Treatment of COVID-19 by stage: any space left for mesenchymal stem cell therapy?

Abstract

In many countries, COVID-19 now accounts for more deaths per year than car accidents and even the deadliest wars. Combating the viral pandemics requires a coordinated effort to develop therapeutic protocols adaptable to the disease severity. In this review article, we summarize a graded approach aiming to shield cells from SARS-CoV-2 entry and infection, inhibit excess inflammation and evasion of the immune response, and ultimately prevent systemic organ failure. Moreover, we focus on mesenchymal stem cell therapy, which has shown safety and efficacy as a treatment of inflammatory and immune diseases. The cell therapy approach is now repurposed in patients with severe COVID-19. Numerous trials of mesenchymal stem cell therapy are ongoing, especially in China and the US. Leader companies in cell therapy have also started controlled trials utilizing their quality assessed cell products. Results are too premature to reach definitive conclusions.

Keywords: Coronavirus, infection, vascular cells, epithelial cells, mesenchymal stem cells, acute respiratory distress syndrome, cytokine storm.

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Text

1. Epidemiology and emergence of new variants

In late 2019, infection with a novel betacoronavirus, subsequently termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was reported in Wuhan, China, where live animals were sold. Since then, the rapid spread of the virus has led to a global pandemic of coronavirus disease 2019 (COVID-19). As of 3 February 2021, over 103 million cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including 2.24 million deaths. Severe lung disease, characterized by "acute respiratory distress syndrome" (ARDS), and multiorgan dysfunction with disseminated intravascular coagulation (DIC) represent the most severe complications.[1] Myocardial injury is present in more than a quarter of critical cases, manifesting either acutely on presentation or more insidiously as illness severity intensifies.[2-4] Moreover, COVID-19 shows a strong age gradient in the risk of death.[5] The long-term health consequences of COVID-19 remain largely unclear. A recent cohort study of 1733 patients with confirmed COVID-19, who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7 and May 29, 2020, showed the frequent persistence of fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severe disease during hospitalization had functional and radiographic evidence of pulmonary alterations.[6]

Multiple variants of the virus that causes COVID-19 are circulating globally. The UK B.1.1.7 variant appeared in the fall of 2020, spreading more easily and quickly than other variants.[7] In January 2021, preliminary evidence was provided that this variant may be also associated with an increased risk of death, but more studies are needed to confirm this finding.[8] The South African 501Y.V2 variant emerged in Nelson Mandela Bay metropolitan area in early October 2020, then spread quickly to become the predominant virus lineage in the Eastern and Western Cape Provinces by the end of November 2020. Cases caused by this variant were reported in the US and UK at the end of January 2021.[9] In early January 2021, a variant called P.1 was discovered during routine screenings at an airport in Japan on passengers from Brazil [10]. This variant contains a set of additional mutations that may compromise the recognition by antibodies.

2. Clinical presentation

COVID-19 can present a variety of manifestations ranging from asymptomatic infection to critical disease (reviewed in [11-13]).

Although no precise guidelines exist to define grade severity, mild disease is diagnosed as a condition characterized by fever, cough, sore throat, and myalgias. Some patients have gastrointestinal symptoms, including nausea, and diarrhea,[14] Anosmia and ageusia were initially not considered but were then realized to manifest in more than 60% of patients, being more frequent in women.[15]

Patients with moderate disease may suffer shortness of breath, presenting 5 to 8 days after initial symptom onset, as the first indication of a worsening state. [16]

Chest radiography confirms lower respiratory tract disease but with a blood oxygen saturation of 94% or higher while the patient is breathing ambient air.

Severe disease is characterized by tachypnea, oxygen saturation, ≤93%, and radiographic evidence of lung infiltrates in >50% of the lung field involved within 24 to 48 hours.[17]

The definition criteria for critical COVID-19 include respiratory rate ≥30 times/min, pulse oxygen saturation at rest ≤93%, the partial pressure of PaO2/FiO2 ≤ 300 mmHg, a requirement for mechanical ventilation and shock. [18]

ARDS is the main cause of poor prognosis in critically ill patients,[19] manifesting in 42% of those with pneumonia, and 61–81% of those requiring intensive care.[20] Classically, ARDS is defined by the following criteria (i) acute hypoxemic respiratory failure; (ii) presentation within 1 week of worsening respiratory symptoms; (iii) bilateral airspace disease on chest x-ray, computed tomography, or ultrasound that is not fully explained by effusions, lobar or lung collapse, or nodules; and (iv) cardiac failure.[21] Anatomically, there is a damage to the pulmonary capillary endothelium and alveolar epithelium, leading to inflammatory exudate in the alveoli, and pulmonary edema. An important feature of COVID-19-associated ARDS is the occurrence of increased thrombotic and microvascular complications. Several studies have assessed the circulating and alveolar levels of markers associated with endothelial damage and platelet activation in critically and non-critically ill patients. [22-24] High levels of fibrin degradation products, D-dimer, soluble thrombomodulin, von Willebrand factor, and plasminogen activator inhibitor-1, and decreased C protein were found in critical patients compared with non-critical patients.[25] Mortality was significantly correlated with von Willebrand factor and soluble thrombomodulin among all patients, while high soluble thrombomodulin concentrations were associated with lower rates of hospital discharge and a lower likelihood of survival.[25] These data support the view that the early identification and treatment of endotheliopathy could improve outcomes in patients with COVID-19.

Altogether these clinical pieces of evidence support the adoption of graded, combinatory therapeutic protocols to control the evolution of symptoms. [26] In the next sections, we summarize the key pathogenic mechanisms providing a rationale for targeted therapies (**Figure 1**). We also focus on the rationale for using mesenchymal stem cell (MSC) therapy, illustrating the current landscape of ongoing clinical trials.

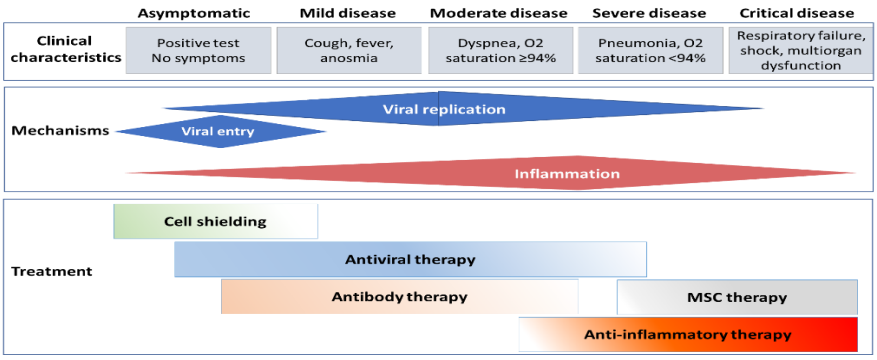

Figure 1. Treatment protocol according to the disease stage and target. The upper part identifies clinical signs of disease progression. The middle part shows the virus-intrinsic and host-related mechanisms. The lower part shows the graded approach.

2.1. Mechanisms of infection

Coronavirus particles consist of a helical structure, formed by the association between nucleocapsid (N) phosphoproteins and the viral genomic RNA, which is surrounded by a lipid bilayer where three or four types of structural proteins are inserted: the spike (S), the membrane (M), and the envelope (E) proteins and, for some coronaviruses only, the hemagglutinin-esterase (HE) protein.[27] While the M and E proteins are involved in viral assembly, the S protein is the leading mediator of viral entry following processing by host cell proteases, such as the serine protease transmembrane protease serine 2 (TMPRSS2),[28] and subsequent binding to cellular receptors.[29] SARS-CoV-2 receptors are classified as entry receptors, some being expressed by different host cells but others exclusively by a specific cell population, and attachment receptors.

SARS-CoV-2 infects the respiratory tract by adhering to components of the airway's epithelia, namely the carbohydrate chains of proteoglycans and glycosphingolipids, and then engaging with often multiple, cellular entry receptors.[30] By disrupting the multi-layered pulmonary barrier formed by epithelial cells, endothelial cells, and pericytes, SARS-CoV-2 can spread through the circulation and infect/damage other organs, including the heart.[31, 32]

3. Anchor receptors

The first target for therapy of COVID-19 is shielding epithelial and endothelial cells from the virus contact. The SARS-CoV-2 anchor receptor heparan sulfate proteoglycan (HSPG), which is ubiquitously expressed within the proteoglycan-rich glycocalyx layer on the cell surface, allows the virus to make primary contact with permissive cells.[33]

An association between the HSPG Syndecan-1 and the CD147 entry receptor is reportedly essential for cyclophilin B-induced activation of p44/42 mitogen-activated protein kinases and promotion of cell adhesion and chemotaxis.[34] Evidence indicates that there are heparin-binding sites both within and outside of the receptor-binding domain (RBD) on S-protein.[35, 36] Heparan sulfate binding sites are thought to reduce the specificity of the receptor required for cell entry. Moreover, attachment of SARS-CoV-2 to HSPG may stabilize the open conformation of the S protein, thereby promoting binding to the angiotensin-converting enzyme 2 (ACE2), which can only occur in the open conformation.[36, 37]

3.1 Inhibition of the virus anchoring

Medications directed at HSPG may be valuable as a potential treatment for COVID-19.[38] Heparin has recently been shown to block SARS-CoV-2 infection of permissible cells by inducing conformational changes of the S protein and competing with HSPG anchors.[39-44] Heparin is an anticoagulant that leads to bleeding risk in patients.[45] Therefore, researchers are focusing on safer HSPG competitors.

Lactoferrin is an 80-kDa iron-binding glycoprotein of the transferrin family, found in secretions such as milk, sputum, lung surfactant, and present in neutrophil granules. It is used for treating stomach and intestinal ulcers and diarrhea and has broad antiviral properties. [46-49] Interestingly, lactoferrin has been shown to protect against SARS-CoV infection by blocking the S protein heparin-binding domains to a similar degree as heparin, without showing the anti-coagulant adverse effects.[50] *In vitro* studies, showed that lactoferrin can inhibit viral infection in the early stages and

is effective against SARS-CoV-2 in the post-infection phase. Furthermore, lactoferrin possesses immunomodulatory and anti-inflammatory effects [51] Considering the protein is available as a supplement, this would be an easy option to administer within the community and may be specifically suited to those in care homes. A recent trial of oral and intranasal administration of lactoferrin was conducted in 32 COVID-19 patients with mild to moderate symptoms.[52] The goal was to test the efficacy in improving symptoms and eliminating the virus. A dose of 1 gram of liposomal apo-lactoferrin in 10 capsules per day was administered orally for 30 days, in addition to the same form administered nasally 3 times per day. All patients showed improvement in symptoms except fatigue, which continued in about a third of the group. Of note, the authors reported a decrease in D-dimer concentration, which is a biomarker of the severe outcome.

