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Mesenchymal stromal cells to fight SARS-CoV-2: Taking advantage of a pleiotropic therapy

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ABSTRACT

The devastating global impact of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has prompted scientists to develop novel strategies to fight Coronavirus Disease of 2019 (COVID-19), including the examination of pre-existing treatments for other viral infections in COVID-19 patients. This review provides a reasoned discussion of the possible use of Mesenchymal Stromal Cells (MSC) or their products as a treatment in SARS-CoV-2-infected patients. The main benefits and concerns of using this cellular therapy, guided by pre-clinical and clinical data obtained from similar pathologies will be reviewed. MSC represent a highly immunomodulatory cell population and their use may be safe according to clinical studies developed in other pathologies. Notably, four clinical trials and four case reports that have already been performed in COVID-19 patients obtained promising results. The clinical application of MSC in COVID-19 is very preliminary and further investigational studies are required to determine the efficacy of the MSC therapy. Nevertheless, these preliminary studies were important to understand the therapeutic potential of MSC in COVID-19. Based on these encouraging results, the United States Food and Drug Administration (FDA) authorized the compassionate use of MSC, but only in patients with Acute Respiratory Distress Syndrome (ARDS) and a poor prognosis. In fact, patients with severe SARS-CoV-2 can present infection and tissue damage in different organs, such as lung, heart, liver, kidney, gut and brain, affecting their function. MSC may have pleiotropic activities in COVID-19, with the capacity to fight inflammation and repair lesions in several organs.

1. Introduction

COVID-19 disease, caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is spreading fast and causing a devastating number of deaths. Even though lungs are the main affected organ, there is evidence that other organs can be compromised by COVID-19, demanding a pleiotropic therapy [1–3]. This requirement could be met by the use of mesenchymal stromal cells (MSC), which are

Abbreviations: COVID-19, Coronavirus Disease of 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MSC, mesenchymal stromal cells; FDA, US food and drug administration; ARDS, acute respiratory distress syndrome; MERS, middle east respiratory syndrome; SARS, severe acute respiratory syndrome; ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane protease serine 2; LPS, lipopolysaccharide; ALI, acute lung injury; GMCSF, granulocyte-macrophage colony-stimulating factor; MCP-1, Monocyte Chemoattractant Protein 1; IL, interleukin; TNF-a, tumor necrosis factor alpha; IFN-y, interferon y; FGF7, fibroblast growth factor 7; IDO, indoleamine 2,3 dioxygenase; BM-MSC, bone marrow mesenchymal stromal cells; MB-MSC, menstrual blood mesenchymal stromal cells; EVs, extracelular vesicules; LVEF, left ventricle ejection fraction; Th, T helper; Treg, T regulatory; GI, gastrointestinal; IBD, inflammatory bowel disease; CD, Crohn's disease; CM, conditioned-medium; VEGF, vascular endotelhial growth factor; DCs, dendritic cells; BBB, blood-brain-barrier; CNS, central nervous system; JEV, Japanese encephalitis virus; NK, natural killer; IV, intravenous.

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multipotent stem cells with the ability to differentiate into other cell types and be used for cell replacement therapy. Furthermore, MSC secrete a wide range of paracrine factors, which can modulate inflammation and promote tissue regeneration (Fig. 1) [4]. Indeed, regardless of the organ, SARS-CoV-2 infection causes disseminated inflammatory reactions, so therapies that bear immunomodulatory effects are welcome to treat COVID-19. Corroborating this idea, several clinical trials using MSC or their derived products are now ongoing and eight clinical studies were already concluded and reported interesting results, as most COVID-19 patients recovered a few days after treatment [5–12]. However, only one of these studies incorporated appropriate control groups and a considerable number of patients. The urgent need to perform larger clinical studies with suitable cohorts are here discussed.

This review discusses the main injuries in organs infected by SARS-CoV-2 and highlights the possible application of MSC to COVID-19 patients by addressing putative mechanisms of these cells or their secretome/Extracellular Vesicles (EVs), based on information of their use in similar pathologies. Anticipated issues are also discussed in order to optimize future therapeutic designs

2. What is COVID-19 and what do we know so far?

An outbreak of atypical pneumonia, now known as COVID-19, upsurged in the city of Wuhan, China, in December 2019. The disease rapidly spread throughout the world and as of 30th November 2020, more than 62 M people have been diagnosed with COVID-19 and over 1.4 M of deaths were confirmed worldwide (coronavirus.jhu.edu/map.html). The pathogenic agent was quickly identified as SARS-CoV-2, a relative of the coronaviruses that caused the SARS outbreak in 2003 (79.5 % genetic similarity) and the Middle East Respiratory Syndrome in 2012 (50 % genetic similarity) [13,14]. SARS-CoV-2 is a betacoronavirus, possessing a positive single-stranded RNA and a total genome of 29,881 bp [15]. Like other coronaviruses, it has a nucleocapsid protein, membrane and spike glycoproteins and another glycoprotein with acetyl esterase and hemagglutination properties [16].

