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REVIEW

DRUG DEVELOPMENT RESEARCH WILEY

# Review of registered clinical trials for the treatment of COVID-19

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## Abstract

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first reported in December 2019 in Wuhan, China, but now more than 200 countries have been affected and the coronavirus pandemic is still ongoing. The severity of COVID-19 symptoms can range from mild to severe. FDA approved remdesivir as a treatment of COVID-19 so far. Various clinical trials are underway to find an effective method to treat patients with COVID-19. This review aimed at summarizing 219 registered clinical trials in *the ClinicalTrials.gov* database with possible mechanisms, and novel findings of them, and other recent publications related to COVID-19. According to our analyses, various treatment approaches and drugs are being investigated to find an effective drug to cure COVID-19 and among all strategies, three important mechanisms are suggested to be important against COVID-19 including antiviral, anti-inflammatory, and immunomodulatory properties. Our review can help future studies get on the way to finding an effective drug for COVID-19 treatment by providing ideas for similar researches.

**KEYWORDS**

anti-inflammatory, antivirals, clinical trials, COVID-19, immunotherapy, SARS-CoV-2

## 1 | INTRODUCTION

In December 2019, a viral disease developed in Wuhan, China. This new virus belongs to the beta-coronavirus family and is called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO) (Zhu, Zhang, et al., 2020). Coronavirus disease (COVID-19) spread rapidly throughout the world, and according to the WHO report more than 200 countries have been affected so far. Recent research projects revealed that SARS-CoV-2 has a high sequence similarity to SARS-CoV-1 that caused respiratory illness in 2002 (Wu et al., 2020). Both of them use the same receptor, angiotensin-converting enzyme 2 (ACE2), for entry in human host cells (Lu et al., 2020; Wan, Shang, Graham, et al., 2020). The ACE2 is a cell surface receptor expressed in various organs, including lung, arteries, heart, kidney, and intestine (Hamming et al., 2004). The ACE2 catalyzes vasoactive angiotensin II to vasodilator angiotensin-[1–7] (Richards & Raizada, 2018). Some of the patients with COVID-19 have underlying diseases, including hypertension, cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (Emami et al., 2020). Older people and those with underlying medical problems are more likely to develop serious illness and have a high mortality rate among COVID-19 patients (Liu et al., 2020; Z. Wu & McGoogan, 2020).

The severity of COVID-19 symptoms can range from mild to severe. Common symptoms are fever, fatigue, dry cough, dyspnea, and myalgia (Guan et al., 2020; Qin et al., 2020; Rodriguez-Morales et al., 2020). Other symptoms can include headache, diarrhea, and vomiting (Huang, Wang, et al., 2020; Qian et al., 2020;

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Rodriguez-Morales et al., 2020). Furthermore, some people have experienced hypogeusia and hyposmia (Bénézit et al., 2020). A summary of the clinical manifestations of COVID-19 disease is illustrated in Figure 1.

COVID-19 and severe acute respiratory syndrome (SARS) have similar pathological characterization (Hui & Zumla, 2019). Organ dysfunctions, including acute respiratory distress syndrome (ARDS), acute kidney injury, acute cardiac injury, liver dysfunction, and secondary inflammation are causes of death in patients with COVID-19 (Chen et al., 2020; Guan et al., 2020; Huang, Wang, et al., 2020; Wan, Xiang, Fang, et al., 2020; Wang, Hu, et al., 2020). FDA approved remdesivir as a treatment of COVID-19 so far and common medical therapies include symptomatic treatment or supportive care. Various therapeutic protocols have been used all over the world and some clinical trials are underway to find an effective and safe strategy to treat COVID-19.

In this review, we collected some registered clinical trials with all types of treatment approaches that are underway and showed the most widely used treatment protocols and drugs that are being investigated for the treatment of COVID-19. Our study can help future studies get on the way to finding an effective drug for COVID-19 treatment by providing ideas for similar researches in basic and clinical studies.

## 2 | SEARCH STRATEGY

*ClinicalTrials.gov* database was searched with the keywords "COVID-19" and "SARS-CoV-2" on April 10, 2020, and found 440 trials. We included clinical trials of COVID-19 treatments and prophylaxis. Epidemiological, observational, descriptive, case–control studies, studies with unclear medications, underlying diseases, and incomplete information about interventions were excluded. We screened titles and study descriptions, design, interventions, outcome measures, and tabular views. Eventually, 219 trials were included from 440 trials and up-to-date until August 6, 2020. See Figure 2 for more details about study selection.

