**Immunoregulatory therapy strategies that target cytokine storms in patients with COVID-19 (Review)**

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**Abstract.** A cytokine storm is an uncontrolled, excessive immune response that contributes to the pathogenesis of coronavirus disease 2019 (COVID-19). Viral infections lead to the loss of negative feedback in immune regulation and an abnormal elevation of the levels of multiple cytokines. In COVID-19, this causes diffuse damage to alveolar functions and may culminate in multiple organ dysfunction. Immunoregulatory therapies target the cytokine storms induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, and include monoclonal antibodies, recombinant granulocyte-macrophage colony stimulating factor, interferon, mesenchymal stem cell-based therapy, thymosin, immunoglobulins and blood purification therapies. These approaches may be effective in the alleviation of COVID-19 symptoms. In this review, cytokine storms caused by SARS-CoV-2 infections are evaluated and discussed, and advances in immunoregulatory therapy strategies for patients with COVID-19 are reviewed.

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**1. Introduction**

At the end of 2019, a coronavirus pneumonia pandemic emerged in Wuhan, China (1). Subsequent genome sequencing and phylogenetic analyses revealed that this virus was a novel coronavirus. The International Committee on Taxonomy of Viruses designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the associated disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). As of August 30, 2020, there have been 24,854,140 confirmed cases of COVID-19 worldwide, including 838,924 deaths, and the disease has been listed as a public health emergency of international concern by the WHO (2). In a similar manner to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), COVID-19 presents with severe respiratory syndrome (3,4). However, researchers are currently attempting to identify treatments that suppress the transmission of SARS-CoV-2 or ameliorate the symptoms of COVID-19 (5). Considerable evidence from preclinical and clinical studies indicates that cytokine storm syndrome may be an important mechanism underlying this respiratory syndrome (6). An imbalance in immune regulation leads to an overwhelming release of cytokines, which is more harmful to the body than SARS-CoV-2 itself (7). In the present review, the progress of preclinical and clinical studies is summarized, and immunomodulatory therapies for patients with COVID-19 are reviewed and discussed.

**2. SARS-CoV-2 and COVID-19**

SARS-CoV-2 is an enveloped coronavirus that contains a single-stranded RNA genome. The particles are 50-200 nm in diameter, and comprise three envelope glycoproteins: Spike...
Several studies have identified interferon (IFN-α), interleukin (IL)-1, IL-6, IL-8, IL-12, interferon-γ (IFN-γ), and monocyte chemotactic protein-1 (MCP-1) as key cytokines in the pathogenesis of COVID-19 (18). The excessive secretion of IL-6 (>1,000 pg/ml in serum) has been associated with systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS) (14,15). The cytokine storm, also known as inflammatory storm or cytokine release syndrome, refers to the release of excessive cytokines and other inflammatory mediators that can induce systemic inflammation and organ dysfunction. This condition is often associated with critical illness, as cytokines accumulate in the blood and cause widespread tissue damage.

4. Targeted cytokine storm therapy - the fight against COVID-19

Monoclonal antibodies. The excessive secretion of IL-6 can lead to systemic inflammatory response, tissue hypoxia, hypotension, and myocardial dysfunction, resulting in MODS and disseminated intravascular coagulation (22). Additionally, IL-6 reduces the release of perforin and granzymes from natural killer (NK) cells and impairs their antiviral activity (23). During a cytokine storm, the duration of elevated IL-6 secretion is longer than that of other cytokines, suggesting that inhibition of IL-6 or its receptor (IL-6R) could be a viable therapeutic strategy during a SARS-CoV-2 infection (24,25).