This novel virus likely originated from bats (as it is closely related with two other bat-derived SARS-like coronaviruses, the bat-SL-CoVZC45 and the SL-CoVZXC21) and may have passed to an unknown reservoir animal; then jumped to humans and promptly spread due to human-to-human transmission through direct contact or droplets [13,14]. On average, the incubation period of COVID-19 is 4 days and it has also been reported that some patients are asymptomatic but can transmit the virus [17,18].

SARS-CoV-2 enters the cells after binding to the Angiotensin-Converting Enzyme 2 (ACE2) through its spike glycoproteins; additionally, the cellular Transmembrane Protease Serine 2 (TMPRSS2) has been shown to play a role in infection [19]. SARS-CoV-2 has the potential to infect cells in tissues where these receptors are widely expressed including the lungs, heart, kidneys, liver, gut and even the brain [1–3]. The main symptoms of COVID-19 are dry cough, fever, fatigue and shortness of breath, along with anosmia and ageusia. Some of the minor symptoms include headache, diarrhea and nausea [20]. The majority of patients have light manifestations of the disease without much requirement for medical assistance. However, in severe cases, patients may develop ARDS, arrhythmia, neurological symptoms, septic shock and metabolic acidosis [17,21,22]. Upon infection, SARS-CoV-2 elicits an initial adaptive immune response that is developed during earlier stages to eliminate the virus. However, patients with dysfunctional bridge in adaptive immunity exhibit an exacerbated innate immune response, generating high levels of free radicals which can culminate in multi-organ failure and death [23–25]. Biochemical analyses showed that most COVID-19 patients have decreased lymphocyte and leucocyte counts as well as increased levels of C-reactive protein (inflammation marker) and lactic dehydrogenase [20,24]. Moreover, ACE2 and ACE, a homologous protein, are both involved in regulating the renin-angiotensin system (RAS), which controls blood pressure and ensures the maintenance of endothelial tissue. When SARS-CoV-2 binds to ACE2, the receptor becomes downregulated and RAS is highly