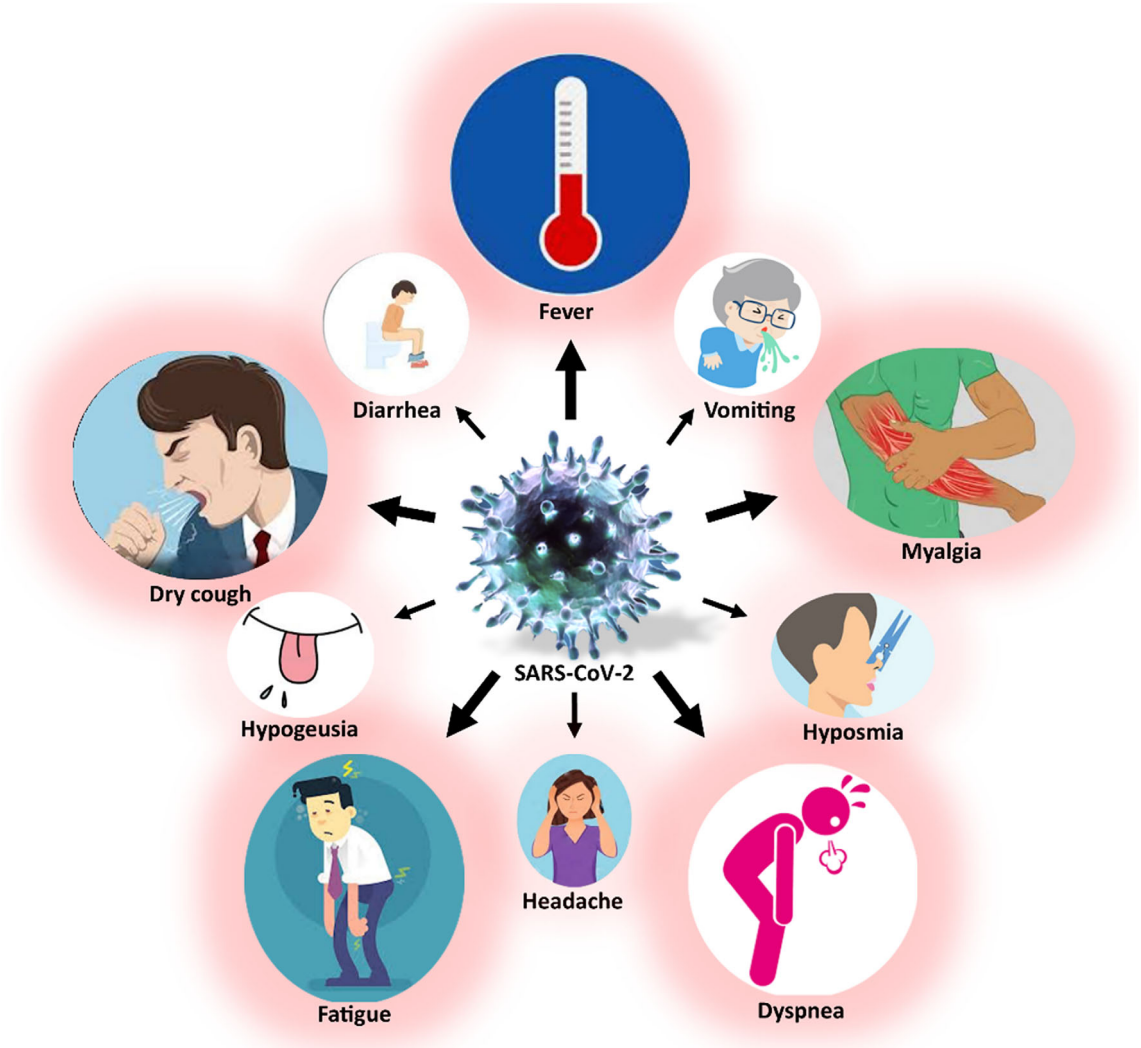


**FIGURE 1** Clinical manifestations of COVID-19 disease

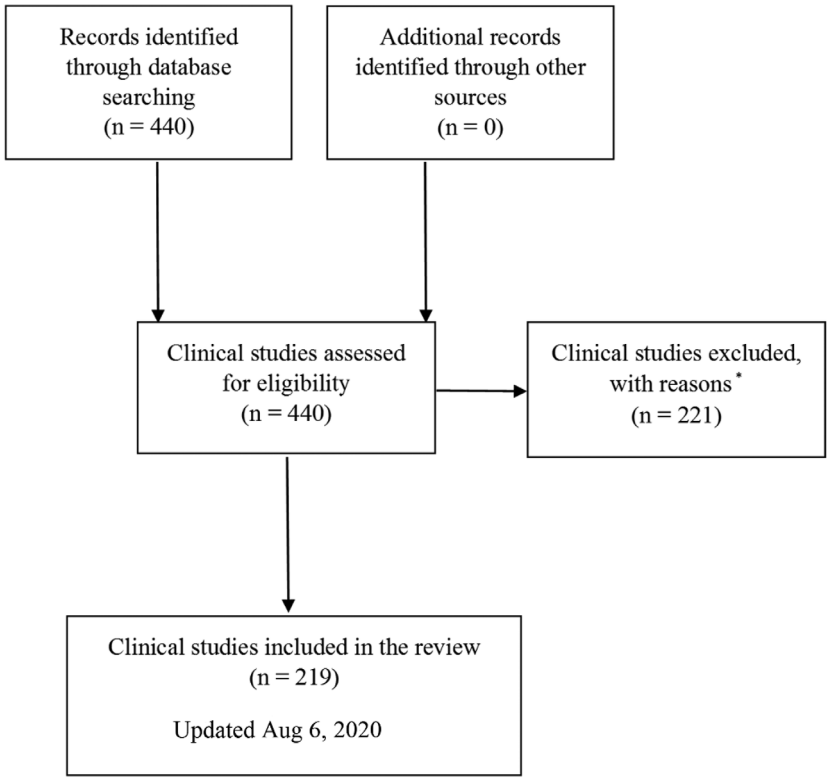


**FIGURE 2** Diagram of the selection process for clinical trials

* Reasons: Epidemiological, observational and descriptive studies= 188
Studies with unclear medications= 6
Studies with underlying disease= 4
Studies with incomplete information about interventions= 15
Case-control studies= 3
Withdrawn studies= 5

## 3 | DATA EXTRACTION AND IDENTIFICATION OF RELEVANT STUDIES

Trials were manually extracted and relevant trials were recorded in a spreadsheet (Word document, available in the supplementary information) and classified according to the treatment protocol, drug classification. The search for clinical trial registries in *ClinicalTrials.gov* with the keywords COVID-19, 2019 novel coronavirus (nCOV), and SARS-CoV-2 yielded 440 trial registry entries. The status of trials is including recruiting, not yet recruiting, enrolling by invitation, active or completed (no result posted).

## 4 | TREATMENT OR PROPHYLACTIC REGIMENS IN CLINICAL TRIALS FOR THE MANAGEMENT OF COVID-19

Following the screening of titles and study descriptions, 440 trials were assessed for eligibility. Among them, after applying the exclusion criteria we found 219 relevant trials (Figure 2). There are various treatment or prophylactic approaches in extracted COVID-19 clinical trials that are shown in Figure 3a that are including cell therapy ($n$ = 15) (Table 1), plasma therapy ($n$ = 9), oxygen support and nitric oxide inhaler ($n$ = 11), vaccines ($n$ = 9) (Table 2), drugs ($n$ = 163), and herbal medicines or supplements or biological agents ($n$ = 15) (Table 3). Three trials are common among the three groups of treatment, then the total of studies is 222. All clinical trials that we have selected with title, intervention, and primary outcome have been shown in a supplemental data file. In this review, treatment or prophylactic regimens by the priority, possible mechanisms, important findings of them, and similar studies against COVID-19 will be explained.

### 4.1 | Cell therapy

Umbilical cord mesenchymal stem cells (UC-MSCs), natural killer (NK) cells, cardiosphere-derived cells (CDCs), dental pulp stem cells, Wharton's Jelly- mesenchymal stem cells (WJ-MSCs), and human embryonic stem cells derived M cells (CAStem) are being used in cell therapy of patients with COVID-19. Today, cell therapy is used for

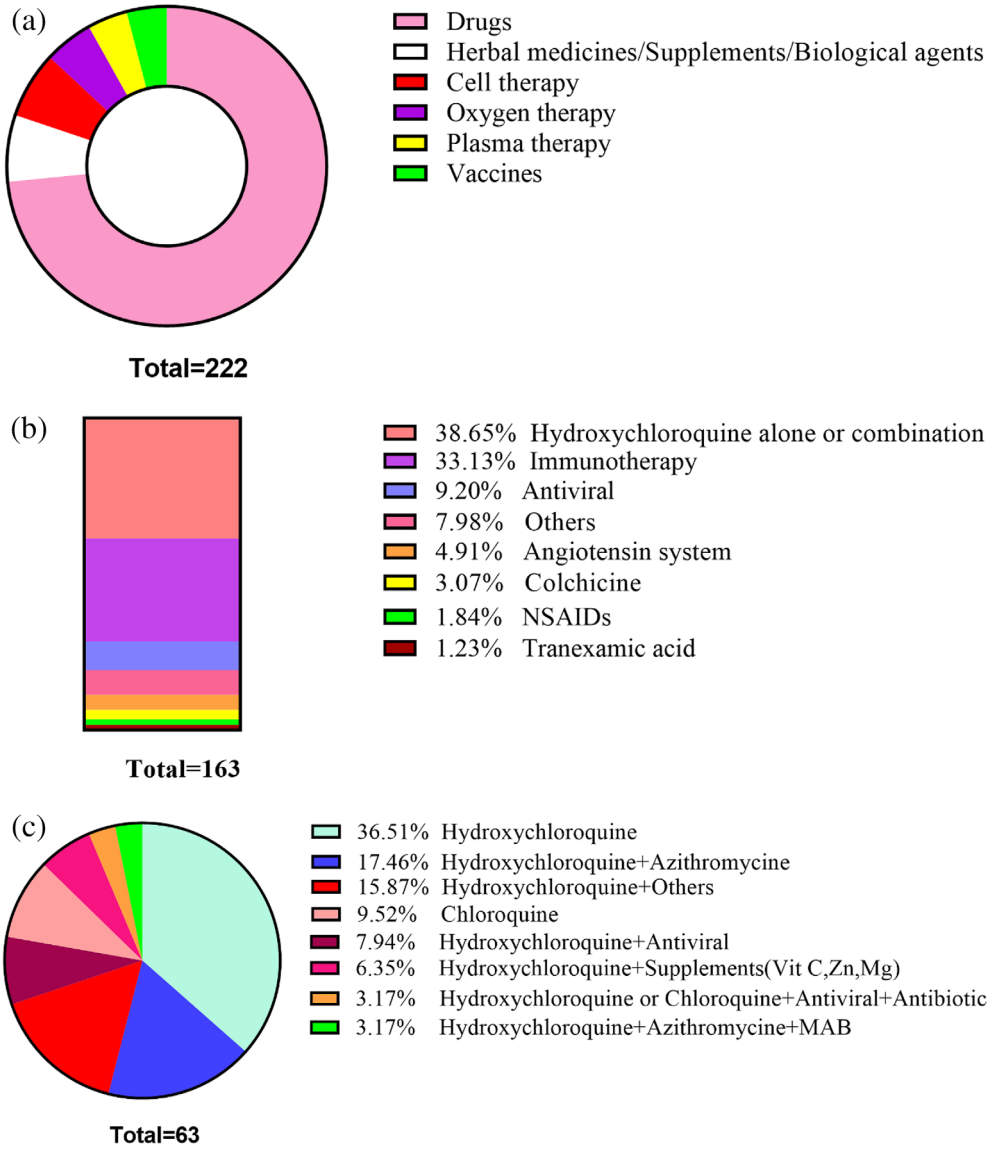


**FIGURE 3** (a) Total studies that have been registered, (b) Classification of drugs that will be used in clinical trials, (c) Hydroxychloroquine regimen

the treatment of many diseases. Recently, one study showed that intravenous transplantation of $ACE2^{-}$ mesenchymal stem cells (MSCs) in seven patients with COVID-19 pneumonia in China could improve the pulmonary function and symptoms of patients. In our review, 12 of 15 studies related to MSCs are under investigation (Table 1).

It seems that MSCs could regulate the inflammatory response by reducing the serum levels of pro-inflammatory cytokines and chemokines and promote tissue repair and regeneration via increasing IL-10 and vascular endothelial growth factor (VEGF). Another important issue in this study is that MSCs are resistant to SARS-CoV-2 due to a lack of ACE2 receptors (Leng et al., 2020). Similarly, anti-inflammatory effects are suggested for MSCs by Saldanha-Araujo et al. Now, several cell therapies are under investigation (Saldanha-Araujo et al., 2020). However, there several questions about various doses, MSCs sources, and short-term therapy that need to be answered.

About the role of NK cells against COVID-19, one hypothesis is that NK cells have dual effects against SARS-CoV-2: (a) Healthy NK in low-risk individuals could clear virus infection and prevent lung damage. (b) Abnormality of NK cells in high-risk individuals, inhibits viral clearance, induces inflammatory responses, and consequence severe lung injury will happen (i.e., cytokine storm) (Market et al., 2020; Saldanha-Araujo et al., 2020). It seems that overexpression of the inhibitory NK group 2 member A (NKG2A) receptors in the exhausted phenotype of NK cells is responsible to suppress T-cell and NK cytotoxic function and result in the progression of proinflammatory events and virus spreading (Masselli et al., 2020). This hypothesis for the first time has been described by Zheng et al. They observed the NKG2A receptor was upregulated compared with healthy controls, while the ability to produce CD107a, IFNγ, IL-2, granzyme B, and TNF-α was low in COVID-19 patients, and the percentage of $NKG2A^{+}$ cytotoxic lymphocytes was decreased in recovered patients (Zheng et al., 2020).

