needs to be further explored.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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TABLE 12 | Summary of clinical trials of JNJ-78436735 vaccine (produced by Johnson and Johnson/Janssen) on COVID-19 treatment.

| Trial title                        | Sponsor          | Trial phase | Primary intervention | Secondary intervention | Status               | Identifier     |
|-----------------------------------|------------------|-------------|----------------------|------------------------|----------------------|-----------------|
| COVID-19 3rd Dose Vaccine in Transplant Patients | Giselle Guerra | III         | BNT162b2             | JNJ-78436735           | Not yet recruiting | NCT05047640    |

(All information in the table are collected from https://clinicaltrials.gov).
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