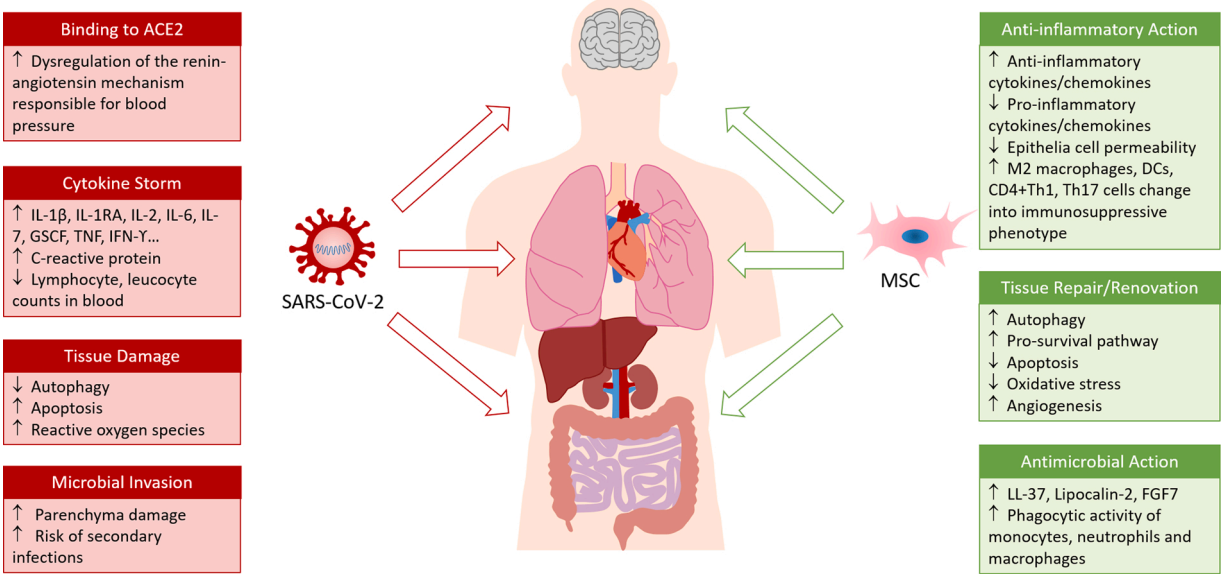

Fig. 1. Mesenchymal stromal cells (MSC) therapeutic potential to treat COVID-19. Upon entering the body, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is able to infect multiple organs (lungs, heart, liver, kidneys, gut and brain) by binding to Angiotensin-Converting Enzyme (ACE2) through its spike glycoproteins. ACE2 modulates the renin-angiotensin mechanism, thus the presence of the virus can lead to dysregulations in blood pressure. Moreover, SARS-CoV-2 can evoke an exacerbated inflammatory response which may lead to multi-organ injury. Besides, extensive damage in the parenchyma can increase the risk of opportunistic infections. MSC therapy is a promising treatment for COVID-19 as they exert potent anti-inflammatory and antimicrobial actions and promote tissue repair and regeneration through the secretion of soluble factors, extracellular vesicles and direct cell-to-cell contact.
List of abbreviations: ACE2 - Angiotensin-Converting Enzyme 2; DCs - Dendritic Cells; GSCF - Granulocyte Colony-Stimulating Factor; FGF7 - Fibroblast Growth Factor 7; IFN-ϒ - Interferon ϒ; IL - Interleukin, MSC – Mesenchymal Stromal Cells, TNF - Tumor Necrosis Factor; Th - T helper; SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2.

disturbed. This mechanism can lead to vasoconstriction, enhanced inflammation and thrombosis [26]. Thus, patients with hypertension or cardiovascular disorders are risk groups for COVID-19. Nonetheless, even though SARS-CoV-2 can infect people of all ages and sexes, the most severe cases usually occur in elder patients and/or patients with comorbidities (e.g., chronic diseases, cancer, obesity, diabetes) [20,21].

Unfortunately, there is still no specific treatment. Hand disinfection, social distancing and the use of masks [27] are the recommended preventive tools so far. Additionally, patients are provided with adequate supportive care and treated for secondary infections. The efficacy of several existing treatments used in other diseases such as antivirals (Remdesivir, Favipiravir, Lopinavir/Ritonavir), anti-inflammatory drugs (glucocorticoids and hydroxychloroquine), and plasma transfusion from recovered patients has been investigated for COVID-19 [28,29]. Nevertheless, the available data is scarce regarding their efficacy and some drugs initially thought to be effective have now shown disappointing performances, as the case of hydroxychloroquine, Lopinavir/Ritonavir and Remdesivir [28,30,31].Currently, a high number of preventive vaccines are being tested and some were shown to be safe and highly effective in conferring immunity against SARS−COV-2 (modernatx.com; pfizer.com [32]).

However, these vaccines still need to be approved by the regulatory authorities and the widespread distribution and administration of vaccines is necessary in order to confer herd immunity. This process will take time to be completed, so effective therapies are needed for the time being. The use of cell therapy in COVID-19, particularly with MSC, demonstrated promising outcomes on preliminary clinical reports [5–7]. Additionally, MSC can be used in conjugation with other favourable therapies, amplifying the treatment's efficacy.

3. MSC: multi-organ protection against acute injury?

MSC are multipotent stem cells that must meet a minimum criteria to be distinguished from other cell types [33]: 1) Plastic adherence; 2) Surface expression of CD105, CD73, CD90, and lack of CD45, CD34, CD14, CD19 and HLA-DR; 3) *in vitro* differentiation into osteoblasts, adipocytes and chondroblasts. They are found in various tissues throughout the body being the most common sources, for research and clinical purposes, bone marrow (BM-MSC), umbilical cord (UC-MSC) and adipose tissue (AD-MSC). Importantly, both allogeneic and autologous transplants are possible as MSC have a low immunogenicity [34]. MSC are commonly administrated through intravenous (IV) injection, although other routes might be more appropriated according to the target organ.