There are two ongoing registered clinical trials NCT04280224 and NCT04324996 with NK cells for the treatment of COVID-19 patients (Table 1). The results of these clinical trials will demonstrate the importance of this hypothesis.

**TABLE 1** Clinical trials of registered cell therapy against COVID-19

| Study | Registry identifier | Title | Interventions |
|---|---|---|---|
| 1 | NCT04339660 | Clinical research of human mesenchymal stem cells in the treatment of COVID-19 pneumonia | Biological: UC-MSCs |
| 2 | NCT04324996 | A Phase I/II study of universal off-the-shelf NKG2D-ACE2 CAR-NK cells for therapy of COVID-19 | Biological: NK cells, IL15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells, NKG2D-ACE2 CAR-NK cells |
| 3 | NCT04338347 | CAP-1002 in severe COVID-19 disease | Biological: CAP-1002 allogeneic cardiosphere-derived cells |
| 4 | NCT04336254 | Safety and efficacy study of allogeneic human dental pulp mesenchymal stem cells to treat severe COVID-19 patients | Biological: Allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC) |
| 5 | NCT04315987 | NestCell® mesenchymal stem cell to treat patients with severe COVID-19 pneumonia | Biological: NestCell® |
| 6 | NCT04313322 | Treatment of COVID-19 patients using Wharton's Jelly-Mesenchymal stem cells | Biological: WJ-MSCs |
| 7 | NCT04288102 | Treatment with human umbilical cord-derived mesenchymal stem cells for severe corona virus disease 2019 | Biological: MSCs |
| 8 | NCT04302519 | Novel coronavirus induced severe pneumonia treated by dental pulp mesenchymal stem cells | Biological: Dental pulp mesenchymal stem cells |
| 9 | NCT04331613 | Safety and efficacy of CAStem for severe COVID-19 associated with/without ARDS | Biological: CAStem |
| 10 | NCT04252118 | Mesenchymal stem cell treatment for pneumonia patients infected with 2019 novel coronavirus | Biological: MSCs |
| 11 | NCT04273646 | Study of human umbilical cord mesenchymal stem cells in the treatment of severe COVID-19 | Biological: UC-MSCs |
| 12 | NCT04333368 | Cell therapy using umbilical cord-derived mesenchymal stromal cells in SARS-CoV-2-related ARDS | Biological: Umbilical cord Wharton's jelly-derived human |
| 13 | NCT04269525 | Umbilical cord (UC)-derived mesenchymal stem cells (MSCs) treatment for the 2019-novel coronavirus(nCOV) pneumonia | Biological: UC-MSCs |
| 14 | NCT04299152 | Stem cell educator therapy treat the viral inflammation in COVID-19 | Combination product: Stem cell educator-treated mononuclear cells apheresis |
| 15 | NCT04280224 | NK cells treatment for novel coronavirus pneumonia | Biological: NK Cells |

A randomized controlled trial NCT04338347 is evaluating CAP-1002 versus placebo for the treatment of severe COVID-19 (Table 1). Allogeneic cardiosphere-derived cells (CAP-1002) is another strategy in cell therapy. Administration of CAP-1002 to six patients with severe COVID-19 as compassionate therapy indicates that it was safe and effective and improved clinical symptoms. It also reduced inflammatory markers (C-reactive protein, IL-6, and Ferritin) in most patients. All patients received conventional therapy against COVID-19 (Singh, Chakravarty, et al., 2020). Taken together, further studies need to evaluate the efficacy and safety of cell therapy in COVID-19 patients.

## 4.2 | Plasma therapy

Convalescent plasma therapy from recovered patients is under investigation. Up to now, some studies have reported that convalescent plasma containing neutralizing antibody could potentially improve clinical outcomes (Ahn et al., 2020; Duan et al., 2020; Shen et al., 2020; Ye et al., 2020; Zhang, Liu, et al., 2020). Convalescent plasma has been administered as a last resort to increase the survival rate of patients with severe acute respiratory syndrome infection in China (Zhang, Liu, et al., 2020). Direct neutralization of virus and decrement of viral load are suggested as possible mechanisms to improve COVID-19 patients' symptoms in all of these published papers. However, other possibilities such as the control of overactivity of the immune system (i.e., cytokine storm) and immunomodulation of hypercoagulable state (i.e., thrombosis) have been discussed by Rojas et al., with two ongoing clinical trials NCT04332835, and NCT04332380 on the convalescent plasma in COVID-19 (Details in supplementary data) (Rojas et al., 2020).

However, patient and donor conditions such as level of plasma antibodies in the donor, administration time of convalescent plasma (early or late stage of disease), and cotherapy with other treatments such as antivirals, steroids, and so forth should be considered as confounding variables in the studies. Further studies in well-designed trials are needed to confirm the efficacy of plasma therapy.

**TABLE 2** Clinical trials of registered vaccines against COVID-19

| Study | Registry identifier | Title | Interventions |
|---|---|---|---|
| 1 | NCT04328441 | Reducing health care workers absenteeism in COVID-19 pandemic through BCG vaccine | Drug: Bacillus Calmette–Guérin (BCG) vaccine |
| 2 | NCT04299724 | Safety and immunity of COVID-19 aAPC Vaccine | Biological: Pathogen-specific aAPC |
| 3 | NCT04276896 | Immunity and safety of COVID-19 synthetic minigene vaccine A | Biological: Injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs |
| 4 | NCT04341389 | Phase II clinical trial to evaluate the recombinant vaccine for COVID-19 (Adenovirus vector) | Biological: Recombinant novel coronavirus vaccine (Adenovirus type 5 vector) |
| 5 | NCT04313127 | Phase I clinical trial of a COVID-19 vaccine in 18–60 healthy adults | Biological: Recombinant novel coronavirus vaccine (Adenovirus type 5 vector) |
| 6 | NCT04327206 | BCG vaccination to protect healthcare workers against COVID-19 | Drug: Bacillus Calmette–Guérin (BCG) vaccine |
| 7 | NCT04324606 | A study of a candidate COVID-19 vaccine (COV001) | Biological: ChAdOx1 nCoV-19\| Biological: MenACWY placebo |
| 8 | NCT04336410 | Safety, tolerability and immunogenicity of INO-4800 for COVID-19 in healthy volunteers | Drug: DNA vaccine (INO-4800) Device: CELLECTRA® 2000 |
| 9 | NCT04283461 | Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection (COVID-19) | Biological: mRNA-1273 |

## 4.3 | Oxygen support and nitric oxide inhaler

Acute respiratory failure is a serious symptom in patients with severe COVID-19. Therefore, respiratory support is critical in the management of patients. He et al. has used high-flow nasal cannula as noninvasive techniques for oxygen therapy in the management of severe COVID-19 patients (He et al., 2020).

Our review shows that in addition to oxygen therapy (registry of studies: NCT04312100, NCT04327505, NCT04332081, NCT04331366, NCT04320056), administration of nitric oxide gas as a method for treatment of COVID-19 patients and prevention of COVID-19 in healthcare providers is also under investigation with registries of clinical trials such as NCT04312243, NCT04306393, and NCT03331445 (For more details see supplementary data).

## 4.4 | Vaccines

In addition to the treatment of COVID-19, disease prevention is also important especially in healthcare providers and housemates of patients with COVID-19. Some registries of clinical trials are trying to design a specific vaccine against COVID-19. For more details, see Table 2.

With regard to the similarity between SARS-CoV and SARS-CoV-2 viruses, previous data about designing a coronavirus vaccine may be important in the development of vaccines against COVID-19.

There are various vaccine development strategies against coronavirus diseases including first-generation vaccine (live-attenuated and inactivated vaccine), second-generation vaccine (protein subunit and vector-based vaccine), and third-generation vaccine (nucleic acid and nanomaterial-based vaccine) (Badgujar et al., 2020). Proposed mechanisms of action for live-attenuated SARS vaccine include the production of neutralizing serum antibodies, induction of anti-virus T cell, and antibody responses, generation of Th-1 based on immune response (Bukreyev et al., 2004; Escriou et al., 2014; Netland et al., 2010).

In some studies, virus inactivation is carried out by using radiation techniques or chemicals such as formalin, and methanol to prepare a vaccine (Stauffer et al., 2006). Various studies have been designed inactivated SARS-CoV vaccine which stimulated neutralizing antibodies production, proliferated lymph node T-cell, and produced cytokines such as IL-2, IL-4, IL-5, IFN-γ, and TNF-α (Takasuka et al., 2004; Tang et al., 2004; Xiong et al., 2004). A protein subunit vaccine has been developed against coronavirus that it contains the synthetic or isolated or recombinant or derived highly antigenic protein-based subunits (Vartak & Sucheck, 2016). The receptor-binding domain is the most widely used protein segment in the coronavirus vaccine (Badgujar et al., 2020). Several studies have reported that protein subunit coronavirus vaccine induces the generation of neutralizing antibodies, IgA, IgG, Th-1, and Th-2 type of immunogenic responses (du et al., 2016; Tang et al., 2015). Another type of vaccine is the vector-based vaccine. Various viral vectors such as adenovirus and lentivirus are used as a delivery tool to produce vector-based vaccines (Bouard et al., 2009). In addition, an adenovirus vector-based vaccine is designed against SARS-CoV which induces a specific humoral immunogenic response. S gene/spike proteins are often encoded in the adenovirus vector (Ababneh et al., 2019; Folegatti et al., 2020).