4. Conventional and unconventional entry receptors

The widely expressed SARS-CoV-2 receptor, ACE2, belongs to a family of dipeptidyl carboxydipeptidases and has considerable homology to ACE.[53] Both enzymes are located on the plasma membranes of various cell types, including epithelial cells of the lung, vascular endothelial cells, and pericytes, and their balance is essential to the maintenance of epithelial-vascular homeostasis.[54, 55]

ACE generates the vasoconstrictor and profibrotic angiotensin II (Ang II) and degrades vasodilator bradykinin (BK) into the pro-inflammatory metabolite [des-Arg^9] BK. Conversely, ACE2 cleaves Ang II into the vasodilator Ang 1-7 peptide and degrades the ACE-generated [des-Arg^9] BK peptide. The binding of SARS-CoV-2 S protein to ACE2 is detrimental in two ways, by allowing the virus to enter the cell and by causing ACE2 internalization/degradation, leaving the ACE-related peptide pathway unopposed and [des-Arg9] BK undegraded. The ensuing damage of the pulmonary epithelial-vascular barrier manifests in the form of vascular extravasation, lung congestion, and typical acute respiratory syndrome as well as the systemic spread of the virus. Therefore, ACE2 has been considered a pivotal target for treatment.

Basigin/CD147, a plasma membrane protein associated with oligomannosidic glycans, has emerged as a novel receptor for SARS-CoV-2.[56] It was found initially to be expressed in both lung epithelium and in immune cells,[57] although, interestingly, in CD147-transfected HEK 293 cells, the S protein was not shown to bind.[58] The binding of S protein to CD147 may necessitate the recruitment of coreceptors present in the cells that constitutively express CD147. The best characterized binding partners of CD147 are monocarboxylate transporters (a family of molecules involved in lactate, pyruvate, and ketone flux across the plasma membrane), caveolin-1, CD98, β1 integrin, and CD44 (a major receptor for hyaluronan). [59]

4.1 Inhibition of the virus entry receptors, processing protease, and downstream mechanisms

Recombinant ACE2 has been used as a virus interceptor to reduce the SARS-CoV-2 infection in cardiovascular organoids[60] and is now investigated in a pilot trial as a treatment for patients with severe COVID-19 (clinical trials.gov#NCT04287686). ACE2 blocking antibodies have been also proposed as a treatment.[61] Nonetheless, ACE2-

based approaches could be insufficient because of the ability of SARS-CoV-2 to use alternative pathways to enter human cells.

An open-label, clinical trial of Meplazumab – a humanized monoclonal antibody against the CD147 receptor- showed clinical improvements in COVID-19 patients.[62] Potent individual antibodies that simultaneously bind the receptor-binding domain of the S protein provide an ideal solution to decrease the potential for virus escape mutants arising due to the selective pressure from a single-antibody administration or vaccination.[63, 64]

Combinatory blocking strategies may be considered, after the assessment of efficacy with a single blockade Weinreich et al. reported the interim results of a trial in patients with early infection, combining two monoclonal antibodies, Casirivimab and Imdevimab (together called REGN-COV2), raised against the S protein.[65] The patients were randomly assigned in a 1:1:1 ratio to receive a single intravenous infusion of either 2.4 g or 8 g of REGN-COV2 or placebo. In the first 275 patients, those who received either dose of REGN-COV2 had lower SARS-CoV-2 RNA levels than those who received placebo. A small number of patients (12) required a medically attended visit within the 29-day follow-up period, with a larger percentage in the placebo group. The U.S. Food and Drug Administration has issued an emergency use authorization for REGN-COV2 to be administered for the treatment of mild to moderate COVID-19 in adults and pediatric patients.

Another trial conducted by Chen et al.,[65, 66] evaluated three doses (700 mg, 2800 mg, and 7000 mg) of a single monoclonal antibody, bamlanivimab (LY-CoV555),5 which was administered to 452 outpatients. Bamlanivimab was associated with a greater reduction in symptoms of COVID-19 than was placebo. An extension of the clinical trial is enrolling patients who will receive a combination of bamlanivimab and etesevimab (LY3832479) to overcome or prevent antibody resistance (ClinicalTrials.gov number, NCT04427501).

Broadly neutralizing antibodies (bnAbs) represent an attractive opportunity for therapeutic drug stockpiling to prevent or mitigate future outbreaks of SARS-related CoVs. An important study used a directed evolution approach to engineer three SARS-CoV-2 antibodies for enhanced neutralization breadth and potency. The variant ADG-2 showed a strong binding activity to a large panel of sarbecovirus RBDs and neutralized representative epidemic sarbecoviruses with high potency. [67] Operation Warp Speed and the National Institutes of Health have the plan to compare several antibodies for treatment in their ACTIV-2 trial involving outpatients with COVID-19 (NCT04518410).

The protease inhibitors lopinavir, ritonavir, and camostat mesylate have been used with the aim to block the activation of S protein by inhibiting the protease TMPRSS2. In order to promote the clinical use of these potential drugs, the World Health Organization and the European Union have promoted new clinical trials testing the efficacy of drug associations including protease inhibitors, such as the SOLIDARITY Trial (NCT04321616) and the DisCoVeRy Trial (NCT04315948).

A fascinating feature of SARS-CoV-2 is that it could use the S protein not only as a passe-partout to enter cells but also as a signaling ligand to activate intracellular pathways, ERK1/2 among the others, instrumental to replication and evasion of host's

defense. Blocking the S protein with available antibodies or interfering with ERK1/2 with inhibitors could be viable ways to suppress the initial steps of cell damage.[68] In line with this, pharmacological inhibition of ERK1/2 or gene knockdown using small interfering RNAs suppressed coronavirus replication. [68, 69] We presented *in vitro* evidence that the S protein alone can elicit functional alterations in pericytes from the human heart, reducing their angiogenic activity and inducing the secretion of pro-inflammatory and pro-apoptotic factors. These adverse phenomena could be mediated by the S protein interaction with CD147, as neutralization of this receptor by a blocking antibody prevented them.[70] Therefore, the use of receptor entry blocker may exert multiple benefits, reducing the intracellular viral load, viral replication, and dampening early inflammatory response. Interventions that block COVID-19 at the early stage could significantly reduce morbidity and mortality, the number of hospitalizations, and the burden on health care systems.[71]

5. Viral replication

Coronaviruses express and replicate their genomic RNA to produce full-length copies that are incorporated into new viral particles. (reviewed in[72]) Coronaviruses possess remarkably large RNA genomes that contain cis-acting secondary RNA structures essential for RNA synthesis. At the 5′ end, two large open reading frames (ORFs; ORF1a and ORF1b) occupy a large part of the capped and polyadenylated genome. ORF1a and ORF1b encode non-structural proteins that are instrumental for viral replication and the transcription complex that includes RNA-processing and RNA-modifying enzymes and an RNA proofreading function necessary for maintaining the integrity of the coronavirus genome.

5.1. Antiviral therapy

Because viral replication is active early during COVID-19, antiviral therapy may exert the greatest benefit before the disease progresses into the hyper-inflammatory state of severe disease. Remdesivir, an inhibitor of the viral RNA-dependent, RNA polymerase was identified as a promising therapeutic candidate for COVID-19 because of its ability to inhibit SARS-CoV-2 in vitro.[73] Moreover, the drug reduced lung virus levels and lung damage in nonhuman primate studies after inoculation with MERS-CoV1.[74] Currently, remdesivir is the only Food and Drug Administration-approved antiviral drug for the treatment of COVID-19. A double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection was superior to placebo in shortening the time to recovery.[75]

Hydroxychloroquine has antiviral effects *in vitro*, and, in association with azithromycin, seemingly decreased SARS-CoV-2 viral load in a small, nonrandomized study.[76] However, a randomized trial of 504 patients with mild-to-moderate COVID-19 demonstrated that the use of hydroxychloroquine, alone or with azithromycin, did not improve the clinical status as compared with standard care.[77] Therefore, the current guidelines recommend against the use of this treatment.

5.2. Antibiotics

Emerging data regarding bacterial superinfections in COVID-19 pneumonia suggest an association between the detection of bacterial products in blood and disease

severity.[78] Broad-spectrum antibiotics are indicated in these patients with COVID-19 with suspected or confirmed bacterial superinfection.[79]

6. Inflammation and immune response

The host immune response SARS-CoV-2 has been a subject of intense investigation. (reviewed in [80, 81]) The humoral response involves the characteristic IgG and IgM production, starting with antibodies against the high immunogenic N protein, while anti-S protein antibodies could be detected after 4–8 days from the appearance of initial symptoms.[82] It was reported that a robust antibody response may be associated with disease severity while a weak response is associated with the elimination of the virus.[83]

SARS-CoV-2 infection impairs interferon responses and suppresses antigen presentation on both MHC class I and class II, thereby evading the innate immune cells response.[84] The infiltration of monocytes/macrophages, neutrophils, and adaptive immune cells leads to increased pro-inflammatory cytokines.[85] A decrease in the innate antiviral response together with hyper-inflammation, and dysfunction of effector and regulatory T cells characterize the immune profile of patients with severe COVID-19 [86, 87] However, there are also arguments about the concept of COVID-19-related cytokine storm syndrome (COVID-CSS). [88, 89] These criticisms argue that the definition of COVID-CSS is vague, levels of IL-6 (a hallmark of the syndrome) are often low, and some COVID-19 patients have a hypo-inflammatory vasculopathy rather than a hyper-inflammatory hyper-cytokinaemia syndrome. [90] In order to reconcile these disparities and guide therapeutic decisions, the following criteria have been proposed to identify patients with COVID-CSS: 1) pneumonia requiring mechanical ventilation; 2) fever (maximum temperature >38°C); 3) CRP >100 mg·L−1; and 4) peak serum ferritin >1000 μg·L−1.[91] Patients meeting these criteria had also markedly elevated research serum IL-6 levels, although not always correlated with CRP or ferritin. [92]

6.1. Convalescent plasma

Convalescent plasma has been used for the treatment of infectious diseases for more than a century, the rationale being that passive immunization can help to limit the disease severity. To date, it is considered the standard treatment of Argentine hemorrhagic fever, but conclusive data in SARS, Middle East respiratory syndrome, influenza A (H1N1), avian influenza (H5N1), Ebola, and eventually COVID-19 are lacking. A trial of 228 patients with severe COVID-19 showed no significant differences in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.[93] Similar conclusions were reached in another trial where the convalescent plasma was administered to patients with moderate COVID-19 to halt the progression to severe disease.[94] In January 2021, the RECOVERY trial (NCT04381936) independent Data Monitoring Committee announced that the study investigating the potential benefits of receiving convalescent plasma has stopped assigning people to receive this treatment after an early analysis showed that overall it did not help to reduce deaths. They also decided to continue the recruitment to the tocilizumab treatment arm, and to the other ongoing comparisons - aspirin, colchicine, and Regeneron's antibody cocktail.