MSC have been extensively researched for their ability to generate strong immunomodulatory and regenerative effects in damaged tissues [4]. This therapeutic potential depends on the microenvironment in which MSC are placed as their response is very sensitive to factors such as the extracellular matrix and substances released by other cells; therefore, they can have highly adaptative responses to different cellular contexts [35]. In fact, the presence of inflammatory factors may alter MSC secretion profile towards a greater immunomodulatory action [36]. In agreement, cultured MSC can also be stimulated by different pre-conditioning protocols to release a myriad of cytokines, growth factors, and EVs containing miRNAs that are relevant for mechanisms involved in inflammation [37]. The EVs and conditioned medium obtained can similarly be used as a cell-free alternative to exploit the strong paracrine communication of MSC without the ethical, technical, and physiological complications that may arise from stem cell transplantation at the clinical level [38].

3.1. Lungs, the most affected organ in COVID-19 patients

For the time being it seems the lungs are the most affected organ in COVID-19 patients, as ARDS is a significant symptom amongst the patients that develop a severe form of the disease [17]. Indeed, the ACE2 receptor, to which SARS-CoV-2 binds, is widely expressed at the surface of lung alveolar type II and capillary endothelial cells [39]. In the lungs, SARS-CoV-2 can elicit a cytokine storm with secretion of high levels of pro-inflammatory cytokines such as Interleukin (IL) 1β, IL-1 Receptor Antagonist (IL-1RA), IL-2, IL-6, IL-7, Granulocyte Colony-Stimulating Factor (GCSF), Interferon (IFN) ϒ and Tumor Necrosis Factor (TNF), as well as infiltration of neutrophils and macrophages in alveolar space [24,40]. This prolonged exacerbated inflammatory response enhances the production of reactive oxygen species that damage the lung tissue and lead to ARDS, which is characterized by pulmonary edema, arterial hypoxia and dysfunction of air exchange function [5,41]. Moreover, the presence of the virus in the lungs also increases the risk of secondary infections [1].

Over the last decades, the therapeutic potential of MSC for the treatments of severe respiratory illnesses has been extensively investigated in pre-clinical studies, namely in ARDS animal models using various injury-inducing mechanisms, including viral infections. MSC are believed to promote a multitude of beneficial actions providing support not only by modulating the immune response and inflammation, but also by promoting tissue repair, impeding fibrosis and improving pulmonary dysfunction [4,42]. A meta-analysis of 57 studies that investigated the efficacy of MSC transplantation in ALI/ARDS animal models revealed that MSC can reduce lung injury, improve lung compliance and animal survival in part by modulating inflammation [43].

The administration of MSC has been shown to reduce Acute Lung Injury (ALI) induced by influenza virus H9N2 and increase mice survival, mainly by attenuating the host inflammatory response. MSC were able to modulate the levels of chemokines (Granulocyte-Macrophage Colony-Stimulating Factor, Monocyte Chemoattractant Protein-1 (MCP-1), Chemokine CXC Motif Ligand 1, Macrophage Inflammatory Protein 1α and Monokine Induced by Gamma Interferon) and cytokines (IL-1α, IL-6, TNF-α, and IFN- ϒ) that greatly contribute to ALI development. An increased expression of IL-10, an anti-inflammatory cytokine was also observed [44]. The higher expression of this specific cytokine may be explained by MSC production of prostaglandin E_2 which can reprogram macrophages to increase their secretion of IL-10 [45]. Moreover, Busto et al. showed that MSC pre-activated by explosion to ALI patients' serum expressed high amounts of IL-10 and IL-1RA, which were linked to MSC ability to reduce pulmonary edema and infiltration of inflammatory cells and cytokine production [46]. Accordingly, MSC have been shown to protect lungs from bleomycin-induced injury (a model of ALI) by expressing IL-1RA which can decrease macrophages' secretion of TNF and inhibit proliferation of T-cell [47]. Another anti-inflammatory protein that contributes to MSC ability to reduce ALI is TNF-α-induced protein 6 [48].

Another important action of MSC in the treatment of ARDS is their antimicrobial effect. Indeed, MSC can enhance the phagocytic activity of host monocytes, neutrophils and macrophages [49,50]. These antimicrobial actions have been linked to MSC production of LL-37, Lipocalin-2 and Fibroblast Growth Factor 7 (FGF7), as the use of blocking agents for these peptides nullified the protective effect of MSC in *in vivo* and *ex vivo* models of lung injury [49,51,52]. Furthermore, it has been demonstrated that mitochondria transference from MSC to macrophages - through tunneling nanotube-like structures or via EVs - also plays an important role in the increment of their phagocytic activity in ARDS [53,54]. In cases of viral-induced injury such as COVID-19, this action could be crucial to prevent or treat opportunistic bacterial infections.