In our review, four studies (NCT04276896, NCT04341389, NCT04313127, and NCT04324606) related to the vector-based vaccine are under investigation (Table 2). Folegatti et al. carried out a Phase 1/2 trial of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) which expresses the SARS-CoV-2 spike protein.

**TABLE 3** Clinical trials related to registered herbal medicines or supplements or biological agents against COVID-19

| Study | Registry identifier | Title | Intervention | Possible mechanism (s) |
|---|---|---|---|---|
| 1 | NCT04291053 | The efficacy and safety of Huai er in the adjuvant treatment of COVID-19 | Drug: Huaier Granule (*aqueous extract of Trametes robiniophila murr*) | Not available |
| 2 | NCT04323228 | Antiinflammatory/antioxidant oral nutrition supplementation in COVID-19 | Dietary supplement: Oral nutrition supplement (ONS) enriched in eicosapentaenoic acid, gamma-linolenic acid, and antioxidants (vitamin A as 1.2 mg β-carotene, 205 mg Vitamin C, 75 IU vitamin E, 18 ug Selenium, and 5.7 mg Zinc) | n3-fatty acids and antioxidant vitamins in extraordinary doses:<br>(a) Modulate the host immune response<br>(b) Ameliorate the cytokine storm associated |
| 3 | NCT04334005 | Vitamin D on the prevention and treatment of COVID-19 | Dietary supplement: Vitamin D | Immune modulator agent<br>It has an important role in adaptive immunity and cellular differentiation, maturation, and proliferation of several immune cells |
| 4 | NCT04323345 | Efficacy of natural honey treatment in patients with novel coronavirus | Dietary supplement: Natural honey | Broad-spectrum antimicrobial effect of honey as an antibacterial, antifungal, antiviral<br>FDA approval for topical wound treatment as the most potent antimicrobial agent |
| 5 | NCT04341688 | A clinical trial of gargling agents in reducing intraoral viral load among COVID-19 patients | Drug: Povidone-Iodine 0.2% (BETADINE®), Hydrogen peroxide 1% (ActiveOxy), Neem extract (*Azadirachta indicia*), Hypertonic saline (2%NaCl), distilled water | Reduction in the viral load through surface debridement could aid the effective immune response |
| 6 | NCT04323514 | Use of ascorbic acid in patients with COVID 19 | Dietary supplement: Vitamin C | Positively affects the development and maturation of T-lymphocytes (i.e., NK cells) involved in the immune response to viral agents<br>Inhibits reactive oxygen species (ROS) production result in inactivation of NLRP3 that has an important role in the maturation and secretion of cytokines in systemic inflammatory syndrome |
| 7 | NCT04334265 | Efficacy and safety of Anluohuaxian in the treatment of rehabilitation patients with coronavirus disease 2019 | Drug: Anluohuaxian (totally 14 flavor medicines: *Radix Rehmanniae*, *Radix Notoginseng*, *Hirudo*, *Pheretima*, *Bombyx Batryticatus*, *Rhizoma Atractylodis Macrocephalae*, *Radix Curcumae*, *Calculus Bovis*, *Pulvis Cornus Bubali Concentratus*, *Concha Arcae*, *Cortex Moutan*, *Radix Et Rhizoma Rhei*, *Endothelium Corneum Gigeriae Galli*, *Fructus Hordei Germinatus*) | Blocks the progression of pulmonary fibrosis and improving lung function in patients<br>The signal pathways and cytokines involved are very similar to hepatic fibrosis |
| 8 | NCT04319731 | A pilot study of human amniotic fluid for COVID19 associated respiratory failure | Biological: Human Amniotic Fluid | Anti-inflammatory effects<br>Human amniotic products are FDA-approved for tissue injury and have been used to reduce inflammation and fibrosis in patients |
| 9 | NCT04279197 | Treatment of pulmonary fibrosis due to 2019-nCoV pneumonia with *Fuzheng Huayu* | Drug: N-acetylcysteine+ *Fuzheng Huayu* (*Radix Salvia Miltiorrhizae*, Cordyceps, Semen Persicae, Gynostemma Pentaphyllammak, *Pollen Pini*, *Fructus Schisandrae Chinensis*) | Inhibits matrix metalloproteinase (MMP) activity to protect subepithelial basement membrane which plays a key role in lung injury and interstitial fibrosis |

**TABLE 3** (Continued)

| Study | Registry identifier | Title | Intervention | Possible mechanism (s) |
|---|---|---|---|---|
| 10 | NCT04334967 | Hydroxychloroquine in patients with newly diagnosed COVID-19 compared with standard of care | Drug: Hydroxychloroquine+ Dietary Supplement: Vitamin C | It has multiple in vivo effects on immune modulation that may prevent the development of the cytokine excess associated with a critical illness |
| 11 | NCT04322344 | Escin in patients with COVID-19 infection | Drug: Escin (the active component of *Aesculus hippocastanum*) or escinate sodium | Antiviral effect |
| 12 | NCT04264533 | Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia | Drug: Vitamin C | Reduces inflammatory response, and decreases the viral risk |
| 13 | NCT04275388 | Xiyanping injection for the treatment of new coronavirus infected pneumonia | Drug: Xiyanping injection (extracted from *Herba Andrographitis Paniculatae*) | May be similar to NCT04295551 |
| 14 | NCT03680274 | Lessening organ dysfunction with vitamin C | Drug: Vitamin C | Vitamin C (IV) may be the first therapy to mitigate the dysregulated immune response that leads to sepsis induced by bacterial and viral pathogens such as COVID-19 |
| 15 | NCT04295551 | Multicenter clinical study on the efficacy and safety of Xiyanping injection in the treatment of new coronavirus infection pneumonia (General and severe) | Drug: Lopinavir/ritonavir tablets combined with Xiyanping injection (extracted from *Herba Andrographitis Paniculatae*) | Anti-inflammatory and immune regulation effects |

The study is ongoing and is registered on *ClinicalTrials.gov*, NCT04324606. This vaccine showed acceptable safety and induced both humoral and cellular immune responses (Folegatti et al., 2020).

Zhu et al. have been investigated a non-randomized Phase 1 trial of an adenovirus type-5 (Ad5) vectored COVID-19 vaccine in China that is registered on *ClinicalTrials.gov*, NCT04313127. The Ad5 vectored COVID-19 vaccine is tolerable and induces both specific antibody and T-cell responses against SARS-CoV-2 (Zhu, Li, et al., 2020). On the other hand, it seems that some researchers have focused on the nucleic acid vaccine against coronaviruses, and various genes are used to design vaccines including N gene, S gene, S1 gene, and S2 gene. The immune response induced by these vaccines includes the production of IL-2, γ-interferon, cytotoxic T lymphocytes, CD4+, CD8+, neutralizing antibodies, and Th-1/Th-2 responses (Badgujar et al., 2020).

Two registries studies (NCT04336410 and NCT04283461) in our review investigate safety, tolerability, and immunogenicity of DNA and mRNA vaccine for COVID-19 respectively (Table 2). In Phase 1 of trial NCT04283461, the mRNA-1273 vaccine which encodes stabilized perfusion SARS-CoV-2 spike protein could induce anti–SARS-CoV-2 antibody on 45 healthy adults, 18–55 years of age in the preliminary report. No serious adverse effects were reported (Jackson et al., 2020). Similarly, Corbett et al. evaluated an mRNA vaccine that expresses SARS-CoV-2 spike protein (SARS-CoV-2 S-2P) as a transmembrane-anchored protein with the native furin cleavage site (mRNA-1273). This vaccine is formulated in the lipid nanoparticles and induces both potent neutralizing antibody and CD8 T cell responses. Now, this vaccine is in Phase 2 clinical trials (Corbett et al., 2020).

In addition to the specific vaccine against COVID-19, few trials investigate the Bacille Calmette-Guérin (BCG) vaccine in the prevention of healthcare workers. BCG is a vaccine against tuberculosis, with cross-protection on viral respiratory infections. Recent publications have proposed that BCG vaccination could have potential protective effects against COVID-19 infection (de Freitas & Pitzurra, 2020; Hegarty et al., 2020). Escobar et al. indicated that every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality. Although, the effectiveness of BCG vaccination to protect from severe COVID-19 should be evaluated in clinical studies (Escobar et al., 2020). Two ongoing randomized clinical trials (NCT04328441 and NCT04327206), in which health workers receive either the BCG vaccine or placebo saline, will help to determine the effect of BCG vaccination on protection from COVID-19 (Table 2). BCG may enhance the antigen-presenting capacity and adaptive responses, according to a study by Leentjens et al. BCG has beneficial effects on the response to the influenza vaccine (Leentjens et al., 2015).