6.2. Cytokine inhibitors

The recognition of a state of hyper-cytokinaemia in severe COVID-19 represents a rationale for immunomodulatory and cytokine-inhibitor therapy.[95]

The COVACTA RCT (NCT04320615) compared tocilizumab, a humanized monoclonal antibody that blocks interleukin 6 from binding to receptors, and placebo in COVID-19 reported no difference in the primary outcomes (clinical status and mortality), although a post hoc sub-analysis of patients requiring high flow oxygen by nasal cannula showed an improved clinical status at day 14.[96]

The EMPACTA (Evaluating Minority Patients with Actemra, NCT04372186.) placebo-controlled trial demonstrated that tocilizumab could reduce the risk of progression to mechanical ventilation or death among patients receiving low flow oxygen, but again the active treatment did not improve 28-day survival.[97]

The REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia, NCT02735707) trial found tocilizumab was effective in decreasing in-hospital mortality compared with standard care (28% v 35.8%, adjusted odds ratio for survival 1.64, 95% confidence interval 1.14 to 2.35) and progression to intubation, extracorporeal membrane oxygenation, or death. [98]

Conversely, Vega et al. reported an increased death rate at day 15 in patients treated with tocilizumab compared to placebo (17% v 3%, odds ratio 6.42, 95% confidence interval 1.59 to 43.2), a result that required an early stop of the trial.[99] The reasons for these different outcomes remain unknown.

Altogether, the results of recent trials remain contradictory, possibly because of the wide heterogeneity of inflammatory markers and difficulty to decipher the patient's phenotype that may benefit from immunomodulation.

6.3. Corticosteroids

Corticosteroids such as dexamethasone (DXM) have been proposed as a potential means to control the complications associated with the cytokine storm.

In the RECOVERY trial, [100] DXM reduced the incidence of death in the group of patients receiving invasive mechanical ventilation (29.3% vs. 41.4% in controls) and to a lesser extent in those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2% in controls). The data also indicated that DXM might increase mortality in hospitalized patients who were not receiving oxygen.[100]

A meta-analysis of clinical trials of DXM in patients with severe COVID-19 confirmed that the active treatment with corticosteroids was associated with lower 28-day all-cause mortality compared with usual care or placebo.[101] This meta-analysis comprises pooled data from seven randomized clinical trials of corticosteroids in critically ill patients with COVID-19. The reported mortality was 32.7% in the corticosteroids group and 41.5%. The results were heavily affected by the RECOVERY trial, whose participants represented 59% of total trialed subjects who were included in the meta-analysis.

These landmark trials have informed subsequent practice guidelines for hospitalized patients on supplemental oxygen or mechanical ventilation.[102] Nonetheless, a significant number of patients were unresponsive to DXM and serious adverse events were reported in 6 of the 7 trials of the above meta-analysis, occurring

in 18.1% of the patients randomized to corticosteroids and in 23.4% of the patients randomized to usual care or placebo. [101]

There are also concerns that, by hindering B cell-mediated antibody production and interfering with the protective function of T cells and macrophage-mediated clearance of apoptotic cells, DXM treatment can result in a higher plasma viral load and an increased risk of secondary infections.[103, 104] Therefore, additional therapeutic approaches should be considered for the treatment of patients with severe COVID-19. For instance, it was suggested that future studies may include remdesivir, which was not part of the RECOVERY trial.[105]

6.4. Mesenchymal stem cells

The term MSC was officially introduced more than 25 years ago to represent a class of cells from human and mammalian bone marrow and periosteum, that could be isolated and expanded in culture while maintaining the capacity of multilineage differentiation.[106, 107] This minimal definition, however, does not reflect the diversity and functional pleiotropism of different MSC populations. MSCs from the stroma of different tissues, like the BM, adipose tissue, and the perivascular niche of solid organs, may share a common antigenic phenotype but are also characterized by heterogeneous profiles.[108]

6.4.1. Previous therapeutic applications of MSCs

More than 1050 clinical trials are registered at FDA.gov that explore MSCs for many clinical applications, including neurodegenerative and cardiac disorders, perianal fistulas, Crohn's disease, graft-versus-host disease, diabetic nephropathy, and organ fibrosis.

About 300 clinical trials using MSCs have been completed as of 2020. Results suggest that the benefit is heterogeneous depending on the modality and purity of the cell preparation and the characteristics of target pathology. The TiGenix/Takeda phase 3 clinical trial studying the use of an MSC product (Alofisel) for complex perianal fistulas in patients with Crohn's disease represents the most successful late-stage MSC trial to date (NCT01541579).[109] In addition to Alofisel, there are 10 globally approved MSC therapies with various indications including cardiovascular disease. (reviewed in [110]) Systematic meta-analyses of trials conducted in patients with myocardial infarction and chronic heart failure showed MSC therapy may improve ventricular function but does not reduce mortality. [111, 112]

6.4.2. Immunological properties and entry receptor expression

The benefit of MSC-based therapies can be reconducted to the paracrine induction of cell repair and the rebalancing of immune cell response in injured or inflamed tissues. Recent review articles have summarized the latest research in the immunological properties of MSCs, their use as immunomodulatory/anti-inflammatory/anti-microbial agents, methods to customize their immunological profile, and their use as vehicles for transferring therapeutic agents.[113, 114]

Figure 2 illustrates key features of the MSCs' capacity to modulate innate and adaptive immunity (also reviewed in [115]). Moreover, MSCs can enhance pathogen engulfment by endocytosis and phagocytosis by macrophages [116] as well as improving killing ability in most of these cells. Another important point is the MSC-

induced enhancement of efferocytosis of apoptotic or infected cells, which would be extremely important during infection.[117]

Noteworthy, another advantage of MSCs is that they do not express the ACE-2 receptor and the priming enzyme that allow SARS-CoV-2 engagement and entry.[118] Cultured MSCs from different tissues were exposed to SARS-CoV-2 wild strain without evidence of cytopathic effects; moreover, under *in vitro* challenges with the virus, the conditioned medium did not contain viral particles. [118] The lack of ACE2 and TMPRSS expression was also interpreted as a key element for the reported clinical success of an MSC therapy trial, described in more detail below, in 7 patients with COVID-19 pneumonia.[119] Yet, it should be noted that no direct evidence has been provided so far that MSCs are resistant to infection or maintain an intact functional activity when challenged with the infectious agent in the patient's body.

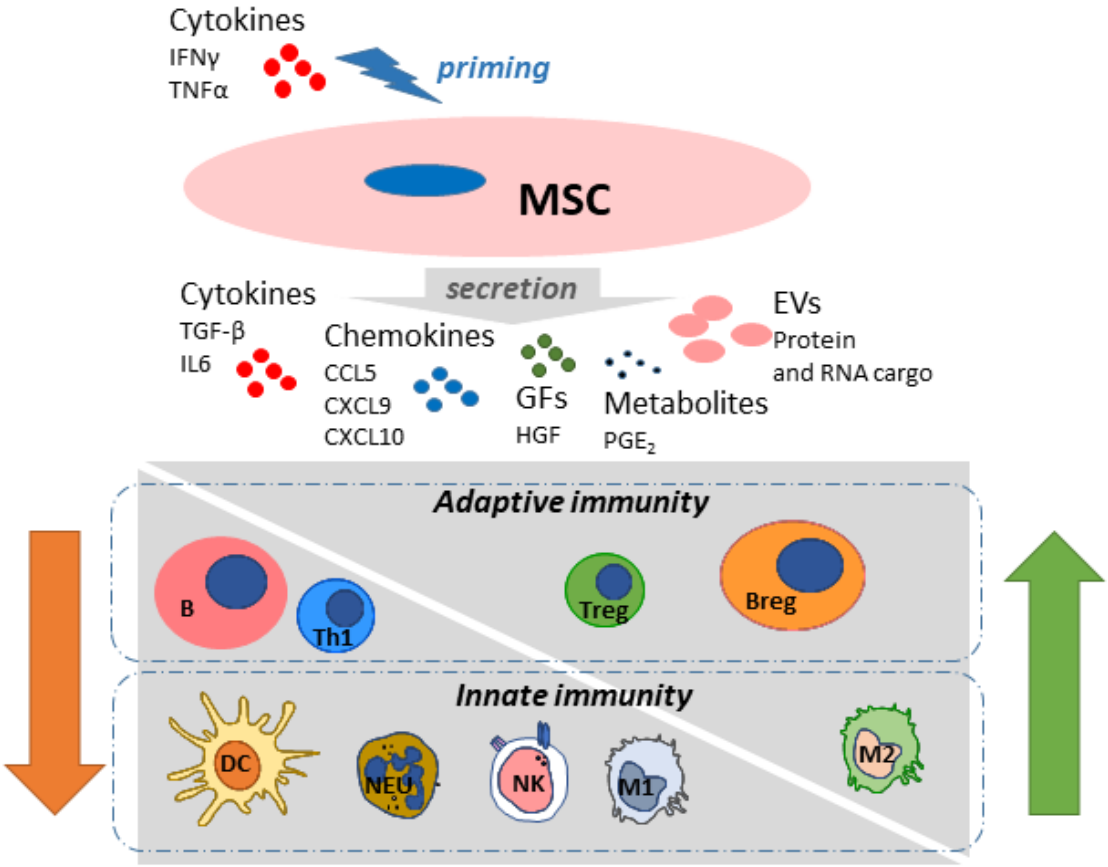

Figure 2. MSCs modulate both innate and adaptive immune cells. MSCs directly regulate immune cells and this regulation can be influenced by the inflammatory milieu of the host tissue. The immunoregulatory activity of MSCs is exerted mainly *via* paracrine recruitment and activation of cells from both the innate and adaptive immune systems. Innate: inhibition of neutrophils (NEU) and dendritic cells (DC) proliferation, natural killer (NK) proliferation and cytotoxic activity, facilitation of monocytes and macrophages M1-M2 transition. Adaptive: inhibition of T helper (Th) 1 and Th17 and promotion of Treg production, inhibition of B cells via the regulatory Breg. Moreover, MSCs have an additional indirect influence on T and B cells. EVs: extracellular vesicles, IFNγ: Interferon-gamma, TNFα: tumor necrosis factor-alpha, TGF-β transforming growth factor-beta, IL6: interleukin 6, HGF: hepatocyte growth factor, PGE2: prostaglandin E2, CCL5: CC chemokine ligand 5, CXCL10 and 11: CXC chemokine ligand 10 and 11.