Furthermore, several studies have shown that MSC and its secretome are able to promote tissue repair and regeneration in models of ALI and ARDS [55,56]. Indeed, MSC secrete Angiopoietin-1 and FGF7 (also known as Keratinocyte growth factor) which promote stability of endothelial cells, thereby repairing the alveolar-capillary barriers, increasing alveolar fluid clearance and reducing pulmonary edema [56–58]. Additionally, MSC have been shown to repair alveolar cells by mitochondrial transfer through direct cell-to-cell contact, increasing their bioenergetic levels [59]. MSC may also protect pulmonary cells by

increasing autophagy via phosphoinositol 3-kinase/protein B pathway [60].

The generally promising pre-clinical findings prompted the design of several clinical trials to investigate the therapeutic potential of MSC for the treatment of ARDS. These studies primarily aimed at evaluating the safety of this approach, showing that MSC transplantation in ARDS patients is safe, since no major side effects related to MSC infusion have been reported [61–64]. Indeed, a phase I clinical study that tested three doses of BM-MSC in patients with moderate to severe ARDS showed that BM-MSC administration was well tolerated even at the highest dose [63]. A description of the experimental conditions in the mentioned clinical trials is given in Table 1.

Clinical effects of MSC in ARDS/ALI were not always consistently found in the literature. In 2014, Zheng and collaborators demonstrated that Adipose-derived (AD)-MSC transplantation decreased inflammation; however, under their experimental conditions, the beneficial outcomes were weak [61]. Moreover, in a phase IIa double-blind placebo-controlled clinical trial, Matthay and colleagues did not find significant favorable effects [65]. Importantly, it was pointed out that MSC viability had to be improved in future studies, since it ranged from 36 % to 85 % after thawing. The primary aim of this study was to evaluate safety and the same group will further assess the efficiency of the approach in a larger phase IIb clinical trial (NCT03818854).

In contrast, Simonson et al. demonstrated that BM-MSC infusion promoted improvements in respiratory and hemodynamic function, decreased inflammation levels and avoided multi-organ failure in 2 severe refractory ARDS patients [62]. Corroborating these results, another study showed that MSC from Menstrual Blood (MB-MSC) could ameliorate ARDS induced by the bird flu virus H7N9 infection as MB-MSC led to a reduction in mortality (54.5 % in the control group vs 17.6 % in the treated group) [64].

Overall, there is evidence that MSC are safe and may be beneficial in inflammatory lung injuries even though further investigation is necessary in order to clarify what are the optimal therapeutic conditions. MSC exert important anti-inflammatory, antimicrobial and reparative actions which could be of great help in the treatment of COVID-19 patients

Table 1
Concise information of some clinical trials performed with MSC in pathologies that affect the lungs, heart, liver, kidneys, gut or brain, and share disease mechanism with COVID-19. Most clinical trials include a control/placebo group except for the ones mentioned.