In total, further studies are needed to investigate the effect of BCG vaccination on the prevention of COVID-19 or protection from severe COVID-19. Recently, a systematic review reported that there is no evidence to recommend BCG vaccination for the prevention of COVID-19 (Riccò et al., 2020). A great concern in vaccine administration and antibody therapies is the risk of antibody-dependent enhancement (ADE) of disease. ADE is a phenomenon in which the binding of antibodies to the virus may enable changes in the viral entry protein that accelerate fusion into host cells and enhance viral

infections (Arvin et al., 2020; Wan, Shang, Sun, et al., 2020). Then, it is necessary to determine the ADE in the development of vaccines and antibodies against SARS-CoV-2 in human clinical trials.

### 4.5 | Herbal medicines or supplements or biological agents

Some clinical trials are trying to treat COVID-19 through the prescription of supplements such as vitamin D and C and zinc, herbal medicines, traditional Chinese medicines alone, or in combination with drugs except two of them (For more details, see Table 3). The possible mechanisms of the two registries of studies NCT04291053 and NCT04275388 were not available.

An important supplement is vitamin D that has immunomodulatory activity. Recently, a population-based study showed an association between low plasma 25(OH)D level and increased likelihood of COVID-19 infection and hospitalization due to the SARS-CoV-2 (Merzon et al., 2020).

Recently the inhibitory effects of natural products on coronavirus targets such as S protein and viral replication were reviewed by Boozari & Hosseinzadeh, 2020. The potential role of natural products in the prevention and treatment of COVID-19 should be considered (Babaei et al., 2020; Boozari & Hosseinzadeh, 2020).

Overall, it seems that one of the most important mechanisms of these agents is modulatory effects on the immune system that prevents inflammatory responses in the battle against COVID-19 (NCT04323228, NCT04334005, NCT04323514, NCT04334967, NCT04275388, NCT03680274, NCT04295551). Also, the antiviral (NCT04323345, NCT0434168, NCT04322344, NCT04264533), and antifibrotic effects (NCT04334265, NCT0431973, NCT04279197) of these agents are other possible mechanisms against COVID-19 (Table 3).

### 4.6 | Drugs studies in clinical trials for the treatment of COVID-19

Drug studies in clinical trials of treatment of COVID-19 were assessed and categorized into eight groups that have been shown in Figure 3b. Hydroxychloroquine alone or in combination therapy is the most widely used or being used in clinical trials of treatment of COVID-19. The second most widely treatment is immunotherapy which is explained below. Antivirals, angiotensin system drugs, Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and tranexamic acid are also being investigated. Some of the trials do not include any of the above groups, which classify as others and include 7.98% of the trials (Figure 3b).

#### 4.6.1 | Hydroxychloroquine or chloroquine regimen in registered clinical trials

Hydroxychloroquine is often prescribing alone in clinical trials of treatment of COVID-19. It is also being used in combination with other drugs such as supplements (Vitamin C, D, zinc), azithromycin, antivirals, monoclonal antibodies. Additional detail is provided in Figure 3c. Among all hydroxychloroquine studies, five studies are suspended after suggesting excess toxicity of hydroxychloroquine and one has withdrawn. In all the registries, we observed that hydroxychloroquine or chloroquine is being used for participants such as prevention (NCT04328285, NCT04335084), treatment mild or severe COVID-19 disease (NCT04340544, NCT04329832, NCT04334382, NCT04332094), prevention and treatment (NCT04329923), and improvement of patients who admit to intensive care with COVID-19 (NCT04339816).

There are several new published papers about the possible mechanisms of hydroxychloroquine /chloroquine against COVID-19. In most of them, two mechanisms have been mentioned: the antiviral and immunomodulatory effects that may be involved in the anti-inflammatory effect (Gies et al., 2020; Quiros Roldan et al., 2020). However other mechanisms such as the antithrombotic effect have been demonstrated (Quiros Roldan et al., 2020). Similarly, the simulation method in silico suggests that hydroxychloroquine/chloroquine may have beneficial effects through increasing cell-mediated immune response and antiviral activity (Tarek & Savarino, 2020).

A recent living systematic review about the role of hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19 reported that there is conflicting evidence about the safeties and toxicities of them (Hernandez et al., 2020). In this way, on June 15, 2020, Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that allowed for both drugs that have been donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable or participation in a clinical trial was not feasible (Coronavirus [COVID-19] Update, 2020). On the other hand, the COPCOV registry (NCT04303507) is the only large, and global clinical trial, testing hydroxychloroquine or chloroquine on 40,000 healthcare workers for COVID-19 prevention. A loading dose of 10 mg/kg followed by 155 mg daily (250 mg chloroquine phosphate salt or 200 mg of hydroxychloroquine sulfate for Asian and European participants respectively) will be taken for 3 months. To sum up, it needs that large clinical trial studies of hydroxychloroquine will be completed to determine efficacy, safety, or even toxicity of it against COVID-19.

#### 4.6.2 | Immunotherapy in registered clinical trials

Immunotherapy is the second most widely used group in clinical trials. Various immunomodulatory drugs are used in COVID-19 clinical trials, including monoclonal antibodies, glucocorticoids, Janus kinase inhibitors, some immunosuppressive drugs (such as anakinra), immunoglobulins, and interferons that are considered as immunotherapy. Table 4 presents a summary of immunotherapy drugs, their mechanism of actions, and the indication that have been mentioned during registration in *ClinicalTrials.gov*. In this section, we describe the major

**TABLE 4** Immunotherapy in clinical trials of COVID-19 treatment

| Study | Drug | Mechanism (s) | Medical indication |
|---|---|---|---|
| **1. Monoclonal antibodies** | | | |
| *N* = 9<br>*N* = 1<br>*N* = 1 | Tocilizumab<br>Tocilizumab + Pembrolizumab<br>Tocilizumab + Favipiravir | IL6R antagonist<br>Anti-PD-1 humanized IgG4<br>Anti-viral | Patients with COVID-19 pneumonia and acute hypoxic respiratory failure and systemic cytokine release syndrome<br>Adult patients with COVID-19 pneumonia and bad prognostic factors who are nonresponsive to frontline therapy within 48 hours from treatment initiation<br>Patient with coronavirus disease 2019 |
| *N* = 1 | Anti-Human C5 Therapeutic Antibody (IFX-1) | Anti-human complement factor C5a | Severe COVID-19 pneumonia |
| *N* = 3 | Sarilumab | IL6R antagonist | Adult patients hospitalized with severe or critical COVID-19 |
| *N* = 1 | Meplazumab | Humanized anti-CD147 antibody | Patients with 2019-nCoVs infection pneumonia |
| *N* = 1 | Anti-GM-CSF Monoclonal Antibody (TJ003234) | Anti-GM-CSF monoclonal antibody | Subjects with severe COVID-19 under supportive care, and to assess the effect of the drug on the levels of cytokines |
| *N* = 2 | Bevacizumab | Anti VEGF recombinant humanized monoclonal antibody | Severe and critical COVID-19 patients |
| Total = 19 | | | |
| **2.Janus kinase inhibitors** | | | |
| *N* = 2 | Baricitinib | Anti-Janus kinase inhibitor (anti-JAK) acting against JAK1 and JAK2<br>Capable to reduce or interrupt the passage of the virus into target cells, and to inhibit the JAK1- and JAK2-mediated cytokine release<br>May lower the hyperinflammation caused by the virus, then, prevent damage to the lungs and possibly other organs | Patients with mild to moderate COVID-19 infection<br>Patients with COVID-19 |
| *N* = 1 | Tofacitinib | JAK1/3 inhibitor and could mitigate alveolar inflammation by blocking IL-6 signal | Patients with early-onset SARS-CoV2 interstitial pneumonia |
| *N* = 4 | Ruxolitinib | Inhibits the protein kinase activities of Jak1/2 which is responsible for proinflammatory signals such as IL-6<br>Immunomodulator and decreased the cytotoxic T lymphocytes and increasing the Treg cells | Patients with severe/very severe COVID-19 illness<br>Patients with severe acute respiratory syndrome caused by COVID-19 |
| Total = 7 | | | |
| **3. Immunosuppressants** | | | |
| **3.1 Glucocorticoids** | | | |
| *N* = 2 | Dexamethasone | The potent anti-inflammatory and antifibrotic properties | Pulmonary and systemic damage in ARDS patients |
| *N* = 4 | Methylprednisolone | | Severe acute respiratory failure |
| *N* = 1 | Methylprednisolone vs. Siltuximab | IL6R antagonist | Hospitalized patients with pneumonia |
| *N* = 1 | Methylprednisolone +Tacrolimus | Tacrolimus: inhibit both pro-inflammatory cytokines and, also, human coronavirus SARS-Cov replication | Severe lung injury |

(Continues)