A number of studies have confirmed the safety and efficacy of the anti-IL-6 antibody siltuximab, and the anti-IL-6R antibodies tocilizumab and sarilumab (25-27). To date, more than 40 clinical trials using anti-IL-6 or anti-IL-6R treatments have commenced for patients with COVID-19, including more than 30 trials using tocilizumab (Table I). This humanized monoclonal antibody inhibits IL-6R by blocking the binding of IL-6 to its receptor and inhibiting its signaling (28). In the past, tocilizumab was primarily used in the treatment of cytokine storms caused by chimeric antigen receptor T cell (CAR-T) therapy (29). In one study, the levels of IL-6, IL-8 and IL-10 were observed to be elevated to varying
Table I. Clinical trials using anti-IL6 or anti-IL-6R for COVID-19 therapy.

| Trial identifier | Title                                                                 | Phase | Interventions                                                                 | Expected completion (Accessed August 30, 2020) |
|------------------|----------------------------------------------------------------------|-------|-------------------------------------------------------------------------------|-----------------------------------------------|
| NCT04332094      | Clinical trial of combined use of hydroxychloroquine, azithromycin, and tocilizumab for the treatment of COVID-19 | 2     | Tocilizumab, hydroxychloroquine, azithromycin                                  | Oct 2020                                     |
| NCT04479358      | Low-dose tocilizumab versus standard of care in hospitalized patients with COVID-19 (COVIDOSE-2) | 2     | Tocilizumab, standard of care                                                  | Mar 1, 2021                                  |
| NCT04317092      | Tocilizumab in COVID-19 pneumonia (TOCIVID-19)                        | 2     | Tocilizumab injection                                                          | Dec 19, 2022                                 |
| NCT04332913      | Tocilizumab in COVID-19 pneumonia (TOCIVID-19)                        | Null  | Tocilizumab                                                                   | Mar 31, 2021                                 |
| NCT04377659      | Tocilizumab for prevention of respiratory failure in patients with severe COVID-19 infection | 2     | Tocilizumab                                                                   | May 1, 2021                                  |
| NCT04445272      | Clinical trial to evaluate the effectiveness and safety of tocilizumab for treating patients with COVID-19 pneumonia | 2     | Tocilizumab                                                                   | Aug 22, 2020                                 |
| NCT04359667      | Serum IL-6 and soluble IL-6 receptor in severe COVID-19 pneumonia treated with tocilizumab (UHID-COVID19) | Null  | Tocilizumab 20 mg/ml intravenous solution (ACTEMRA)                            | May 15, 2021                                 |
| NCT04345445      | Study to evaluate the efficacy and safety of tocilizumab versus corticosteroids in hospitalised COVID-19 patients with high risk of progression | 3     | Tocilizumab, methylprednisolone                                                | Oct 31, 2020                                 |
| NCT04331795      | Tocilizumab to prevent clinical decompensation in hospitalized, non-critically ill patients with COVID-19 pneumonia (COVIDOSE) | 2     | Tocilizumab                                                                   | Jun 5, 2020                                  |
| NCT04412772      | Trial of tocilizumab for treatment of severe COVID-19: ARCHITECTS (ARCHITECTS) | 3     | Tocilizumab, placebo                                                           | Dec 31, 2021                                 |
| NCT04335071      | Tocilizumab in the treatment of coronavirus induced disease (COVID-19) (CORON-ACT) | 2     | Tocilizumab, placebo                                                           | Oct 2020                                     |
| NCT04412291      | A study in patients with COVID-19 and respiratory distress not requiring mechanical ventilation, to compare standard-of-care with anakinra and tocilizumab treatment. The immunomodulation-CoV assessment (ImmCoVA) study | 2     | Anakinra prefilled syringe, tocilizumab prefilled syringe, standard-of-care treatment | Feb 2021                                     |
| NCT04346355      | Efficacy of early administration of tocilizumab in COVID-19 patients | 2     | Tocilizumab                                                                   | Jun 6, 2020                                  |
| NCT04320615      | A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA) | 3     | Tocilizumab, placebo                                                           | Jul 28, 2020                                 |
| NCT04372186      | A study to evaluate the efficacy and safety of tocilizumab in hospitalized participants with COVID-19 pneumonia (EMPACTA) | 2     | Tocilizumab                                                                   | Aug 3, 2020                                  |
| 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) | 3     | Tocilizumab injection, deferoxamine                                            | Oct 4, 2020                                  |
| NCT04409262      | A study to evaluate the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized participants with severe COVID-19 pneumonia (REMDACTA) | 3     | Remdesivir, tocilizumab, placebo                                               | Jul 31, 2020                                 |