Reference/Trial Identification	Title	Disease	Phase	Cells/ product	Dose/frequency of administration	Delivery rote	No of patients
NCT01902082 [61]	Adipose-derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome	ARDS	I	AD-MSC	one time 1×10^6 Cells/Kg administration	IV	6
[62]	In Vivo Effects of Mesenchymal Stromal Cells in Two Patients With Severe Acute Respiratory Distress Syndrome	ARDS	NR	BM-MSC	one time 2×10^6 Cells/Kg administration	NR	2
NCT01775774 [63]	Human Mesenchymal Stem Cells For Acute Respiratory Distress Syndrome	ARDS	I	BM-MSC	one time G1: 1×10^6 G2: 5×10^6 G3: 10×10^6 Cells/Kg administration	IV	9
NCT02095444 [64]	Using Human Menstrual Blood Cells to Treat Acute Lung Injury Caused by H7N9 Bird Flu Virus Infection	ALI	I/II	MB-MSC	Four times 1×10^7 administration	IV	61
NCT02097641 [65]	Human Mesenchymal Stromal Cells For Acute Respiratory Distress Syndrome (START)	ARDS	IIa	BM-MSC	one time 10×10^6 Cells/Kg administration	IV	60
[83]	Efficacy of mesenchymal stem cell therapy in systolic heart failure: a systematic review and meta-analysis	HF	RCT	BM-MSC UC-MSC	NS $1 \times 10^6 \sim 1 \times 10^7$ Cells/Kg	IC TESI IV	612
[84]	Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis	AMI IHF	RCT NC		One to three times $0.1 \times 10^6 \sim 1 \times 10^7$ Cells/Kg	IC IV IMY EC EP	1148
[90]	Human mesenchymal stem cells for hepatitis B virus-related acute-on-chronic liver failure: a systematic review with meta-analysis	HBV-ACLF	RCT PC	BM-MSC UC-MSC	three time 0.5×10^5 Cells/Kg four times $1 \times 10^5 \sim 1 \times 10^6$ Cells/Kg	IV Hepatic artery	198
NCT00733876 [101]	Allogeneic Multipotent Stromal Cell Treatment for Acute Kidney Injury Following Cardiac Surgery	AKI	I	BM-MSC	one time 2×10^6 Cells/Kg (optimal)	Suprarenal aorta	16
NCT01602328 [102]	A Study to Evaluate the Safety and Efficacy of AC607 for the Treatment of Kidney Injury in Cardiac Surgery Subjects	AKI	II	BM-MSC	one time 2×10^6 Cells/Kg	Suprarenal aorta	156
NCT01090817 [118]	A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy	Crohn's disease	II	BM-MSC (allogeneic)	Four times 1×10^6 cells/Kg	IV	15
NCT01659762 [119]	The safety of autologous and metabolically fit bone marrow mesenchymal stromal cells in medically refractory Crohn's disease – a phase 1 trial with three doses	Crohn's disease	I	BM-MSC (autologous)	One time 2, 5 or 10×10^6 cells/Kg (n = 4/group)	IV	12
NCT02497443 [141]	Treatment of Refractory Epilepsy Patients with Autologous Mesenchymal Stem Cells Reduces Seizure Frequency: An Open Label Study	Epilepsy	I	BM-MSC (autologous)	One time 1×10^6 cells/Kg IV administration + one time 1×10^6 cells/Kg IT	IV/IT	22

List of abbreviations: ARDS – Acute respiratory distress syndrome; ALI - Acute lung injury; AMI - Acute Myocardial Infarction; AD-MSC – adipose tissue-derived mesenchymal stromal cells; BM-MSC – bone marrow-derived mesenchymal stromal cells; UC-MSC – umbilical cord-derived mesenchymal stromal cells; EC- endocardial; EP- epicardial; HBV-ACLF - hepatitis B virus-related acute-on-chronic liver failure; HF – heart failure; IC - intracoronary; IMY – intramyocardial; IV – intravenous; IHF - Ischemic Heart Failure; NC - Non Randomized control trial; PC- prospective cohort; RC - Randomized control trial; NR – Not Reported.

exhibiting ARDS symptoms [66–68].

3.2. Heart, Liver and Kidney, three organs that can lead to body failure in COVID-19

3.2.1. The heart

Several reports have shown that COVID-19 is associated with cardiovascular complications such as arrythmia [2,69], myocarditis [70,71], acute coronary syndrome [72], coagulopathies [69,73], and Kawasaki syndrome [73]. The origin of these clinical manifestations is somewhat questionable, as it may be a consequence of direct infection of cardiac tissue [74], systemic inflammation and multi-organ injury, or combination of both. Nevertheless, a retrospective analysis indicates that mortality is very high in patients with myocardial injury associated with COVID-19 (37.5 % in this study).

MSC or their derived products have shown protective effects in a large range of cardiovascular diseases due to their immunomodulatory, antifibrotic, neoangiogenic, and antiapoptotic potential [75–77]. As an example, AD-MSC can suppress severe coronary arteritis in mice with experimental Kawasaki syndrome by lowering the levels of IL-1B, IL-12, IL-17, C-C Motif Chemokine Ligand 5, INF-ϒ, and TNF-αa, therefore reducing systemic inflammation [78]. Moreover, the use of MSC [79] presents encouraging results in murine models of viral myocarditis caused by Coxsackievirus b3 (+SSRNA) through immunomodulatory mechanisms. Exosomes were also able to regulate autophagy in this model by modulating the 5′AMP-activated Protein Kinase/Mammalian Target of Rapamycin pathways and reducing apoptosis of cardiomyocytes [80].