6.4.3. Preclinical studies using MSC therapy in ARDS

A review from Xiao and colleagues illustrated the results of preclinical research on MSC therapy in models of ARDS and acute lung injury (ALI).[120] In the H9N2-infected mouse model, MSC treatment increased the survival rate and decreased lung edema and signs of ALI compared to those of the placebo group.[121] Moreover, cell therapy with MSCs improved gas exchange and reduced the levels of alveolar chemokines and cytokines.[121]

Likewise, MSCs were effective in treating an H1N1-infected pig model, reducing viral shedding in nasal swabs and viral replication in the lungs, and lowering the release of proinflammatory cytokines, including TNF-α and CXCL-10.[122] Rogers et al reported the results of studies in animal models and *ex vivo* human lung models showing the MSC's capacity to inhibit lung damage, reduce inflammation, dampen immune responses, and improve alveolar fluid clearance.[114]

6.4.4. Clinical studies using MSC therapy in ARDS

There have been recent notable studies evaluating the efficacy of MSCs for the treatment of ARDS. The START study was a Phase 1 pilot trial (NCT01775774), [123] now extended to Phase 2a (NCT02097641). In the Phase 1 trial, patients were followed daily for adverse events through day 28, death or hospital discharge, whichever occurs first. Vital status was collected at 6 and 12 months after study enrolment. The phase 2a was a prospective, double-blind, multicentre, randomized trial, comparing a single intravenous dose of cryopreserved bone marrow-derived MSCs of (10×10^6 cells/kg) with placebo in patients with moderate to severe ARDS.[124] The benefit was only marginal, mainly consisting of a reported trend of improved oxygenation in the MSC group.

These findings were in sharp contrast with the results of a clinical study that examined the performance of menstrual blood-derived MSCs for the treatment of 17 critically ill patients with H7N9 influenza induced ARDS.[125] In this case, patients received either 3 or 4 infusions of 1×10^6 cells/kg. The MSC group benefitted a remarkably improved survival outcome (54.5% versus 17.6%), with no long-term adverse events being noted. It is not clear whether the difference could be attributed to the methods of preparation and storage (cryopreservation) or the modality of single or repeated injections. It should be noted that studies of this group size are not suited for a definitive conclusion on efficacy.

A systematic literature review and random-effects meta-analysis reported the potential value of MSC therapy in ARDS.[126] MSCs were intravenously or intratracheally administered in 117 participants, who were followed for 14 days to 5 years. All MSCs were allogeneic from bone marrow, umbilical cord, menstrual blood, adipose tissue, or unreported sources. No related serious adverse events were reported. Although favorable trends were observed, neither mortality nor functional and biochemical markers were significantly improved by the active treatment.

6.4.5. Initial studies of MSC therapy in critical patients with COVID-19

MSCs have been recently trialed for the treatment of severe COVID-19, the main indication being critically patients with the manifestation of ARDS (reviewed in [127, 128]).

Small-size trials of MSCs for critically ill COVID-19 patients have been initially conducted in China. A single-center open-label pilot study used MSCs, of an undefined source, to treat 7 patients with ARDS in a Beijing Hospital.[119] The disease severity varied among the 7 patients studied and only 1 required mechanical ventilation. All patients receiving MSCs showed clinical improvement after 2 days, and 3 were discharged from the hospital after 10 days. The authors reported remarkable improvements in inflammatory markers and in the immune cell repertoire, especially regulatory T cells and dendritic cells, in treated patients.

A second anecdotical report covered the case of a 65 year-old woman in China treated with three doses of 5×10^7 umbilical cord-derived MSCs. The patient manifested significant clinical improvement, resulting in the cessation of mechanical ventilation, after the second dose, which was matched by a reduction of pneumonia detected in chest CT scans.[129]

These results led to an Emergency Use Authorization by the US Food and Drug Administration.[127] Conversely, both the International Society for Cellular and Gene Therapies and the International Society for Extracellular Vesicles do not endorse cell products or their subcellular derivatives for any purpose in COVID-19, including but not limited to reducing cytokine storm, exerting regenerative effects, or delivering drugs.[130]

6.4.6. Recent trials of MSC in critical patients with COVID-19

In September 2020, 69 clinical trials utilizing MSCs for the treatment of COVID-19 were registered on the WHO International Clinical Trial Registry Platform.[131] At the time of this review article compilation, a search of the same Registry Platform revealed the number of studies has increased to 103 (**Supplementary Table 1**). Of these. 49 studies were effectively recruiting, while the remaining 54 were inactive, having been approved but not started yet.

As shown in **Figure 3**, most trials are from China (30) followed by the US (19), Iran (14), Spain (12), Mexico (3), and Brazil (3). Notably, other European countries contributed with only 5 studies, of which only 2 are actively recruiting. Considering the declared patient target, the whole 103 studies encompass a population of 4,366 patients (mean, 42.3 patient per study), of which 2,119 in those that are effectively recruiting (mean, 43.2). In addition, only 7 studies have a plan to recruit more than 100 patients and 30 do not include a control group.

In relation to the tissue of origin for the derivation of MSCs, we could confirm the distribution reported by others in September. [131] Only 5 trials are investigating MSCs from the bone marrow, the preferred tissue source for other clinical uses. Cord derived MSCs (including from Wharton's Jelly) are the most common source with 37 trials, followed by 15 from adipose tissue, 5 from dental pulp, and 4 from the placenta, while 18 were using MSCs of undefined origin. A few trials employ either MSC conditioned media or vesicles/exosomes, which are acknowledged to exert similar

immunomodulatory and reparative activities of the cells from which they are derived.[132-134]

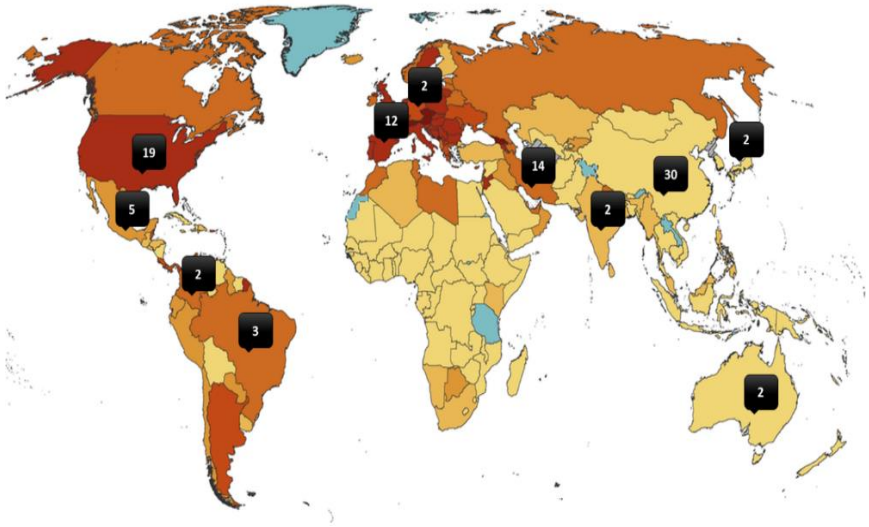

Figure 3: Distribution of clinical trials using MSCs in the world (only countries with 2 trials or more are shown).

6.4.7. Personal considerations on current trial methodology

In a critical situation like the current pandemic, all possible solutions with the potential to alleviate the consequences of COVID-19 merit consideration. It is currently premature to draw conclusions about the efficacy and safety of MSC trials as most of them are still ongoing. The current challenge in COVID-19 therapeutics, including MSC therapy, is the quality of trial studies, the imbalance of their subjects, and the quality and robustness of preliminary reports. [135]

A view of **Supplementary Table 1** summarizing MSC trials clearly indicates that these studies differ greatly from each other about preparation, dosage (from a few million to a hundred million), administration schedule (single or repeated dosage), and the best combination with other anti-inflammatory agents. In addition, there is a large variation on primary endpoints. Ten out of the 49 trials currently recruiting participants have safety as a primary endpoint, alone or in combination with efficacy. Thirteen (of which 11 are controlled trials) focus on mortality. The remaining assess softer endpoints, such as clinically, laboratory, or imaging data (mainly blood oxygen saturation and CT scan of the lungs).

The current scenario does not differ from the typical stem cell therapy landscape: a plethora of small size trials that are unlikely to provide definitive conclusions, due to the diversity of cell source, dosages, and protocols of administration. Unfortunately, these drawbacks can also preclude the applicability of meta-analyses (often incorrectly employed with the hope to amend the initial errors), due to concerns regarding statistical power and confusion from two major sources of variation: (1) pitfalls in trial design and (2) inconsistencies in reporting and interpreting trial results.

In addition, in the authors' opinion, several caveats reduce the enthusiasm for the cell therapy approach. First, unless MSC-based therapy demonstrates to be effective in patients unresponsive to DXM, corticosteroids remain formidable competitors due to the much lower cost and more flexible dosage. Second, no biomarker exists to predict the safety and efficacy of MSCs in COVID-19. The cytokine storm profile differs among patients affected by severe COVID-19, this being, as

mentioned above, a burden also for the proper use of cytokine-targeting inhibitors.[136] Third, after IV injection, MSCs are captured in the capillary bed of the lungs. Here, they are supposed to reduce inflammation and restore endothelial integrity,[137] yet this mechanism may be dysfunctional in COVID-19 patients with ARDS due to the severe microvascular damage favoring clotting of infused cells. In fact, one of the few identified complications is the risk of MSC therapy-induced thrombosis, reported in several patients before the insurgence of COVID-19.[138-140] A recent clinical trial showed that intravenous infusion of allogeneic adipose tissue-derived MSCs exerted mixed pro- and anti-inflammatory as well as procoagulant effects during human endotoxemia.[141] The procoagulant activity of MSCs was associated with a mechanism involving phosphatidylserine and tissue factor, which requires further analysis to avoid adverse effects of MSC therapy in patients with a risk of thrombosis.[142] Finally, while ARDS remains the main clinical indication for the cellular approach, there is no experimental evidence that supports the utilization of MSCs for the treatment of cardiac complications of COVID-19, an extended application that might be instigated by previous experience of cell therapy in patients with myocardial infarction or heart failure.[143]

6.4.8. Commercial MSC trials for COVID-19

Cell therapies are advanced therapy medicinal products. Their development according to the highest quality standards and needs for off-the-shelf deployment is preferentially achieved through a commercial route. Therefore, an overview of MSC trials conducted by companies may help to gauge the validity of this approach.

Several companies are repurposing their MSC products for therapeutic use in COVID-19. For example, Mesoblast Limited (Nasdaq: MESO; ASX: MSB), a global leader in allogeneic cellular medicines for inflammatory diseases, has recently proposed the use of Ryoncil (remestemcel-L) to treat patients with moderate to severe ARDS. The compound is currently under priority review by the US Food and Drug Administration for steroid-refractory acute graft versus host disease. Pilot data indicate the survival rate was 83% in ventilator-dependent COVID-19 patients when treated with two intravenous infusions of remestemcel-L, whereas the survival rate was only 12% in those receiving standard of care during the same period. Remestemcel-L is believed to counteract the pathological process by down-regulating the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines.