**TABLE 4** (Continued)

| Study | Drug | Mechanism (s) | Medical indication |
|---|---|---|---|
| *N* = 1 | Levamisole with<br>Inhaler Budesonide/Formoterol<br>Lopinavir/Ritonavir + hydoxychloroquine | Levamisole: Immunostimulator<br>Budesonide can suppress the immune reaction locally in the respiratory system | Positive COVID-19 patients |
| *N* = 1 | Ciclesonide metered dose inhaler<br>Ciclesonide metered dose inhaler and hydroxychloroquine | Eradicates SARS-CoV-2 from respiratory tract earlier in patients with mild COVID-19 | Adults with mild COVID-19 |
| Total = 10 | | | |
| **3.2 Other immunosuppressive drugs** | | | |
| *N* = 1 | CD24Fc human IgG Fc fusion protein | CD24 is an innate checkpoint against the inflammatory response to tissue injuries | Hospitalized adult subjects who are diagnosed with severe COVID 19 |
| *N* = 1 | Fingolimod | Sphingosine-1-phosphate receptor regulators | Severe patients with SARS-CoV-2 pneumonia to prevent ARDS development |
| *N* = 1 | Sirolimus | | Hospitalized patients with COVID-19 pneumonia |
| *N* = 2 | Thalidomide | Anti-inflammatory, anti-fibrotic, anti-angiogenesis, and immune regulation effects | Pneumonia patients with new coronavirus (COVID-19) pneumonia<br>Severe COVID-19 Patient |
| *N* = 1 | PD-1 blocking antibody + Thymosin | Blocking PD-1 could prevent T cell death, regulate cytokine production, reduce organ dysfunction and reduce death in sepsis in animal models<br>Thymosin: regulate cellular immunity in sepsis patients | Patients with severe pneumonia associated with lymphocytopenia in 2019 novel coronavirus infection |
| *N* = 1 | Anakinra or tocilizumab | Anakinra: IL-1R antagonist<br>Tocilizumab: IL-6R antagonist | In case of diagnosis of macrophage activation syndrome (MAS) treatment with anakinra<br>In case of diagnosis of immune dysregulation treatment with tocilizumab |
| *N* = 1 | Anakinra or emapalumab | Anakinra: IL-1 receptor antagonist<br>Emapalumab: Anti-interferon gamma (Anti-IFNγ) monoclonal antibody | Patients with COVID-19 infection that have hyper-inflammation and respiratory distress |
| *N* = 1 | Tocilizumab<br>Tocilizumab + Anakinra<br>Siltuximab<br>Siltuximab + Anakinra | IL-6R antagonist<br>IL-6R antagonist+ IL-1R antagonist<br>IL-6R antagonist<br>IL-6R antagonist+ IL-1R antagonist | Patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic cytokine release syndrome |
| *N* = 1 | Anakinra | Blocks IL-1α and IL-1β | Adult patients hospitalized with COVID-19 either diagnosed with moderate or severe pneumonia |
| *N* = 10 | | | |
| **4. Immunoglobulins** | | | |
| *N* = 1 | Intravenous Immunoglobulin | Provides passive immunity and anti-inflammatory, the immunomodulatory effect | Patient with severe 2019-nCoV infected pneumonia |
| *N* = 1 | Immunoglobulin of cured patients | | Acute severe 2019-nCoV pneumonia |
| Total = 2 | | | |
| **5. Interferons** | | | |
| *N* = 1 | Recombinant human interferon α1β | Inhibits MERS-CoV and closely related coronavirus severe acute respiratory syndrome (SARS)-CoV | Patients with a new type of coronavirus infection |
| *N* = 1 | Peginterferon Lambda-1a | | Patients with uncomplicated COVID-19 disease |

**TABLE 4** (Continued)

| Study | Drug | Mechanism (s) | Medical indication |
|---|---|---|---|
| *N* = 1 | Lopinavir/ritonavir, Ribavirin and INF Beta 1b combination versus Lopinavir/ritonavir alone | | Patients with 2019-n-CoV infection |
| **5.1 Inhaler IFN** | | | |
| *N* = 1 | Recombinant human interferon alpha-1b (nasal drop)<br>or<br>Recombinant humaninterferon-alpha-1b + Thymosin alpha 1 (s.c.) | | In medical staff in the epidemic area |
| *N* = 1 | Umifenovir (Abidol) hydrochloride<br>or<br>Umifenovir (Abidol) hydrochloride +Interferon (PegIFN-α-2b) atomization | | Patient with 2019-nCoV pneumonia |
| *N* = 1 | Danoprevir+ritonavir with or without interferon nebulization | | Patient with SARS-CoV-2 infection |
| Total = 6 | | | |

challenges about treatment options in immunotherapy that have been proposed and discussed in different studies.

Tocilizumab, pembrolizumab, sarilumab, meplazumab, bevacizumab, IFX-1 (anti-human complement factor C5a), and TJ003234 (anti-GM-CSF monoclonal antibody) are monoclonal antibodies that being used in COVID-19 clinical trials. Among our selected studies, most registry trials focus on tocilizumab and prescribe it to reduce cytokine release syndrome (CRS) and systemic inflammation, and improve respiratory distress (NCT04317092, NCT04331795, NCT04332094, NCT04320615, NCT04332913, NCT04335305, NCT04335071, NCT04310228, NCT04339712, NCT04306705, NCT04315480, NCT04331808). Additional detail is provided in Table 4.

Administration of tocilizumab to ICU and non-ICU patients could improve severe COVID-19 pneumonia with the hyperinflammatory syndrome (*n* = 43, *n* = 57, respectively) (Toniati et al., 2020). The IL-6 serum levels were significantly higher in nonsurvivors than in survivors in COVID-19 patients in post-tocilizumab therapy. It is suggested that IL-6 levels can discriminate nonsurvivors from survivors in post tocilizumab treatment in COVID-19 pneumonia (Quartuccio et al., 2020).

However, it should pay attention to this issue that the initial treatment of tocilizumab is associated with elevation of IL-6 levels. This may be due to the block of the IL-6 receptors by tocilizumab. This point is reported in a systematic review by Antwi-Amoabeng who analyzed individual data of 29 COVID-19 patients on baseline characteristics, laboratory findings, and clinical outcomes (Antwi-Amoabeng et al., 2020).

Clinical trials registered related to other monoclonal antibodies including pembrolizumab (NCT04335305), sarilumab (NCT04315298, NCT04341870, NCT04327388, NCT04324073), meplazumab (NCT04275245), bevacizumab (NCT04305106, NCT04275414), IFX-1 (anti-human complement factor C5a) (NCT04333420), and TJ003234 (anti-GM-CSF monoclonal antibody) (NCT04341116) are under investigation. Molecular mechanisms and medical indications of these monoclonal antibodies are summarized in Table 4.

Clinical studies about glucocorticoids including dexamethasone (NCT04325061, NCT04327401), methylprednisolone alone, or combined with other drugs (NCT04343729, NCT04244591, NCT04329650, NCT04273321, NCT04341038, NCT04263402), budesonide inhaler (NCT04331470), ciclesonide (NCT04330586) are under investigation (Table 4).

Recently the results of "Randomized evaluation of COVID-19 therapy (RECOVERY)" have shown that a low dose of dexamethasone (6 mg/day, for 10 days) could reduce deaths by one-third in ventilated patients ($p$ = .0003) and by one fifth in other patients receiving oxygen only ($p$ = .0021). In this study, a total of 2104 patients were randomized to receive dexamethasone 6 mg once per day (p.o., or IV) for 10 days compared with 4321 patients randomized to usual care alone (For more detail see *Clinical Trials.gov*: NCT04381936, www.recoverytrial.net) (Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respirator complications of COVID-19, 2020).

It seems that the immunomodulatory effects of glucocorticoids will be effective in the hyperinflammatory phase of COVID-19 in some patients possibly by breaking the inflammatory feedforward loop. But, the immunosuppressive effects of glucocorticoids at the early stage of disease may be dangerous and disturbs antiviral responses (Cain & Cidlowski, 2020). On the other hand, a retrospective study on 216 patients who received low-dose methylprednisolone (0.75–1.5 mg/kg/d, the median duration of 6 days) showed that glucocorticoid therapy did not significantly influence the clinical course, outcome, and adverse events of COVID-19 pneumonia compared with the nonglucocorticoid group (*n* = 92) (Hu et al., 2020). Indeed, it is suggested the stage of the COVID-19 disease, a dose of glucocorticoid, duration of administration, and patient's condition should be considered and investigated in the large clinical trial studies.

Baricitinib is a JAK1/JAK2 inhibitor. It interrupts the passage and intracellular assembly of SARS-CoV-2 into the target cells mediated by the ACE2 receptor and also inhibits the proinflammatory signal of

several cytokines such as IL-6, IL-12, IL-23, and IFN-γ, result in reducing inflammation induced by a cytokine storm in sever COVID-19 (Zhang, Zhang, et al., 2020). Details of registries of JAK kinase inhibitors including baricitinib (NCT04331808), tofacitinib (NCT04332042), ruxolitinib (NCT04337359, NCT04334044, NCT04331665, NCT04338958) are in Table 4, and supplementary data.

Other registry studies contain anakinra (NCT04341584, NCT04330638, NCT04339712, NCT04324021), tacrolimus (NCT04341038), sirolimus (NCT04341675), thalidomide (NCT04273529, NCT04273581), PD-1 blocking antibody (NCT04268537), and thymosin combined with other drugs (NCT04268537, NCT04320238) are under investigation due to immunosuppressive activities. For more detail of mechanisms see Table 4.