So far, most clinical trials using MSC are focused on ischemic/non-ischemic cardiomyopathy [81] and myocardial infarction [82] (Table 1). A meta-analysis of 9 clinical trials compared different delivery approaches (IV, trans-endocardial, or intracoronary), donor (allogenic or autologous) and tissue source (BM-MSC or UC-MSC) [83]. The overall rate of death for patients with systolic heart failure was shown to be reduced by 36 % and up to 70 % in the intracoronary injection subgroup. Additionally, allogeneic were more effective than autologous MSC and the 6-minutes' walk test and Left Ventricle Ejection Fraction (LVEF) were significantly improved in treated patients. There were no significant differences in efficacy between different tissue sources although the readmission rate was lower in the BM-MSC subgroup. Another analysis of 23 clinical trials, focusing on acute myocardial injury or ischemic heart failure [84], conducted with MSC from different sources (BM-MSC, UC-MSC or AD-MSC) and administration routes (IV, intracoronary, intramyocardial, endocardial, or epicardial) also found an improvement in LVEF but not in mortality. UC-MSC and intracoronary administration were more effective than other procedures. No major adverse effects were reported except for a mild and short fever in the first study [83] and some neurological delayed adverse effects (of unspecified nature) in the second, although these were rarely correlated with MSC treatment [84].

Hence, pre-clinical data suggests that MSC or MSC-derived products could have cardioprotective effects against SARS-CoV-2 by reducing the levels of pro-inflammatory cytokines, inhibiting apoptosis, enhancing angiogenesis [76], and polarizing macrophages towards an anti-inflammatory state [77], in agreement to what has been observed in other pathologies where the heart tissue is also inflamed. Clinical data also suggests that MSC might be able to improve heart's mechanics [84] and reduce mortality [83]. Therefore, MSC may be beneficial in COVID-19 patients with associated heart failure.

3.2.2. The liver

Research in *ex vivo* models of COVID-19 using human liver duct organoids suggests the possibility of direct liver injury through infection and apoptosis of cholangiocytes in the bile ducts [85]. To support these claims, cholestasis and hepatitis were already described in association with COVID-19 [86]. The bile ducts, which have higher ACE2 expression than hepatocytes [87], are particularly affected in severe patients. Despite these suggestive facts, liver injury may also be promoted by sepsis or hepatoxic drugs administered as standard medical care.

Pre-clinical studies involving the use of MSC in animal models of sclerosing cholangitis showed positive effects mainly through immunomodulation of T helper (Th) cells [88], reduction of Cytokeratin 19, Metallopeptidase 9, TNF-α, MCP-1, and improvement of monocyte infiltration in bile ducts [89]. Thus, in inflammatory conditions, MSC are able to decrease inflammation and apoptosis of cholangiocytes while improving the bile duct mechanics.

Moreover, some clinical studies revealed that MSC can ameliorate acute-on-chronic liver failure associated with Hepatitis B virus [90] (Table 1). This type of infection can lead to fibrosing cholestatic hepatitis - a type of severe cholestasis with high mortality [91]. Indeed, a meta-analysis of 3 Chinese clinical trials found a significant decrease in mortality (52.3 %–23.1 %) and hepatic inflammation markers 12 weeks post-treatment with MSC of either allogeneic or autologous source [90]. Despite the potential benefits in terms of enhancing patients' life quality and prognosis, more trials with larger cohorts are required to consolidate these findings.

Even though the use of MSC in hepatic conditions is yet preliminary, the immunomodulatory and regenerative effects described above could be beneficial in COVID19 patients experiencing hepatic injury.

3.2.3. The kidneys

The kidneys are one of the most afflicted organs during COVID-19 infection. Acute Kidney Injury (AKI) has been reported in a high percentage of patients admitted to intensive care with most of them requiring renal replacement therapy [92]. The presence of urinary sodium <35 mEq/l associated with high urine-specific gravity observed in many COVID-19 hospitalized patients is indicative of pre-renal causes of AKI, although it may also appear in certain types of acute tubular necrosis [93]. A high number of viral particles is present in post-mortem analysis of renal cells, suggesting a possible relation between viral infection and necrosis in proximal tubule endothelial cells [92], where the expression of ACE2 is higher than in type II pneumocytes [94]. Moreover, complement activation, coagulopathy, and endothelial dysfunction may be relevant for the establishment of AKI in COVID-19 patients [95].