| NCT04377750      | The use of tocilizumab in the management of patients who have severe COVID-19 with suspected pulmonary hyperinflammation | 4     | Tocilizumab                                                                   | May 8, 2021                                  |
| Trial identifier | Title                                                                 | Phase | Interventions                                                                 | Expected completion (Accessed August 30, 2020) |
|-----------------|----------------------------------------------------------------------|-------|-------------------------------------------------------------------------------|-----------------------------------------------|
| NCT04435717    | Efficacy of tocilizumab in modifying the inflammatory parameters of patients with COVID-19 (COVITOZ-01) | 2     | Tocilizumab 20 mg/ml intravenous solution (ACTEMRA) single and double doses     | Aug 4, 2020                                   |
| NCT04377503    | Tocilizumab versus methylprednisolone in the cytokine release syndrome of patients with COVID-19 | 2     | Tocilizumab 180 mg/ml, methylprednisolone sodium succinate                     | Nov 2020                                      |
| NCT04363853    | Tocilizumab treatment in patients with COVID-19                       | 2     | Tocilizumab                                                                   | Aug 1, 2021                                   |
| NCT04356937    | Efficacy of tocilizumab on patients with COVID-19                     | 3     | Tocilizumab, placebos                                                         | Aug 30, 2020                                  |
| NCT04310228    | Favipiravir combined with tocilizumab in the treatment of coronavirus disease 2019 | N/A   | Favipiravir combined with tocilizumab, favipiravir, tocilizumab               | May 2020                                      |
| NCT04306705    | Tocilizumab vs CRRT in management of cytokine release syndrome (CRS) in COVID-19 (TACOS) | Null  | Tocilizumab, standard of care, continuous renal replacement therapy            | Jun 20, 2020                                  |
| NCT04424056    | A trial using anakinra, tocilizumab alone or in association with ruxolitinib in severe stage 2 and 3 of COVID-19-associated disease | 3     | Anakinra +/- ruxolitinib, tocilizumab +/- ruxolitinib                        | Nov 1, 2022                                   |
| NCT04403685    | Safety and efficacy of tocilizumab in moderate to severe COVID-19 with inflammatory markers (TOCIBRAS) | 3     | Tocilizumab                                                                   | Aug 31, 2020                                  |
| NCT04315480    | Tocilizumab for SARS-CoV2 (COVID-19) severe pneumonitis               | 2     | Tocilizumab                                                                   | May 2020                                      |
| NCT04370834    | Tocilizumab for patients with cancer and COVID-19 disease             | 2     | Tocilizumab                                                                   | Nov 1, 2021                                   |
| NCT04476979    | Comparison of tocilizumab plus dexamethasone vs. dexamethasone for patients with COVID-19 (TOCIDEX) | 2     | Tocilizumab, dexamethasone                                                   | Dec 31, 2021                                  |
| NCT04335305    | Checkpoint blockade in COVID-19 pandemic (COPERNICO)                 | 2     | Tocilizumab, pembrolizum                                                      | Aug 30, 2020                                  |
| NCT04423042    | Tocilizumab in coronavirus-19 positive patients                       | 3     | Tocilizumab                                                                   | Jun 2021                                      |
| NCT0433914     | Prospective study in patients with advanced or metastatic cancer and SARS-CoV-2 infection (IMMUNONCOVID) | 3     | Chloroquine analog (GNS651), nivolumab, tocilizumab, standard of care, advoralimab, monalizumab | Aug 2020                                      |
| NCT04331808    | CORIMUNO-19 - tocilizumab trial - TOCI (CORIMUNO-TOCI)               | 2     | Tocilizumab                                                                   | Dec 31, 2021                                  |
| NCT04361552    | Tocilizumab for the treatment of cytokine release syndrome in patients with COVID-19 (SARS-CoV-2 infection) | 3     | Tocilizumab, best practice                                                   | Jun 2, 2020                                   |
| NCT04327388    | Sarilumab COVID-19                                                    | 3     | Sarilumab, placebo                                                           | Aug 2020                                      |
| NCT04315298    | Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19 | 2,3   | Sarilumab, placebo                                                           | Aug 31, 2020                                  |
| NCT04357808    | Efficacy of subcutaneous sarilumab in hospitalised patients with moderate-severe COVID-19 infection (SARCOV ID) | 2     | Sarilumab, standard of care                                                  | Dec 2020                                      |
Table I. Continued.