To confirm these pilot data, Mesoblast has launched a Phase 3 randomized controlled trial (NCT04371393) of up to 300 ventilator-dependent adults with moderate or severe COVID-19 ARDS. The dosing regimen in Phase 3 is the same as in the pilot trial and the endpoint is the reduction in mortality. The Data Safety Monitoring Board will perform an interim analysis of the trial's primary endpoint of all-cause mortality within 30 days of randomization. Further interim analysis is planned after 60% of the trial has been enrolled.

It is not surprising that leading companies are pursuing an accelerated approval pathway for their advanced cell products. They have already robust manufacturing and quality control data, preclinical evidence of safety and efficacy, and an adequate budget for pre-clinical and clinical experimentation. Their return is potentially massive and commensurate to the pandemic impact of COVID-19. It is estimated that 25% of

hospitalized patients require intensive treatment and 1% develop severe COVID-19. Projected to the total number of cases and considering a $4,000 cost for a single MSC treatment, the total cost to treat previous cases would have been equivalent to $2,320 billion.

7. Conclusions

As massive vaccination programs against SARS-CoV-2 are now ongoing, the open question is how to manage newly infected patients suffering from COVID-19 and whether immunization will be sufficient to eradicate the problem. It is, therefore, crucial to implement different treatments and refine current guidelines according to the severity and stage of the disease. While the pilot studies showed a promising stance for some of these products, large and well-designed trials are warranted. In addition, preclinical research in cellular and animal models should define a stronger rationale in support of clinical experimentation. Additional investigation is also needed on biomarkers guiding the choice of anti-inflammatory and immunomodulatory drugs.

8. Future Perspectives

There are important lessons from the COVID-19 pandemic. The first lesson is that the Coronavirus does not respect national boundaries. Therefore, everyone in the scientific community bears great responsibility for collaborating and sharing results, with great attention to the ethics and robustness of the provided evidence.

On the one hand, we need that data are collected and analyzed rapidly. On the other hand, it is crucial that researchers take primary responsibility for the production and use of knowledge making sure about the quality of basic, translational, and clinical studies and related reports. This review contains many references that are pre-print articles, which have not received regular scrutiny through referees' evaluation. Readers need to be aware of the limitations of this new method to communicate the results. These challenges are highlighted by a recent article illustrating how the health research system may have to deal with the inevitable imperfections of rapid scientific reporting in the current and future crises.[144]

The second lesson has medical, commercial, and governmental implications. It regards the pressing need for global-readiness programs aiming to develop treatments and vaccines that can mitigate future viral pandemics.[145] Developing novel antiviral agents, including blocking antibodies, antiviral drugs, and vaccines is financially costly. Creating vaccines, especially under the pressure of an acute health emergency, has not proved very rewarding in the past, meaning pharmaceutical companies may be reluctant in investing their budgets in such long-term programs. Therefore, governments should continue to invest in pandemic strategies the same way they do now in defense. In the US alone, deaths due to SARS-CoV-2 have reached today (the 3rd of February 2021) 447,000, a figure that surpasses the 405,399 losses that occurred during World War II. Academic institutions should participate and/or lead these global-preparedness endeavors. Repurposing clinically available drugs, as exemplified by the use of corticosteroids in COVID-19, could be cost/benefit advantageous.

The third lesson is that COVID-19 has prompted a remarkable change in medical practice, providing the battlefield for a new army of doctors and nurses to nurture experience in capturing critical needs in real-time selecting options from a growing armamentarium of approved medicines and support devices. In the future, machine learning technologies could be harnessed to help to integrate scientific and medical knowledge into rapid diagnostic flow-charts and personalized treatments.

Executive summary

1. Epidemiology and emergence of new variants

As of 3 February 2021, over 103 million cases of COVID-19 have been reported, including 2.24 million deaths. Severe lung disease characterized by "acute respiratory distress syndrome" (ARDS) represents the most severe complication. Multiple variants of the virus that causes COVID-19 are emerging globally.

2. Clinical presentation

COVID-19 can present a variety of manifestations ranging from asymptomatic infection to critical disease. No precise guidelines for classification have been established, although the current definition refers to mild, moderate, and critical disease with or without ARDS. Treatment protocols follow this classification as well as what is known about target pathogenic mechanisms during disease progression. The S protein is the leading mediator of viral entry following processing by host cell protease.

3. Anchor receptors

The first target for therapy of COVID-19 is shielding epithelial and endothelial cells from the virus contact.

4. Conventional and unconventional entry receptors

The second target is to interfere with entry receptor engagement.

5. Viral replication

The third target is to use anti-viral agents to inhibit viral replication together with antibiotics if superinfection occurs.

6. Inflammation and immune response

Anti-inflammatory therapy and immunomodulatory drugs are indicated in severe disease to combat the state of hyper-inflammation and cytokine storm together with evasion of the immune response. Different approaches include the use of convalescent plasma, cytokine inhibitors, steroids, and immunomodulatory stem cells. The latter have been trialed in small studies and now examined in patients with ARDS. Pharmaceutical companies have repurposed their approved cell products to this clinical application.

7. Conclusions

The massive vaccination campaign will not resolve the problem entirely and the above approaches need to be further refined and incorporated in an approved protocol.

8. Future perspectives

We have learned lessons that will inform future decisions at the level of research, communication, and readiness plans to face new emergencies.

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Figure legends:

Figure 1. Treatment protocol according to the disease stage and target. The upper part identifies clinical signs of disease progression. The middle part shows the virus-intrinsic and host-related mechanisms. The lower part shows the graded approach.

Figure 2. MSCs modulate both innate and adaptive immune cells. MSCs directly regulate immune cells and this regulation can be influenced by the inflammatory milieu of the host tissue. The immunoregulatory activity of MSCs is exerted mainly via paracrine recruitment and activation of cells from both the innate and adaptive immune systems. Innate: inhibition of neutrophils (NEU) and dendritic cells (DC) proliferation, natural killer (NK) proliferation and cytotoxic activity, facilitation of monocytes and macrophages M1-M2 transition. Adaptive: inhibition of T helper (Th) 1 and Th17 and promotion of Treg production, inhibition of B cells via the regulatory Breg. Moreover, MSCs have an additional indirect influence on T and B cells. EVs: extracellular vesicles, IFNγ: Interferon-gamma, TNFα: tumor necrosis factor-alpha, TGF-β transforming growth factor-beta, IL6: interleukin 6, HGF: hepatocyte growth factor, PGE2: prostaglandin E2, CCL5: CC chemokine ligand 5, CXCL10 and 11: CXC chemokine ligand 10 and 11.

Figure 3: Distribution of clinical trials using MSCs in the world (only countries with 2 trials or more are shown).

Trial ID	Scientific title	Country	Source / Dose	Participants
EUCTR2020-001505-22-ES	Double-blind, randomized, parallel, placebo-controlled pilot clinical trial, nested in a prospective cohort observational study, for the evaluation of the efficacy and safety of two doses of WJ-MSC in patients with acute respiratory distress syndrome secondary to infection by COVID-19 - COVIDMES	Spain	Umbilical cord **Dose:** No information available	15 Control 15 Exp
ChiCTR2000030173	Key techniques of umbilical cord mesenchymal stem cells for the treatment of novel coronavirus pneumonia (COVID-19) and clinical application demonstration	China	Umbilical cord **Dose:** no information available	30 Control 30 Exp
ChiCTR2000030138	Clinical Trial for Human Mesenchymal Stem Cells in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	China	Umbilical cord **Dose:** IV injection, no information available	30 Control 30 Exp
ChiCTR2000030088	Umbilical cord Wharton's Jelly derived mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	China	Wharton's Jelly **Dose:** IV injection of mesenchymal stem cells (1*10E6/kg), cell suspension volume	20 Control 20 Exp
ChiCTR2000030261	A study for the key technology of mesenchymal stem cells exosomes atomization in the treatment of novel coronavirus pneumonia (COVID-19)	China	MSC Exosomes (origin not specified) **Dose:** Aerosol inhalation of exosomes	13 Control 13 Exp

EUCTR2019-002688-89-ES	Clinical Study to Assess the Safety and Preliminary Efficacy of HCR040 in Acute Respiratory Distress Syndrome	Spain	Adipose tissue, HCR040® cells **Dose:** IV, No information available	14 Control 14 Exp
EUCTR2020-001682-36-ES	Treatment of COVID-19 with allogeneic mesenchymal cells (MSVÂ®)	Spain	Allogeneic mesenchymal cells, MSV® **Dose:** No information available	12 Control 12 Exp
EUCTR2020-001266-11-ES	Clinical trial of administration of MSC to patients with respiratory distress type COVID-19	Spain	Adipose tissue **Dose:** No information available	50 Control 50 Exp
NCT04377334	Prospective Phase II Study: MSCs in Inflammation-Resolution Programs of SARS-CoV-2 Induced ARDS	Germany	Bone marrow **Dose:** No information available	20 Control 20 Exp
EUCTR2020-001364-29-ES	Study with stem cells from allogenic adipose tissue, in patients with coronavirus severe pneumonia	Spain	Adipose tissue **Dose:** Allogenic cells, no information available	13 Control 13 Exp
ChiCTR2000029817	Clinical Study of Cord Blood NK Cells Combined with Cord Blood Mesenchymal Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	China	Cord blood **Dose:** High dose group: High-dose NK cells (>5*10E9)and mesenchymal stem cells(>5*10E9), Intravenous infusion once every two days for a total of five times; Conventional dose group: Conventional dose NK cells (>3*10E9) and mesenchymal stem cells(>3*10E9),Intravenous infusion once every two days for a total of three times; Preventive dose group: Preventive dose NK cells (>3*10E9)and mesenchymal stem	60 Exp

			cells(>3*10E9),Intravenous infusion once every week for a total of one time;	
ChiCTR2000029816	Clinical Study of Cord Blood Mesenchymal Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	China	Cord blood **Dose:** No information available	30 Control 30 Exp
NCT04349631	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	USA	Adipose tissue, HB-adMSCs **Dose:** Five IV infusion of autologous adipose-derived mesenchymal stem cells.	56 Exp
NCT04302519	Clinical Study of Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	China	Dental Pulp **Dose:** No information available	24 Exp
ChiCTR2000030224	Clinical study of mesenchymal stem cells in treating severe novel coronavirus pneumonia (COVID-19)	China	Cord blood **Dose:** No information available	30 Control 30 Exp
ChiCTR2000031319	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe Pneumonia of COVID-19:a Single-center, Prospective, Randomised Clinical Trial	China	Dental pulp **Dose**: IV, no information available	10 Control 10 Exp
IRCT20140528017891N8	Evaluation of the efficacy and safety of cord-derived mesenchymal stem	Iran	Umbilical cord	5 Control 5 Exp