Anakinra is an IL-1 antagonist. A retrospective cohort study showed that a high dose of anakinra (5 mg/kg twice per day, IV, for 21 days) was safe and associated with clinical improvement in 72% of COVID-19 and ARDS patients who were out of ICU ($n$ = 29) (Cavalli et al., 2020).

van de Veerdonk and Netea proposed a preventive strategy for COVID-19 patients in their paper. They believe that targeting the innate inflammatory response with anakinra in combination with supportive care and the antiviral drug could reduce admission of COVID-19 patients to ICU. Since it is suggested that the upregulation of the IL-1/IL-6 pathway has a pivotal role in the progression of inflammation and consequence respiratory failure in severe COVID-19 patients and anakinra could inhibit IL-1 and consequence decrease IL-6 which is induced by IL-1. Therefore, anakinra not only inhibits IL-1 but also reduces the production of IL-6 similar to tocilizumab. Also, anakinra does not block the IFN-STAT1/STAT2 pathway compared with JAK inhibitors, which is crucial for host defense against viruses. The advantage of anakinra over the other immunosuppressive is that a mild immunosuppressive agent and does not disturb the antiviral capacity of host cells (van de Veerdonk & Netea, 2020).

Some registry trials investigate the immunoglobulin of cured patients (NCT04261426, NCT04264858), peginterferon Lambda-1a (NCT04331899), recombinant human interferon α1β (NCT04293887), and inhaler interferons (NCT04320238) as a treatment for COVID-19. An experimental trial of rhIFNα nasal drops is ongoing in medical staff to prevent them against COVID-19 (NCT04320238) (Phase 3). Intravenous immunoglobulin (IVIG) is produced from the plasma of thousands of donors and provides passive immune protection against a broad range of pathogens (Nguyen et al., 2020). Siddiqi and Mehra classified COVID-19 disease states and potential therapeutic targets into three stages: Stage I (early infection), Stage II (pulmonary phase), and Stage III (hyper inflammation phase) (Siddiqi & Mehra, 2020). The rationale for use of IVIG in COVID-19 is that it may provide an immunomodulatory effect in hyper inflammation state and competitively bind Fcγ receptor to prevent ADE triggered by virus-antibody immune complexes (Nguyen et al., 2020).

IFN-I can control viral infection, and IFN-I deficiency is believed to play a key role in SARS-CoV-2 pathogenesis (Sa Ribero et al., 2020). Chinese guideline recommends administration of inhaler IFN-α (5 million U, 2 times per day, no more than 10 days) as antiviral therapy for new coronavirus (Dong et al., 2020). IFNβ1 may be used to treat COVID-19 in the early stages of infection (Sallard et al., 2020). The administration of immunomodulatory or anti-inflammatory drugs that reduce inflammation has been recommended at the late stage of the disease, and in this stage, IFN-I maybe promotes disease severity causes excessive inflammation and direct tissue damage. Therefore, treatment with IFN-I should be with caution (Lee & Shin, 2020; Sa Ribero et al., 2020).

Overall, as the important role of immunotherapy, these ongoing clinical trials provide us clues about the efficacy and safety of this regimen in the clinical management of COVID-19 infection.

### 4.6.3 | Antiviral drugs in clinical trials

Antiviral drugs, as other groups are using in COVID-19 clinical trials. These drugs are lopinavir/ritonavir, favipiravir, remdesivir, oseltamivir, ASC09/ritonavir (ASC09F), umifenovir (arbidol, abidol), ribavirin, darunavir, and cobicistat (Figure 3b).

*Lopinavir/ritonavir*

In our review, there are 15 ongoing registries of clinical trials related to lopinavir/ritonavir (NCT04321993, NCT04328285, NCT04330690, NCT04307693, NCT04331470, NCT04286503, NCT04303299, NCT04328012, NCT04295551, NCT04315948, NCT04255017, NCT02735707, NCT04321174, NCT04261907, NCT04276688) that evaluate the effects of lopinavir/ritonavir in patients with COVID-19 (More details in supplementary data). Lopinavir and ritonavir are two protease inhibitors that are widely used to treat human immunodeficiency virus (HIV) infection (Costanzo et al., 2020).

The main protease of SARS-CoV is a 3-chymotrypsin-like protease ($3CL^{pro}$) that has a key role in proteolytic processing of polyproteins and is important for viral replication (Nukoolkarn et al., 2008). There is a similarity between the genome sequence of SARS-CoV-2 and SARS-CoV (Tahir Ul Qamar et al., 2020). It is reported that the binding affinities of both lopinavir and ritonavir to SARS-CoV $3CL^{pro}$ are very similar to each other (Nukoolkarn et al., 2008). Chu et al. found that lopinavir/ritonavir has anti-SARS-CoV activity in in vitro and improved clinical outcomes (Chu et al., 2004). Recent researches have proposed lopinavir/ritonavir as potential drugs for the treatment of COVID-19 (Huang, Wang, et al., 2020; Lu, 2020). Osborne et al. carried out a systematic benefit–risk assessment on seven studies and declared that there was no clear benefit for the use of lopinavir/ritonavir compared with standard of care in severe COVID-19. Although, one study showed a reduction in ARDS with lopinavir/ritonavir. The standard of care is defined as no use of a specific pharmaceutical treatment for COVID-19. However, standard supportive therapy is provided in the hospital. Of course, the standard of care in the hospital setting of each country can be different (Osborne et al., 2020). Completed clinical trials will help us to determine the efficacy of lopinavir/ritonavir in COVID-19 treatment.

*Favipiravir*

In our review, four registries of clinical trials are currently underway (NCT04336904, NCT04303299, NCT04333589, NCT04310228) to evaluate the effects of favipiravir in patients with COVID-19 (Supplementary data). Favipiravir is an inhibitor of RNA dependent RNA polymerase (RdRp) (Furuta et al., 2017). It is administrated to Ebola virus-infected patients and approved for influenza type A and B in Japan (Nagata et al., 2015).

Now, favipiravir is being used in clinical trials against COVID-19. Any data about selected doses and safety is based on previous clinical trials about the treatment of influenza, and Ebola viruses or experimental studies (Du & Chen, 2020). Recently, it has been reported that the trough concentration of favipiravir in critically ill patients with COVID-19 was much lower than that of healthy individuals in a previous clinical trial (Irie et al., 2020). It seems that in addition to studying the efficacy and safety of favipiravir, evaluating the pharmacokinetics is also necessary.

*Remdesivir*

In our review, there are eight ongoing registries of clinical trials (NCT04292899, NCT04252664, NCT04315948, NCT04323761, NCT04321616, NCT04257656, NCT04302766) that investigate the effects of remdesivir in patients with COVID-19 (More details in supplementary data). Remdesivir is a nucleoside analog that has effects on the broad-spectrum of RNA viruses (Costanzo et al., 2020). Triphosphate form of remdesivir acts as a substrate for RdRp of three coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2) and inhibits the viral RNA synthesis by delayed chain termination of RdRp (Gordon et al., 2020). It has an inhibitory effect against SARS-CoV-1, MERS-CoV, and SARS-CoV-2 in vitro and in vivo study (Singh, Singh, et al., 2020; Wang, Zhou, et al., 2020). A possible favorable benefit–risk profile is suggested for remdesivir compared with placebo as the preliminary results of a clinical trial in severe COVID-19 infection (Davies et al., 2020).

A randomized, double-blind, placebo-controlled clinical trial with registry number NCT04257656 was carried out to evaluate the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19. In both groups, concomitant use was continued with conventional therapy and the remdesivir group did not show any significant clinical or antiviral effects in patients compared with the placebo group (Wang, Zhang, et al., 2020). Remdeisvir has compassionate use in severe COVID-19 and Singh et al. have conducted a systematic search to evaluate the pharmacological effects and safety of remdesivir. They found that remdesivir has shown different results in clinical studies (Singh, Singh, et al., 2020). Recently, the results of the trial "Adaptive COVID-19 Treatment Trial (ACTT)" with registry number NCT04280705 which underwent on 1062 patients, has shown that remdesivir ($n$ = 541) has superior effects against the placebo group ($n$ = 521) in shortening the time of recovery in adults who were hospitalized with COVID-19. The respiratory infection was also lower compared with the placebo (Beigel et al., 2020). On October 22, 2020, FDA approved remdesivir for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization (FDA's approval of Veklury [remdesivir] for the treatment of COVID-19, 2020).

*Oseltamivir and umifenavir*

Several clinical trials are investigating the effect of oseltamivir in the treatment of COVID-19. In our review, five registries of clinical trials are underway (NCT04303299, NCT04338698, NCT04255017, NCT04261270, NCT02735707) to evaluate the efficacy and safety of oseltamivir in patients with COVID-19. Oseltamivir is neuraminidase glycoprotein inhibitors that could prevent the replication of influenza A and B viruses (McClellan & Perry, 2001).