| Trial identifier | Title                                                                 | Phase | Interventions                                                                 | Expected completion (Accessed August 30, 2020) |
|------------------|----------------------------------------------------------------------|-------|-------------------------------------------------------------------------------|-------------------------------------------------|
| NCT04386239      | Study on the use of sarilumab in patients with COVID-19 infection    | 1     | Sarilumab prefilled syringe                                                   | Dec 2020                                        |
| NCT04359901      | Sarilumab for patients with moderate COVID-19 disease                 | 2     | Sarilumab                                                                     | Apr 2023                                        |
| NCT04341870      | Study of immune modulatory drugs and other treatments in COVID-19 patients: Sarilumab, azithromycin, hydroxychloroquine trial - CORIMUNO-19 - VIRO (CORIMUNO-VIRO) | 2,3   | Sarilumab, azithromycin, hydroxychloroquine                                   | Aug 2020                                        |
| NCT04357860      | Clinical trial of sarilumab in adults with COVID-19 (SARICOR)        | 2     | Sarilumab 200 mg/1.14 ml or 400 mg/2.28 ml subcutaneous solution (KEVZARA), best available treatment | Jul 27, 2020                                    |
| NCT04324073      | Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients - sarilumab Trial - CORIMUNO-19 - SARI (CORIMUNO-SARI) | 2,3   | Sarilumab                                                                     | Dec 31, 2021                                    |
| NCT04329650      | Efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID-19 pneumonia | 2     | Siltuximab, methylprednisolone                                                 | May 20, 2020                                    |
| NCT04322188      | An observational study of the use of siltuximab (SYLVANT) in patients diagnosed with COVID-19 infection who have developed serious respiratory complications (SISCO) | Null  | Null                                                                          | May 8, 2020                                     |

COVID-19, coronavirus disease 2019; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; N/A, not applicable.
degrees in four cases of CAR-T-induced cytokine storm. However, after treatment with tocilizumab, the symptoms of systemic toxicity were significantly ameliorated, the cytokine levels decreased, and the requirements for adjuvant and other therapies, including vasoactive drugs, glucocorticoids and respiratory support, were reduced (30). Tocilizumab has also been observed to attenuate the excessive production of other cytokines, namely IFN-γ, IL-10 and IL-2, and the expansion of cytotoxic T and NK cells in refractory hemophagocytic lymphohistiocytosis (31). Retrospective Chinese studies have also confirmed the positive effects of tocilizumab in severe or critical cases of COVID-19 (32,33). However, as patient numbers were low in these studies, the clinical efficacy of tocilizumab requires further testing.

Recombinant granulocyte-macrophage colony stimulating factor. Alveolar type II epithelial cells accurately regulate the production of granulocyte-macrophage colony stimulating factor (GM-CSF), which activates innate and adaptive immune responses, and improves the ability of the body to fight against viruses (34). GM-CSF also stimulates the proliferation of alveolar epithelial cells in order to repair broken lung barriers, and protect the lungs from secondary bacterial infection following viral infection (35). SARS-CoV-2 infects type II alveolar epithelial cells via the ACE2 receptor, thereby destroying pulmonary physiological barriers and leading to imbalanced GM-CSF regulation (36). A recent study showed that G-CSF levels in the peripheral blood of patients with COVID-19 were elevated, particularly those critically ill in intensive care (12). It is speculated that blocking GM-CSF or using anti-GM-CSF drugs could be a viable treatment strategy for COVID-19. Notably, in recent months, more than 10 clinical trials have been initiated using this strategy (Table II).