	cell transplantation in the treatment of COVID-19		**Dose:** IV 0.5-1*10E6/ kg body weight on the first, third and sixth days.	
IRCT20200325046860N2	Mesenchymal stem cell utilization in reducing complications and enhancing pneumonia healing in patients infected with 2019-nCoV (phase I clinical trial)	Iran	Not specified **Dose:** IV 7*10E6 cells at day 0, 3 6	5 Exp
NCT04273646	Clinical Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	China	Umbilical cord **Dose**: IV transfusion one round (4 times) of 5.0*10E6 cells/kg of UC-MSCs	24 Control 24 Exp
NCT04346368	Safety and Efficacy of Intravenous Infusion of Bone Marrow-Derived Mesenchymal Stem Cells in Severe Patients With Coronavirus Disease 2019 (COVID-19): A Phase 1/2 Randomized Controlled Trial	China	Bone marrow **Dose:** IV 1*10E6 /kg body weight at Day 1	10 Control 10 Exp
NCT04348461	Two-treatment,Randomized, Controlled, Multicenter Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Expanded Allogeneic Adipose Tissue Adult Mesenchymal Stromal Cells in Critically Ill Patients COVID-19	Spain	Adipose tissue **Dose:** Two serial doses of 1.5 million cells/ kg body weight	100 Exp
NCT04352803	IV Infusion of Autologous Adipose Derived Mesenchymal Cells for Abatement of Respiratory	Spain USA	Adipose tissue **Dose:** IV infusion of autologous cells, no information available	10 Control 10 Exp

	Compromise in SARS-CoV-2 Pandemic (COVID-19)			
NCT04366830	Intermediate-size Expanded Access of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells for Acute Respiratory Distress Syndrome Due to COVID-19 Infection	USA	Not specified, Remestemcel-L **Dose:** Remestemcel-L, two IV infusions of 2 * 10E6 / kg body weight	50 Exp
NCT04371601	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	China	Umbilical cord **Dose:** 10E6 / Kg body weight / time, once every 4 days for a total of 4 times	30 Control 30 Exp
NCT04341610	Allogeneic Adipose Tissue Derived Mesenchymal Stromal Cell Therapy for Treating Patients With Severe Respiratory COVID-19. A Danish, Double-blind, Randomized Placebo-controlled Study	Denmark	Adipose tissue **Dose:** 100*10E6 cells	20 Control 20 Exp
IRCT20200217046526N1	Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome in Coronavirus Infection : A Phase 1 and 2 clinical trial	Iran	Not specified **Dose:** IV, three doses of 200*10E6 cells at day 0, day 2, day 4.	6 Exp
NCT04315987	Exploratory Clinical Study to Assess the Efficacy of NestaCellÂ® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia	Brazil	NestCell® MSCs **Dose**: IV 2*10E7 cells on days 1, 3, 5 and 7	45 Control 45 Exp

NCT04429763	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19	Colombia	Umbilical cord **Dose:** 1*10E6 cells/Kg body weight	15 Control 15 Exp
IRCT20200426047206N2	Clinical trial of efficacy and safety of mesenchymal stem cell transplantation in patients with COVID-19 pneumonia	Iran	Umbilical cord **Dose:** 1*10E6 cells/Kg body weight	15 Control 15 Exp
NCT04390152	Mesenchymal Stem Cell Plus Standard Therapy for the Treatment of Patients With Acute Respiratory Distress Syndrome Diagnosis Due to COVID 19: A Randomized Controlled Trial	Colombia	Wharton's jelly **Dose:** 50*10E6 cells, two doses	20 Control 20 Exp
NCT04467047	Safety and Feasibility of Allogenic Mesenchymal Stromal Cells in the Treatment of COVID-19	Iran	Umbilical cord **Dose:** IV 1*10E6 cells	15 Control 15 Exp
NCT04456361	A Study of Mesenchymal Stem Cells as a Treatment in Patients With Acute Respiratory Distress Syndrome Caused by COVID-19	Mexico	Wharton Jelly **Dose:** IV single-dose 1 * 10E8 cells	9 Exp
NCT04288102	A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Human Umbilical Cord-derived Mesenchymal Stem Cells in the Treatment of Severe COVID-19 Patients	China	Umbilical cord **Dose:** IV transfusion 3 times of MSCs (4.0*10E7 cells per time)	30 Control 60 Exp

NCT03042143	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST): An Open Label Dose Escalation Phase 1 Trial Followed by a Randomized, Double-blind, Placebo-controlled Phase 2 Trial (COVID-19)	UK	Umbilical cord, Realist Orbcel-C CD362 enriched MSCs **Dose:** dose escalation pilot study in which cohorts of subjects with moderate to severe ARDS will receive increasing doses of a single infusion of Realist Orbcel-C in a 3+3 design. Initially 3 cohorts with 3 subjects/cohort. i	9 Exp followed by 75 Exp
NCT04348435	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	USA	Adipose tissue, HB-adMSCs **Dose:** IV, Allogeneic cells 200*10E6 5 Infusions at weeks 0, 2, 6, 10, and 14.	50 Controls 50 Exp
NCT04522986	An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection	Japan	Adipose tissue **Dose:** IV 1*10E8 cells are administered once a week, total four times	6 Exp
NCT04276987	A Pilot Clinical Study on Aerosol Inhalation of the Exosomes Derived From Allogenic Adipose Mesenchymal Stem Cells in the Treatment of Severe Patients With Novel Coronavirus Pneumonia	China	Adipose Tissue—MSC Exosomes **Dose**: 5 times aerosol inhalation of MSCs-derived exosomes (2.0*10E8 nano vesicles/3 ml at Day 1, Day 2, Day 3, Day 4, Day 5).	24 Exp
NCT04490486	Phase I, Randomized, Double Blinded, Placebo Control Study to Evaluate the Safety and Potential	USA	Umbilical cord **Dose:** IV 100 * 10E6 cells at day 0 and 3	10 Control 10 Exp

	Efficacy of Intravenous Infusion of Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 With Moderate to Severe Symptoms			
NCT04527224	A Phase I/?a Trial to Explore the Safety and Efficacy of Allogenic Adipose Tissue-derived Mesenchymal Stem Cell (AstroStem-V) Therapy in Patients With COVID-19 Pneumonia	China	Adipose tissue AstroStem-V **Dose:** no information available	10 Exp
ChiCTR2000029569	Safety and efficacy of umbilical cord blood mononuclear cells conditioned medium in the treatment of severe and critically novel coronavirus pneumonia (COVID-19): a randomized controlled trial	South Corea	Conditioned Media from Umbilical Cord MSCs **Dose:** no information available	15 Control 15 Exp
NCT04452097	A Phase 1 Study of the Safety and Tolerability of BX-U001 for the Treatment of Severe COVID-19 Pneumonia With Moderate to Severe Acute Respiratory Distress Syndrome (ARDS).	USA	Umbilical cord **Dose:** single IV BX-U001 at 0.5*10E6, 1.0*10E6, or 1.5*10E6 cells/kg of body weight	9 Exp
JPRN-JapicCTI-205465	Umbilical cord-derived mesenchymal stromal cells therapy for SARS-CoV-2	Japan	Umbilical cord **Dose:** IV 2*10E6 cells / kg body weight or 1*10E6 cells/kg body weight once a	12 Exp

	infection (COVID-19) related Acute Respiratory Distress Syndrome		day two days apart in between. One cycle is defined as 2 administraitons and patient will be treated with total 2 cycles (4 administrations).	
NCT04573270	A Pilot Phase Study Evaluating the Effects of a Single Mesenchymal Stem Cell Injection in Patients With Suspected or Confirmed COVID-19 Infection and Healthcare Providers Exposed to Coronavirus Patients	USA	Umbilical cord **Dose:** No information available	40 Exp
NCT04445220	A Multi-center, Randomized, Case Controlled, Double-blind, Ascending-dose Study of Extracorporeal Mesenchymal Stromal Cell Therapy (SBI-101 Therapy) in COVID-19 Subjects With Acute Kidney Injury Receiving Renal Replacement Therapy	USA	SBI-101 is a biologic/device combination product that combines two components: allogeneic human MSCs and an FDA-approved plasmapheresis device **Dose:** SBI-101 device containing 250 * 10E6 MSCs SBI-101 device containing 750 * 10E6 MSCs	11 Control 11 Exp
NCT04456439	Intermediate-size Expanded Access of Remestemcel-L, Human Mesenchymal Stromal Cells, for Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With Coronavirus Disease (COVID-19)	USA	Not specified **Dose:** 2 infusions of 2 *10E6 remestemcel-L within a 5-day period.	50 Exp
NCT04535856	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients: Randomized,	Indonesia	Not specified, DW-MSC **Dose:** Low-dose group (5* 10E7cells), 2 vials High-dose group (5* 10E8cells),4 vials	3 Control 6 Exp

	Double-blind, and Placebo-controlled			
CTRI/2020/08/027043	A Phase 1 clinical trial of intravenous administration of mesenchymal stem cells derived from umbilical cord and placenta in patients with novel COVID-19 virus pneumonia.	India	Umbilical cord and placenta **Dose:** 100 * 10E6 cells in 10 patients and 100 * 10E6 cells in 10 patients in two doses on day 1 and day 4	20 Exp
CTRI/2020/10/028250	A Randomized, Controlled, Open Label, Multicentre, Two Arm, Two Dosage, Phase II Study Assessing the Efficacy and Safety of Intravenous Administration of Adult Human Bone Marrow Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells in Patients with Acute Respiratory Distress Syndrome Caused by Pneumonia due to COVID-19	India	Bone Marrow **Dose:** Ex - vivo cultured allogeneic Mesenchymal stromal cells at a dose of 200 *10E6 cells at Day 0 and Day 3	20 Control 20 Exp
RBR-3fz9yr	Use of mesenchymal cells for the treatment of patients with severe acute respiratory syndrome caused by SARS-CoV-2 - : Coronavirus infections	Brazil	Umbilical cord **Dose:** Three doses of 500.000 cells/kg body weight	5 Control 10 Exp
NCT04345601	Single Donor Banked Bone Marrow Mesenchymal Stromal Cells for the Treatment of COVID19-Induced ARDS: A Randomized, Controlled Study	USA	Bone Marrow **Dose:** IV injection,1 x 10^8 cells	30 Exp