In our review, two registries of clinical trials related to umifenovir, NCT04286503, and NCT04260594 are being registered to evaluate the effects of it in patients with COVID-19. Umifenovir (Arbidol) is an antiviral drug that has been used against some viruses such as influenza, Ebola, and hepatitis B and C. It inhibits the membrane fusion process of influenza viruses (Kadam & Wilson, 2017). Sequence analysis indicated that s short region of the trimerization domain (S2) of SARS-CoV-2 spike glycoprotein is similar to the haemagglutinin protein of influenza. On the other hand, arbidol targets influenza haemagglutinin. Therefore, arbidol blocks the trimerization of SARS-CoV-2 spike protein and inhibits host cell adhesion and entry (Vankadari, 2020). Arbidol has shown an inhibitory effect on SARS-CoV-2 at a concentration of 10–30 μM in vitro (Dong et al., 2020). Huang et al. conducted a systemic review and meta-analysis to evaluate the efficacy and safety of umifenovir in COVID-19. They showed that umifenovir is safe and associated with a higher negative rate of PCR on day 14 in COVID-19 patients. But, there is no supportive evidence for using umifenovir to improve patient outcomes with COVID-19 (Huang, Yu, et al., 2020). It seems that more clinical investigation is still required to judge the efficacy of umifenovir against COVID-19.

### 4.6.4 | Azithromycin

Azithromycin is a macrolide antibiotic that inhibits bacterial mRNA translation and protein synthesis (Parnham et al., 2014). It is prescribed for different types of infections such as respiratory infections, skin infections, and sexually transmitted diseases (Peters et al., 1992). It has shown that azithromycin has immunomodulatory and anti-inflammatory effects (Parnham et al., 2014). In our review, many trials are currently investigating the efficacy of combination therapy of azithromycin and hydroxychloroquine on COVID-19 in registries of trials such as NCT04339816, NCT04329832, NCT04334382, and NCT04336332.

Azithromycin has shown antiviral effects and for this effect, it has been added to hydroxychloroquine to enhance clearance of COVID-19 (Rameshrad et al., 2020). But, some of the other clinical trials are also evaluating the efficacy of azithromycin in combination with antiviral drugs (NCT04338698) or alone (NCT04332107) (More details in supplementary data). No reasonable preclinical or clinical evidence still found about azithromycin efficacy in the treatment of COVID-19 (Gbinigie & Frie, 2020; Lighter & Raabe, 2020).

### 4.6.5 | Clinical trials related to the renin-angiotensin system

Some drugs such as losartan ($n$ = 5), valsartan ($n$ = 1), angiotensin 1–7 ($n$ = 1), and recombinant human angiotensin-converting enzyme 2 (rhACE2) ($n$ = 1) are under investigation (Figure 3b) (Supplementary data). Both ACEIs and angiotensin II type-1 receptor blockers (ARBs) are the most widely used for cardiovascular diseases in clinical practices. ACEIs inhibit the production of Ang II and suppress harmful Ang II-AT1R signaling and provide activation of Ang 1–7 signaling (producing from Ang I by neprilysin), consequently anti-hypertensive, anti-oxidative, anti-inflammatory, anti-fibrotic, and anti-hypertrophic effects will happen. As hypothesis 1, cell uptake of SARS-CoV-2 by receptor-mediated endocytosis lowers the surface expression of ACE2 and reduces the conversion of Ang II into Ang 1–7. Thus, a misbalance in the activities of the ACE/AngII/AT1R and ACE2/Ang 1–7/MasR (Mas receptor) axes occurs and detrimental ACE/AngII/AT1R signaling results in severe lung injury in COVID-19 patients. It is suggested that ACEIs and ARBs may alleviate COVID-19 by inhibiting the harmful ACE/AngII/AT1R axis. Hypothesis 2, ACEIs, and ARBs may aggravate COVID-19 by upregulating ACE2, causing increased SARS-CoV-2 entry and replication (de Vries, 2020).

For this reason, we refer to recently published studies as follow: The result of a retrospective cohort study on 4480 patients with COVID-19 showed that prior use of ACEI/ARBs in 895 patients was not significantly associated with a higher incidence rate of COVID-19 diagnosis among patients with hypertension or with mortality or severe disease compared with ACEI/ARB nonusers (Fosbøl et al., 2020). According to the results of a meta-analysis, there was no significant association between the use of ACEI/ARB and the severity and mortality of COVID-19 (Grover & Oberoi, 2020). Furthermore, the results have shown that in COVID-19 patients with hypertension who received ACEI/ARB have a lower rate of severe disease compared with the non-ACEI/ARB group. Also, the viral load and level of IL-6 are decreased and the number of CD3 and CD8 T cells in peripheral blood was increased (Meng et al., 2020). The results of a recent retrospective single-center study on 614 hospitalized hypertensive COVID-19 patients showed that continued use of ACEI/ARB reduced mortality rate, and intensive care unit admission (ICU) compared with the non-ACEI/ARB group. Also, the percentages of developed hypotension and acute kidney injury in these hospitalized patients were higher in the discontinued ACEI/ARB group (Lam et al., 2020). Overall, it seems that further clinical trial studies on a large population need to confirm these two mentioned hypotheses.

### 4.6.6 | NSAIDs

NSAIDs are being studied against COVID-19. In the LIBERATE study (NCT04334629), three doses of lipid ibuprofen will be administrated to patients with acute hypoxemic respiratory failure due to COVID-19. The antiviral effects of naproxen have been reported in several experimental studies. Naproxen inhibited influenza A virus nucleoprotein (NP) and result in inhibiting replication of the virus in the mouse model of intranasal infection (Lejal et al., 2013). Also, the binding affinity influenza B virus NP to naproxen was higher than the influenza A virus. Naproxen has anti-influenza B properties both in vivo and in vitro studies. It is suggested that naproxen acts as an anti-influenza drug with broad, and multi-mechanistic potential (Zheng et al., 2019).

In our review, aspirin as another NSAID is being used as an anti-thrombotic and cardioprotective agent in two registries of trials NCT04333407, and NCT04324463. Overall, there is no published clinical trials research about the role of NSAIDs in the treatment of COVID-19. There are only some published papers as case-series, case reports, and systematic reviews about NSAIDs. Recently, a systematic review of the application of NSAIDs on viral respiratory infections recommends using acetaminophen for managing fever and inflammation of COVID-19 patients in this condition. Furthermore, as the data, it is suggested that naproxen could be a good option in clinical trials for COVID-19 patients (Yousefifard et al., 2020).

### 4.6.7 | Colchicine

In our review paper, we have evaluated the five registries of clinical trials about the role of colchicine to prevent the progression of COVID-19 infection, in high risk or hospitalized patients (NCT04326790, NCT04328480, NCT04324463, NCT04322565, NCT04322682) (Supplementary data). In all of these clinical trials, it is suggested that colchicine has anti-inflammatory effects. The first case–control study of colchicine that is reported that administration of colchicine (1 mg/day, 21 days) with the standard of care (without antiviral drugs) to 122 consecutive inpatients with COVID-19 could significantly increase the survival rate compared with 144 treated control group (84.2% vs. 63.6%) with the standard of care (hydroxychloroquine and/or intravenous dexamethasone; and/or lopinavir/ritonavir) (Scarsi et al., 2020).

Deftereos et al. published the results of the GRECCO-19 randomized clinical trial (NCT04326790) among 105 hospitalized patients with COVID-19 in 16 tertiary care hospitals in Greece. They found that patients who received colchicine (1.5 mg loading dose, 0.5 mg after 60 min, and maintenance doses of 0.5 mg/twice daily until hospital discharge or maximum 21 days) significantly had less clinical deterioration compared with the control group and the time to clinical deterioration was shorter in the control group than in the colchicine. C-reactive protein and high-sensitivity cardiac troponin levels were not a significant difference between the two groups (Deftereos et al., 2020). Although the results of the GRECCO-19 trial show the safety and efficacy of colchicine, larger and longer-term studies are needed to confirm the useful effects of it in patients with COVID-19 (Rabbani et al., 2020).

### 4.6.8 | Others

A few clinical trials are also underway on some other drugs with a different mechanism of effects against COVID-19 such as sildenafil

citrate, deferoxamine, piclidenoson, sargramostim, tetrandrine, tradipitant, eicosapentaenoic acid gastro-resistant capsules, aviptadil, PUL-042 (Pam2-ODN) (TLR 2/6/9 agonist), BLD-2660 (inhibitor of calpains 1, 2, and 9), camostat mesilate (serine protease inhibitor) (Figure 3b).

## 5 | CONCLUSION

This review aimed at summarizing some of the registries of clinical trials in *ClinicalTrials.gov* database with possible mechanisms, and novel findings of them related to COVID-19. Various treatment or prophylactic approaches are underway to treat COVID-19, including cell therapy, oxygen therapy, and ventilator support, using plasma of the convalescent patient, herbal medicines, traditional Chinese medicine, supplements, vaccine, and drugs. Hydroxychloroquine, antivirals, monoclonal antibodies, or other immunomodulatory drugs, renin-angiotensin system drugs are the most commonly registered drugs in COVID-19 clinical trials. It seems that among the various proposed therapeutic mechanisms, antiviral, anti-inflammatory, and immunomodulatory properties, have pivotal roles to combat COVID-19 disease. Our study can help future studies get on the path to finding an effective drug for COVID-19 treatment by providing ideas for similar researches. However, terminating the clinical trials and performing meta-analysis for each treatment approach is necessary.

### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

### DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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