IFN. As a major effector cytokine of the host immune response to viral infection, IFN serves as an immunomodulator by promoting macrophage-mediated antigen phagocytosis, and mediating the clearance of infected cells by NK cells, thus limiting viral transmission. IFNs are also often used to treat viral diseases such as hepatitis B and C (37). Evidence from preclinical and clinical studies indicates that the earlier IFN production occurs after coronavirus infection, the less viral replication occurs and the lower the mortality rate (38,39). Chu et al (40) compared immune activation between the lung tissues of patients with SARS-CoV-2 and SARS-CoV infections, and found that the lungs infected with SARS-CoV-2 did not produce elevated quantities of IFNs. Therefore, it is suggested that exogenous IFN should be administered to stimulate host antiviral immunity in patients infected with SARS-CoV-2. In addition, IFN-λ has been demonstrated to reduce the risk of SARS-CoV-2 transmission and the severity of COVID-19 (41).

Mesenchymal stem cell (MSC)-based therapy. MSCs are a type of non-hematopoietic stem cell, derived from several tissues, including Wharton's jelly, umbilical cord blood, placenta, bone marrow, adipose tissue, dental pulp and menstrual blood (42). Evidence from preclinical and clinical studies has confirmed that MSCs function by promoting tissue regeneration and protecting against injury through self-renewal, multiple differentiation and paracrine functions (43,44). Importantly, MSCs also exert strong immunomodulatory functions (45). Studies have shown that these cells regulate the activation, proliferation and differentiation of NK cells, dendritic cells, B and T lymphocytes, and other immune cells, and also increase the proportion of Tregs, thus maintaining immune system stability (42,46,47). MSCs interact with immune cells, and potentially inhibit localized immune responses via the secretion of regulatory factors, including transforming growth factor β, hepatocyte growth factor and IL-10 (48). The immunomodulatory properties of MSCs have been shown to be effective in acute graft-versus-host disease (49), type 1 diabetes (50), rheumatoid arthritis (51), systemic lupus erythematosus (52), inflammatory bowel disease (53) and other immune and inflammation-associated diseases (54). The cells attenuate acute lung injury by inhibiting the infiltration of immune cells and reducing the secretion of inflammatory factors. Therefore, the immunomodulatory functions of MSCs may be effective in reducing the occurrence of cytokine storms in severe cases of COVID-19 (55). Indeed, at least 20 COVID-19 clinical trials using MSCs are ongoing (Table III). Although most preclinical studies on the immune effects of MSCs have shown benefits, further studies are required to evaluate the safety of MSC transplantation, particularly with regard to potential tumorigenic effects (56).

Thymosin. Thymosin induces T-cell differentiation, proliferation and maturation (57). In addition, it promotes the production of IL-2, thereby inducing anti-inflammatory effects (58). As an immune enhancer, thymosin is widely used in the adjuvant treatment of hepatitis (59), autoimmune diseases (60) and several types of tumors (61). The pathology report of a COVID-19 patient revealed that the numbers of CD4+ and CD8+ T cells in the peripheral blood were significantly decreased, and it was suggested that lymphopenia may be associated with severity disease and mortality (62). Therefore, thymosin may be useful in contributing to the reconstruction of effective T-cell immunity in patients with COVID-19, thereby potentially inhibiting cytokine storms. However, the safety and validity of thymosin in the treatment of COVID-19 requires investigation in clinical trials.

Immunoglobulin. Intravenous immunoglobulin (IVIG) preparations can neutralize antigens, and also regulate cytokine responses and immune cell functions. A retrospective study of 15 patients with severe sepsis reported that treatment with IgM-enriched immunoglobulins decreased endotoxin activity and ameliorated platelet loss and fibrinogen depletion (63). Another retrospective observational study evaluated the effects of IVIG in patients with bacterial or septic shocks, including 17 trials in adults and 8 in newborn infants (64). IVIG significantly reduced the mortality rates in adult sepsis, but not in neonatal sepsis. Notably, Cao et al (65) reported on three patients with severe COVID-19 who were treated with high-dose IVIG during an ARDS attack; following the treatment, their clinical conditions and associated laboratory and imaging examinations were improved, suggesting that a high-dose of IVIG in the early stages of clinical deterioration is able to prevent disease progression and improve the prognosis of COVID-19.
Table II. Clinical trials using anti-GM-CSF for COVID-19 therapy.