NCT04355728	Umbilical Cord-derived Mesenchymal Stem Cells for COVID-19 Patients With Acute Respiratory Distress Syndrome (ARDS)	USA	Umbilical cord **Dose:** IV, 100*10E6 cells at 1 and 3 day	12 Control 12 Exp
NCT04428801	Clinical Study for the Prophylactic Efficacy of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells (AdMSCs) Against Coronavirus 2019 (COVID-19)	USA	Adipose tissue **Dose:** IV three doses of 200 * 10E6 cells every 3 days	100 Control 100 Exp
NCT04625738	Efficacy of Infusions of Mesenchymal Stem Cells From Wharton Jelly in the Moderate to Severe SARS-Cov-2 Related Acute Respiratory Distress Syndrome (COVID-19): A Phase IIa Double-blind Randomized Controlled Trial	USA	Wharton Jelly Dose: Day 0 (or 1): 1*10^6 MSC/kg (maximum 80*10^6 MSC) Day 3 (or 4): 0.5 *10^6 MSC/kg (maximum 40* 10^6 MSC) Day 5 (or 6): 0.5*10^6 MSC/kg (maximum 40* 10^6 MSC) An interval of 2 days will be respected between 2 infusions.	15 Control 15 Exp
ChiCTR2000030484	HUMSCs and Exosomes Treating Patients with Lung Injury following Novel Coronavirus Pneumonia (COVID-19)	China	Umbilical Cord + Exosomes **Dose**: Group 1, IV infusion 1: 5 *10E7 cells / time, once / week, twice / course group 2: IV infusion, 5 * 107 cells / time, 1 time / week, 2 times / course, a total of 2 courses; Exosomes: IV administration, 180mg / time, 1 time / day, 7 days / course, 2 courses in total	30 Control 30 Exp
Recruiting trials	**Scientific title**	**Country**	**Source / Dose/ primary endpoint**	**Participants**

ChiCTR2000030116	Safety and effectiveness of human umbilical cord mesenchymal stem cells in the treatment of acute respiratory distress syndrome of severe novel coronavirus pneumonia (COVID-19)	China	Umbilical Cord **Dose:** no information available **Primary Outcome(s):** Time to leave ventilator on day 28	16 Exp
NCT04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	China	Umbilical Cord **Dose:** Different stem cell doses **Primary Outcome(s):** Oxygenation index [Time Frame: on the day 14 after enrollment]	10 Exp
ChiCTR2000030020	The clinical application and basic research related to mesenchymal stem cells to treat novel coronavirus pneumonia (COVID-19)	China	Not Specified **Primary Outcome(s):** Coronavirus nucleic acid markers negative rate; Symptoms improved after 4 treatments; Inflammation (CT of the chest)	20 Exp
ChiCTR2000029990	Clinical trials of mesenchymal stem cells for the treatment of pneumonitis caused by novel coronavirus (COVID-19)	China	Not specified **Dose:** no information available **Primary Outcome(s):** Improved respiratory system function (blood oxygen saturation) recovery time	60 Control 60 Exp
ChiCTR2000029580	Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial	China	MSCs (origin not specified) + Ruxolitinib **Dose**: No information available **Primary Outcome(s):** Safety	35 Control 35 Exp

ChiCTR2000030866	Open-label, observational study of human umbilical cord derived mesenchymal stem cells in the treatment of severe and critical COVID-1	China	Umbilical cord **Dose:** IV infusion of 1×10^6 UCMSCs/kg/time on day 0, 3, 6 **Primary Outcome(s):** Oxygenation index (arterial oxygen partial pressure (PaO2) / oxygen concentration (FiO2)); Conversion rate from serious to critical patients; Conversion rate and time from critical to serious patients; Mortality in serious and critical patients	30 Exp
ChiCTR2000030835	Clinical study on the efficacy of Mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19)	China	Umbilical cord **Dose**: MSc (2 x10^6 / kg / time) or MSc (1x10^6 / kg / time) **Primary Outcome(s):** C-reactive protein; Detection of lymphocyte subsets; Procalcitonin; Routine blood test; Chest CT;cytokine; Blood biochemistry;	20 Exp
NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Jordan	Wharton's Jelly—MSCs **Dose:** No information available **Primary Outcome(s):** Clinical outcome [Time Frame: 3 weeks] CT Scan [Time Frame: 3 weeks] RT-PCR results [Time Frame: 3 weeks]	5 Exp
ChiCTR2000031494	Clinical study for stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	China	Umbilical cord **Dose:** IV infusion, no information available	18 Control 18 Exp

			Primary Outcome(s): Chest Imaging; lung function;ADL	
ChiCTR2000031430	Evaluation of the safety and efficacy for human umbilical cord mesenchymal stem cells in COVID-19 induced pulmonary fibrosis	China	Umbilical cord **Dose:** No information available **Primary Outcome(s):** Laboratory tests	100 Control 100 Exp
ChiCTR2000029606	Clinical Study for Human Menstrual Blood-derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	China	Human Menstrual Blood-derived Stem Cells preparations **Dose:** IV infusion of cells, no information available Artificial liver therapy with or without Human Menstrual Blood-derived Stem Cells preparations **Dose:** IV infusion of cells, no information available **Primary Outcome(s):** Mortality in patients	15 Control 18 Exp 10 Control 10 Exp/10 Exp
NCT04336254	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe Pneumonia of COVID-19:a Single-center, Prospective, Randomised Clinical Trial	China	Dental pulp **Dose:** IV injection of 3.0x10e7 cells solution (30ml) on day 1, day 4 and day 7 **Primary Outcome(s):** TTCI [Time Frame: 1-28 days]	10 Control 10 Exp
NCT04339660	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	China	Umbilical cord **Dose:** IV 1*10E6 UC-MSCs/kg body weight in a single dose eventually repeated depending on the condition	15 Control 15 Exp

			of the need to be given again at an interval of 1 week. **Primary Outcome(s):** Blood oxygen saturation, immune function	
ChiCTR2000030300	Umbilical cord mesenchymal stem cells for the treatment of patients at high risk of novel coronavirus pneumonia (COVID-19): a single-center, prospective, open clinical study	China	Umbilical cord **Dose:** No information available **Primary Outcome(s):** Time to disease recovery; Exacerbation (transfer to RICU) time	9 Exp
IRCT20140911019125N6	Study the effect of intravenous injection of dental pulp mesenchymal stem cells in treatment of patients with COVID-19 pneumonia	Iran	Dental pulp **Dose:** IV 1*10E6 cells **Primary Outcome(s):** Expression of nucleic acid of virus, Lymphocytes count, Patients clinical sign, Pulmonary Conditions at TC scan	10 Exp
NCT04252118	Safety and Efficiency of Mesenchymal Stem Cell in Treating Pneumonia Patients Infected With COVID-19	China	Not specified **Dose:** IV, 3 times of MSCs (3.0*10E7 MSCs intravenously at Day 0, Day 3, Day 6). **Primary Outcome(s):** Side effects in the MSCs treatment group, Size of lesion area by chest radiograph or CT	10 Control 10 Exp
NCT04366063	Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome in Coronavirus Infection: A Phase 2-3 Clinical Trial	Iran	Not specified **Dose:** protocol 1, two doses of cells 100×10E6 (±10%) at Day 0 and Day 2. Protocol 2, the same plus two doses of EVs at Day 4 and Day 6	20 Control 20 Exp 1 20 Exp 2

			Primary Outcome(s): Adverse events assessment [Time Frame: From baseline to day 28], Blood oxygen saturation [Time Frame: From baseline to day 14]	
IRCT20200217046526N2	Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome in Coronavirus Infection: A Phase 2-3 Clinical Trial	Iran	Not specified **Dose:** IV two doses of MSCs 100*10E6 (±10%), at Day 0 and Day 2 or two doses of MSCs 100*10E6 (±10%), at Day 0 and Day 2 plus two doses of extracellular vesicles (EVs) on Day 4 and Day 6 **Primary Outcome(s):** Adverse events, Blood oxygen saturation	20 Control 40 Exp
IRCT20200413047063N1	Placental Mesenchymal Stem cells for treatment of ARDS in Coronavirus infection, Phase 1 and 2 Clinical Trials	Iran	Placenta **Dose:** 3 doses, no available information **Primary Outcome(s):** Adverse events, Blood oxygen saturation	10 Control 10 Exp
IRCT20200418047121N2	Investigation the adipose and placenta-derived mesenchymal stem cells effect on the respiratory distress syndrome in patients with COVID-19: a pilot study	Iran	Adipose tissue **Dose:** No information available **Primary Outcome(s):** Biomarker expression, Blood oxygen saturation, CT scan	3 Control 3 Exp
NCT04366271	Phase II Clinical Trial to Explore the Efficacy of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in	Spain	Umbilical cord **Dose:** 1 infusion of undifferentiated allogeneic cells, no information available	53 Control 53 Exp

	Patients With Severe Pulmonary Involvement by COVID-19		**Primary Outcome(s):** Mortality due to lung involvement due to SARS-CoV-2 virus infection at 28 days of treatment	
NCT04390139	Prospective, Double-blind, Randomized, Parallel, Placebo-controlled Pilot Clinical Trial for the Evaluation of the Efficacy and Safety of Two Doses of WJ-MSC in Patients With Acute Respiratory Distress Syndrome Secondary to Infection by COVID-19	Spain	Wharton-Jelly **Dose:** IV 1E106 cells at day 1 and 3 **Primary Outcome(s):** All-cause mortality at day 28 [Time Frame: Day 28] weeks]	15 Control 15 Exp
NCT04392778	What is the Effect of Mesenchy, mal Stem Cell Therapy on Seriously Ill Patients With COVID 19 in Intensive Care? (Prospective Double Controlled Study)	Turkey	Not specified **Dose:** IV 3*10E6 at day 0, 3 and 6 **Primary Outcome(s):** Clinical improvement [Time Frame: 3 months]	15 Control 15 Exp
NCT04382547	Treatment of COVID-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	Belarus	Olfactory-Mucosa **Dose:** No information available **Primary Outcome(s):** Number of cured patients [Time Frame: 3 weeks]	20 Control 20 Exp
NCT04416139	Mesenchymal Stem Cells for the Treatment of Severe Acute Respiratory Distress Syndrome Due to COVID-19. Pilot Study	Mexico	Umbilical cord **Dose:** 1 * 10E6 in single administration **Primary Outcome(s):** Clinical signs, Functional Respiratory changes: PaO2 / FiO2 ratio [Time Frame: Three weeks]	5 Control 5 Exp
IRCT20200421047150N1	Assessment of safety, efficacy and effective dose determination of human umbilical cord Whartonâ€™s	Iran	Wharton's jelly **Dose:** 0.5 or 2 * 10E6 cells / kg body weight on day 1, 3, and 6	45 Control 45 Exp

	jelly mesenchymal stem cell transplantation on treatment of COVID-19 (coronavirus) pneumonia and complications in humans		**Primary Outcome(s):** Mortality. Timepoint: Up to 28 days after starting the study.	
IRCT20160809029275N1	Evolution of Allogenic Mesenchymal stem cell- derived Umbilical cord transplantation for ARDS patients infected with COVID19.	Iran	Umbilical cord **Dose:** IV 1 * 10E6 cells at 1, 3, and 6 days **Primary Outcome(s):** Biomarker expression, Blood oxygen saturation, CT scan	10 Control 10 Exp
NCT04366323	Phase I / II Clinical Trial, Multicenter, Randomized and Controlled, to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19	Spain	Adipose tissue **Dose:** 80 * 10E6 cells **Primary Outcome(s):** Mortality [Time Frame: 28 days], Adverse Event Rate [Time Frame: 12 months]	13 Control 13 Exp
ISRCTN33578935	Rationale and investigational study for the treatment of COVID-19 with severe viral pneumonia with isolated, placental, mesenchymal stem cell exosomes	Germany	**Dose:** IV purified exosomes, XoGlo®, which are isolated, neonatal, mesenchymal stem cell-derived extracellular vesicles at a dose of 0.2 mg/kg body weight each in a total of 15ml on day 1 and day 3 **Primary Outcome(s):** adverse events, Blood oxygen saturation	32 Control 32 Exp
NCT04399889	Pilot Study of Safety and Efficacy of Cord Tissue Derived Mesenchymal	USA	Umbilical cord	15 Control 15 Exp