| Trial identifier   | Title                                                                 | Phase | Intervention                                                                 | Expected completion (Accessed August 30, 2020) |
|--------------------|----------------------------------------------------------------------|-------|------------------------------------------------------------------------------|-----------------------------------------------|
| NCT04400929        | Using GM-CSF as a host directed therapeutic against COVID-19          | 2     | Sargramostim, normal saline 0.9%                                             | June 2022                                     |
| NCT04411680        | Study of sargramostim in patients with COVID-19 (iLeukPulm)          | 2     | Sargramostim, standard of care                                               | Jan 2021                                     |
| NCT04326920        | Sargramostim in patients with acute hypoxic respiratory failure due to COVID-19 (SARPAC) | 4     | Sargramostim, control                                                        | Dec 31, 2020                                 |
| NCT04324996        | A phase I/II study of universal off-the-shelf NKG2D-ACE2 CAR-NK cells for therapy of COVID-19 | 1,2   | NK cells, IL-15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells, NKG2D-ACE2 CAR-NK cells | Sep 30, 2020                                 |
| NCT04341116        | Study of TJ003234 (anti-GM-CSF monoclonal antibody) in subjects with severe coronavirus disease 2019 (COVID-19) | 1,2   | TJ003234, placebo                                                            | Sep 2020                                     |
| NCT04386252        | Phase I-II trial of dendritic cell vaccine to prevent COVID-19 in adults | 1,2   | AV-COVID-19                                                                  | Mar 2021                                     |
| NCT04351152        | Phase 3 study to evaluate efficacy and safety of lenzilumab in patients with COVID-19 | 3     | Lenzilumab, standard of care                                                  | Sep 2020                                     |
| NCT04397497        | Mavrilimumab in severe COVID-19 pneumonia and hyper-inflammation (COMBAT-19) | 2     | Mavrilimumab, placebo                                                        | Nov 22, 2020                                 |
| NCT03348670        | Discovery stage (proof-of-concept) COVID-19 antigen presentation therapeutic biologics (COVID-19-AP) (AP-TP-Bio) | 1     | COVID-19 therapeutic vaccine - nucleocapsid-GM-CSF protein lactated Ringer's injection | Nov 10, 2020                                 |
| NCT03305341        | Proof-of-concept clinical pharmacology trial for COVID-19 antigen presentation therapeutic biologics (COV19-APTP-B) | 1     | COVID-19 therapeutic vaccine - nucleocapsid-GM-CSF protein lactated Ringer's injection | Nov 8, 2020                                 |
| NCT04351243        | A study to assess the efficacy and safety of gimsilumab in subjects with lung injury or acute respiratory distress syndrome secondary to COVID-19 (BREATHE) | 2     | Gimsilumab, placebo                                                          | Mar 2021                                     |

COVID-19, coronavirus disease 2019; GM-CSF, granulocyte-macrophage colony stimulating factor; ACE2, angiotensin-converting enzyme 2; CAR-NK, chimeric antigen receptor-natural killer; IL-15, interleukin-15.
Table III. Clinical trials using MSC-based therapy for COVID-19.

| Trial identifier   | Title                                                                                                                                                                                                 | Phase | Interventions                                                                 | Expected completion (August 30, 2020) |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------|----------------------------------------|
| NCT04377334        | Mesenchymal stem cells (MSCs) in inflammation-resolution programs of coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome (ARDS)                                                | 2     | MSCs                                                                       | Jul 2021                               |
| NCT04490486        | Umbilical cord tissue (UC) derived mesenchymal stem cells (MSCs) versus placebo to treat acute pulmonary inflammation due to COVID-19                                                                   | 1     | UC-MSCs, placebo                                                           | Jun 1, 2024                            |
| NCT04399889        | hCT-MSCs for COVID-19 ARDS                                                                                                                                                                          | 1, 2  | Human cord tissue mesenchymal stromal cells                                | July 31, 2021                          |
| NCT04444271        | Mesenchymal stem cell infusion for COVID-19 infection                                                                                                                                                  | 2     | UC-MSCs, placebo                                                           | Sep 30, 2020                           |
| NCT04355728        | Use of UC-MSCs for COVID-19 patients                                                                                                                                                                   | 1, 2  | UC-MSCs + heparin + best supportive care + vehicle + heparin + best supportive care | May 1, 2022                            |
| NCT04371393        | MSCs in COVID-19 ARDS                                                                                                                                                                                | 3     | Remestemcel-L, placebo                                                     | Apr 2022                               |
| NCT04269525        | Umbilical Cord (UC)-derived mesenchymal stem cells (MSCs) treatment for the 2019-novel coronavirus (nCoV) pneumonia                                                                                 | 2     | UC-MSCs                                                                   | Dec 30, 2020                           |
| NCT04457609        | Administration of allogenic UC-MSCs as adjuvant therapy for critically-ill COVID-19 patients                                                                                                            | 1     | Oseltamivir, azithromycin, UC-MSCs                                      | Sep 2020                               |
| NCT04467047        | Safety and feasibility of allogenic MSC in the treatment of COVID-19                                                                                                                                  | 1     | Mesenchymal stromal cells infusion                                         | Dec 30, 2020                           |
| NCT04366830        | Intermediate-size expanded access program (EAP), mesenchymal stromal cells (MSC) for acute respiratory distress syndrome (ARDS) due to COVID-19 infection                                                                 | Null  | Remestemcel-L                                                             | Null                                   |
| NCT04456439        | Intermediate-size expanded access program (EAP), mesenchymal stromal cells (MSC) for multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19)                                                   | Null  | Remestemcel-L, hydrocortisone, diphenhydramine                           | Null                                   |
| NCT04397796        | Study of the safety of Therapeutic Tx with immunomodulatory MSC in adults with COVID-19 infection requiring mechanical ventilation                                                                  | 1     | BM-Allo.MSC, placebo                                                      | Jun 2021                               |
| NCT04452097        | Use of hUC-MSC product (BX-U001) for the treatment of COVID-19 with ARDS                                                                                                                               | 1     | Human UC-MSCs + best supportive care                                      | Dec 31, 2021                           |
| NCT04390139        | Efficacy and safety evaluation of mesenchymal stem cells for the treatment of patients with respiratory distress due to COVID-1 (COVIDM3ES)                                                                 | 1, 2  | XCEL-UMC-BETA, placebo                                                   | Dec 2020                               |
| NCT04313322        | Treatment of COVID-19 patients using Wharton's jelly-mesenchymal stem cells                                                                                                                            | 1     | WJ-MSCs                                                                   | Sep 30, 2020                           |
| NCT04397471        | A study to collect bone marrow for process development and production of BM-MSC to treat severe COVID19 pneumonitis (COMET20d)                                                                        | Null  | Bone marrow harvest                                                       | Dec 2021                               |
Blood purification therapy. A newly developed, non-specific, broad-spectrum blood purification therapy may also have applications in the targeting of cytokine storms during COVID-19 infections. Hemodialysis, hemofiltration, plasma exchange and hemoperfusion are four classical blood purification techniques used to combat drug poisoning, renal failure, multiple organ failure and septicemia (66). A retrospective Chinese study evaluated three patients who were diagnosed with severe or critical COVID-19 and treated with plasma exchange (67). The rate of plasma separation and infusion was 25-30 ml/min, and the volume of each plasma exchange was 2,600-3,000 ml (67). The authors reported that this therapy significantly decreased C-reactive protein and IL-6 levels, and improved lymphocyte and prothrombin times, suggesting that it is a viable treatment for patients with severe COVID-19. However, a prospective observational study evaluated the efficacy of blood purification in 9 patients with sepsis/septic shock (68). After blood purification treatment, except for the plasma levels of IL-8 decrease, the level of other cytokines did not vary significantly, such as TNF-α, IL-1β, IL-6 and IL10 (68). Therefore, further investigations are required to explore the clinical benefits of blood purification for cytokine storms induced by SARS-CoV-2 infection. Similarly, other factors for this therapy, such as the appropriate model, timing, course and frequency of treatment require investigation.