	Stromal Cells (hCT-MSC) in COVID-19 Related Acute Respiratory Distress Syndrome (ARDS)		**Dose:** IV 1 * 10E6 cells/kg body weight (max dose 100 million cells) **Primary Outcome(s):** Safety	
NCT04389450	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase II Study to Evaluate the Efficacy and Safety of Intramuscular Injections of PLX PAD for the Treatment of Severe COVID-19	USA	Placenta **Dose:** (i) PLX-PAD interval high dose - PLX-PAD cells administered via 15 IM injections (1 mL each). Each subject will be treated twice, with an interval of 1 week between treatments, (ii) PLX-PAD low dose - LX-PAD 300, single administration, second administration of placebo after 1 week. (iii) PLX-PAD low dose PLX-PAD 300, single administration, second administration of placebo after 1 week. **Primary Outcome(s):** Number of ventilator free days [Time Frame: 28 days]	70 Control 70 Exp
NCT04445454	Mesenchymal Stromal Cell Therapy for Severe COVID-19 Infection	Belgium	Bone marrow **Dose:** 3 infusions of (1.5)-3.0 *10E6/kg body weight (from the same donor) at 3-4 days interval **Primary Outcome(s):** Safety and efficacy (unspecified) [Time Frame: Day 28]	20 Exp
NCT04444271	Prospective, Randomized Phase 2 Clinical Trial of Mesenchymal Stem	Pakistan	Bone marrow	10 Control 10 Exp

	Cells(MSCs) for the Treatment of Coronavirus Disease 2019(COVID-19)		**Dose:** 2 *10E6 cells/kg MSCs on days 1 and 7 **Primary Outcome(s):** Mortality Time Frame: 30 days post intervention]	
NCT04457609	Application of Umbilical Cord Mesenchymal Stem Cells as Adjuvant Therapy for Critically-Ill COVID-19 Patients	Indonesia	Umbilical cord **Dose:** 1*10E6 unit cells/kg body weight **Primary Outcome(s):** Clinical improvement, Blood oxygen saturation [Time Frame: 15 days]	20 Control 20 Exp
NCT04461925	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic Multipotent Mesenchymal Stem Cells of the Placenta and Umbilical Cord	Ukraine	Placenta **Dose:** Cryopreserved allogeneic cells(1 * 10E6 cells/kg body weight) at 2-days intervals: Day 1, 4, and 7 **Primary Outcome(s):** Clinical improvement [Time Frame: At baseline, Day 1, Week 1, Week 2, Week 4, Week 8]	15 Control 15 Exp
NCT04397796	Phase 1b Randomized, Double-Blind, Placebo-Controlled Study Of The Safety Of Therapeutic Treatment With Immunomodulatory Mesenchymal Stem Cells In Adults With COVID-19 Infection Requiring Mechanical Ventilation	USA	Bone marrow **Dose:** IV, no information available **Primary Outcome(s):** Mortality, [Time Frame: 30 days] Number of ventilator-free days [Time Frame: 60 days]	23 Control 23 Exp
NCT04466098	Multi-center, Randomized, Placebo Controlled, Interventional Phase 2A Clinical Trial Evaluating the Safety	USA	Not specified **Dose:** 300 * 10E6 cells	10 Control 20 Exp

	and Potential Efficacy of Multiple Dosing of Mesenchymal Stromal Cells in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)		**Primary Outcome(s):** Safety [Time Frame: Within 6 hours of the start of the infusion]	
ACTRN12620000840987	Phase I trial on safety and tolerability of bone-marrow derived mesenchymal stromal cells (MSC) for deteriorating COVID-19 pneumonia	Australia	Bone marrow **Dose:** 2 * 10E6 cells/kg body weight at day 0 and 3 **Primary Outcome(s):** Safety [Time Frame: Within 30 days of the start of the infusion], Blood oxygen saturation, biochemistry Day 3, 7, 14, 30 and 90 following study intervention]	10 Exp
NCT04525378	Mesenchymal Stromal Cell-based Therapy for COVID-19-associated Acute Respiratory Distress Syndrome: a Pilot Clinical Study	Brazil	Not specified **Dose:** 3 doses 2.5, 5, or 10 *10E7 cells with repeat after 2 days (either at low or intermediate dose **Primary Outcome(s):** Mortality	10 Control 10 Exp
ACTRN12620000612910	A pilot, open-label, randomised controlled clinical trial to investigate early efficacy of CYP-001 in adults admitted to intensive care with COVID-19	Australia	Mesenchymo-Angioblast (CYP-001) **Dose:** IV 2 *10E6 cells/kg body weight (up to a maximum of 200 million cells) on two occasions (Day 1 and Day 3) **Primary Outcome(s):** Safety, Blood oxygen saturation [at day 7]	12 Control 12 Exp
NCT04400032	Cellular Immuno-Therapy for COVID-19 ARDS (CIRCA-19) the Vanguard Study	Canada	Bone marrow **Dose:** IV on each of 3 consecutive days, (i) 5*10E6 cells/unit dose (cumulative dose: 75 million MSCs), (ii)	3x3 Exp

			50 *10E6 cells/unit dose (cumulative dose: 150 million MSCs), (iii) up to 90 *10E6 cells/unit dose (cumulative dose: up to 270 million MSCs). Primary Outcome(s): Safety [Time Frame: At time of infusion until one year post-infusion]	
IRCT20190717044241N2	Cell therapy in patients with COVID-19 using mesenchymal stem cells	Iran	Not specified **Dose:** IV 2*10E6 / kg body weight by intravenous injection three times **Primary Outcome(s):** Mortality, Number of Participants with ventilator-free Days by Day 28 [Time Frame: Day 28]	5 Exp
IRCT20140911019125N8	Study the effect of intravenous injection of dental pulp mesenchymal stem cells in treatment of patients with COVID-19 pneumonia- A Phase 2&3 Clinical Trial	Iran	Dental pulp **Dose:** IV 40 * 10E6 cells **Primary Outcome(s):** Clinical improvement, CT scan at the beginning of the study and 1 day and 2 days, 4 days, 7 days and 14 days after the start of the study.	50 Control and 50 Exp
NCT04361942	Double Blind, Placebo-controlled, Phase II Trial to Evaluate Safety and Efficacy of Allogenic Mesenchymal Stromal Cells MSV_allo for Treatment of Acute Respiratory Failure in Patients With COVID-19 Pneumonia (COVID_MSV)	Spain	Not specified **Dose:** allogenic, 1 *10E6 cells/Kg body weight **Primary Outcome(s):** Mortality [Time Frame: 28 days], number of patients withdrawal of invasive mechanical ventilation [Time Frame: 0-7 days]	12 Control 12 Exp

NCT04565665	Emergency Use Pilot Study of Cord Blood Derived Mesenchymal Stem Cells for Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	USA	Cord blood **Dose:** IV over 1-2 hours on day 1. Patients may receive a second infusion of MSCs within 7 days after the first infusion per physician discretion. No information available on dosage. **Primary Outcome(s):** Safety [Time Frame: At day 30 post MSC infusion], Mortality [Time Frame: At day 30 post MSC infusion	35 Control 35 Exp
NCT04371393	Mesenchymal Stromal Cells for the Treatment of Moderate to Severe COVID-19 Acute Respiratory Distress Syndrome	USA	Mesenchymal Stromal Cells (Remestemcel-L) **Dose:** 2*10E6 cells/kg of body weight IV plus standard of care, administered twice during the first week, with the second infusion at 4 days following the first infusion (± 1 day) **Primary Outcome(s):** Number of all-cause mortality [Time Frame: 30 days]	150 Control 150 Exp
NCT04611256	Adjuvant Therapy With Mesenchymal Stem Cells in Patients Diagnosed With COVID-19 in Critical Condition	Mexico	Adipose tissue **Dose:** Two IV infusion of 1*10E6 cells /kg body weight **Primary Outcome(s):** Days to clinical improvement [Time Frame: up to 25 days], Blood oxygen saturation [at day 25]	10 Control 10 Exp
NCT04615429	Double-blind, Randomized, Controlled, Clinical Trial to Assess the	Spain	Not specified **Dose:** 1*10E6 cells /kg body weight	10 Control 10 Exp

	Efficacy of Allogenic Mesenchymal Stromal Cells in Patients With Acute Respiratory Distress Syndrome Due to COVID-19		**Primary Outcome(s):** Blood oxygen saturation [Time Frame: 7 days]	

Footnote: The information to compile the table was obtained consulting the (1) EU Clinical Trials Register at https://www.clinicaltrialsregister.eu/ctr-search/search, (2) Chinese Clinical Trial Registry at http://www.chictr.org.cn/enindex.aspx, (3) ClinicalTrials.gov database at https://clinicaltrials.gov/, (4) Iranian Registry of Clinical Trials at https://www.irct.ir/, (5) Japanese Registry of Clinical Trials at https://www.clinicaltrials.jp/, (6) Australian Clinical Trials at https://www.australianclinicaltrials.gov.au/, (7) SRCTN registry at https://www.isrctn.com/, (8) Clinical Trial Registry – India at - http://ctri.nic.in, and (9) Registro Basileiro de Ensaios Clinicos at https://ensaiosclinicos.gov.br/.