Others. During coronavirus-mediated pneumonia, the massive release of cytokines is an imbalanced antiviral immune response that can lead to life-threatening ARDS. Glucocorticoids exert anti-inflammatory, anti-toxic, anti-allergic and anti-shock effects (69,70). A morbidly obese COVID-19 patient with urticaria and angioedema was successfully treated with glucocorticoids (70). However, long-term and high-dose use of glucocorticoid can cause secondary infection, osteonecrosis, diabetes and hypertension (71). Therefore, the timing of administration, dosage and treatment course require extensive clinical exploration.

The glycoproteins of coronavirus facilitate viral entry into target cells by binding to receptors and by driving fusion of viral and host cell membranes. However, the host cell protease activity determines the efficiency of glycoprotein synthesis (72). A recent study used a panel of cell lines to verify that ACE2 and transmembrane protease serine 2 (TMPRSS2) proteins are required for the infection of cells by SARS-CoV-2, similarly to SARS-CoV infection (73). TMPRSS2 inhibitors blocked the entry of SARS-CoV-2 into the cells, and thus displayed potential as antiviral inhibitors. Indeed, camostat mesylate, a serine protease inhibitor that inhibits TMPRSS2 protease activity, is widely used in Japan to alleviate acute inflammation during chronic pancreatitis (74). Therefore, this protease inhibitor may have therapeutic potential for the treatment of patients with COVID-19.

5. Conclusion and perspectives

The pathogenesis of COVID-19 resembles a prolonged battle between the virus and the immune system. When confronted by viral infection, the immune system must recognize and clear the virus in a timely manner. However, imbalanced and excessive immune responses may result
in the excessive expression of inflammatory cytokines. Furthermore, these locally maladjusted immune responses may damage the oxygenation functions of the lungs, potentially resulting in MODS. Therefore, it is surmised that the excessive release of inflammatory cytokines may lead to severe COVID-19.

Antiviral, anti-inflammatory and organ-supporting therapies are considered to be the primary treatment strategies for patients with COVID-19. Antiviral therapies require antiviral drugs and vaccines; however, drug and vaccine development and preparation are challenging to achieve in the short term. Organ support therapy is an effective therapy in the treatment of severe COVID-19 patients with respiratory failure or ARDS (75,76). However, in the context of the COVID-19 pandemic, organ support therapy may not be a widely used treatment due to the resource constraints and availability problems (77). Currently, a plethora of experimental and conventional drugs are actively undergoing clinical trials for the treatment and prevention of COVID-19. Some of these drugs exert therapeutic efficacies that are associated with regulation of the immune system. In addition, since MSCs have an immunosuppressive effect, and associated clinical trial data have shown significant therapeutic efficacy in severe cases of COVID-19 (78-80), MSC-based therapy could be a promising strategy for the reduction of inflammatory cytokine release in these patients. Therefore, we hypothesize that immunoregulatory therapy is currently the most promising treatment for severe COVID-19, especially for the elderly patients or those with underlying diseases. However, the stage during the development of COVID-19 at which cytokine storms occur, and the incidence and mortality rates of patients who experience cytokine storms are not yet known. Therefore, evidence from immunoregulatory preclinical and clinical studies is required for further verification.

It must be noted that the key to solving the SARS-COV-2 pandemic is the emergence of a vaccine. The research community must continue to comprehensively explore immune response mechanisms in the pathogenesis of COVID-19, in order to clarify relevant targets and signaling pathways. In adopting this approach, the promotion and advancement of novel therapeutic drugs and vaccines is likely to occur, providing a solid scientific foundation for the clinical diagnosis and treatment of COVID-19.

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Authors’ contributions

XW wrote the original draft, edited and critically revised the manuscript. XZ and ZH contributed substantially to the writing of the manuscript, and critically revised and edited the manuscript. All authors substantially contributed to the conception, writing and revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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