Over the last decades, various pre-clinical studies showed that MSC have nephroprotective effects in models of AKI induced by chemotherapy (cis-platinum), ischemic reperfusion, or renal transplantation through several mechanisms such as immunomodulation, inhibition of apoptosis, and promotion of angiogenesis [96]. Furthermore, some studies have emphasized the important role of MSC-derived EVs [97,98]. These vesicles carry miRNAs that can alter the expression of genes involved in cellular adhesion and extracellular matrix remodeling in tubular epithelial cells, contributing to kidney regeneration [99,100].

In light of the regenerative properties mentioned above, a few clinical trials investigating the use of MSC to treat Chronic Kidney Disease (CKD) or AKI have been registered in clinicaltrials.gov (Table 1). However, so far only two studies in AKI have published results and even though MSC were safe in both, the results were somewhat contradicting and the authors didn't report any objective biochemical parameter. In a phase I study, infusion of allogeneic BM-MSC via the suprarenal aorta prevented the deterioration of kidney function in cardiac surgery patients at high risk of developing AKI [101,102]. The hospitalization time and hospital readmission rate decreased approximately 40 % when compared with well-matched historical case-control from the same institution [101]. Contrarily, in a phase II study, Swaminathan et al. did not find any differences regarding the number of days to recover and mortality rate 30 days after treatment with allogeneic MSC through intra-aortic administration [102].

Thus, the relevance of MSC in promoting regeneration of renal tubular cells has been demonstrated in pre-clinical studies and their administration shown to be safe in subsequent clinical trials with AKI

patients. An ongoing clinical trial is set to investigate the efficacy of MSC therapy in COVID-19 patients with AKI (NCT04445220).

3.3. The gut and virus spread by fecal-oral transmission

The gut is another organ that can be severely damaged by SARS-CoV-2 [103]. Indeed, it has been described that gastrointestinal (GI) alterations appear as early symptoms in the course of COVID-19 disease [104]. Clinical studies reported that GI symptoms are present in a relatively high percentage of COVID-19 patients and may contribute to viral spread by fecal-oral transmission [105,106]. Indeed, deep alterations in gut microbiota were reported in COVID-19 [107] and some infected patients presented SARS-CoV-2 mRNA in stool, even after the nasopharyngeal symptoms had disappeared and they were considered recovered from the disease [108]. Corroborating these statements through elegant assays performed in human gut organoids, Clever's Lab showed that human gut enterocytes can be actively infected by SARS-CoV-2 and also support viral replication [109].

MSC therapeutic application for inflammatory gut conditions showing similar symptoms to COVID-19 has been extensively evaluated. In Inflammatory Bowel Disease (IBD), MSC have been proposed to exert a therapeutic effect in dysbiosis by 1) regulating inflammation; 2) potentiating the restoration of diversity and composition of colonic bacteria; 3) promoting the eradication of pathogenic bacteria; 4) inducing tissue remodeling, due to their strong immunomodulatory and tissue regenerative potential [110,111]. An interesting study analyzed the effects of CM-MSC in an experimental colitis model and found that pleiotropic gut trophic factors are released by these cells. Specifically, Wingless-related Integration Site and Secreted Frizzled-related Protein were identified to be important regulators of epithelial cell proliferation and differentiation, whereas Vascular Endothelial Growth Factor (VEGF) and MCP-1 induced basement membrane angiogenesis and remodeling, respectively [112].

The immunosuppressive effects in CD's mucosal T cells were evaluated in *ex vivo* cultures. MSC effect was highly dependent on IDO and cell-cell contact [113]. By performing co-cultures with T cells from CD mucosa, the authors realized that in the presence of MSC the activated subset of CD4+CD25+ T cells was reduced whereas the CD3+CD69+ population increased. Moreover, these cells promoted the secretion of the pro-inflammatory cytokines TNF-α, IFN-γ, IL-17A, IL-21, and over-expression of the Transforming Growth Factor-β and IL-6. These effects were almost eradicated by blocking IDO [113]. Another study demonstrated that the anti-inflammatory response of MSC is dependent on secreted MCP-1 and C-X-C motif chemokine 12 [114]. Overall, MSC anti-inflammatory effects relied on the following actions: M1 macrophages; Dendritic Cells (DCs); CD4+Th1 and Th17 cells, which are able to change their phenotype into immunosuppressive M2 macrophages, tolerogenic DCs and Treg cells, as shown by several groups [45, 115–117].

Lately, their application in IBD has even been tested in clinical trials (clinicaltrials.gov), but only a Phase I and a Phase II studies presented reports [118,119] (Table 1). The Phase I clinical study aimed at evaluating the safety/tolerability of three different doses of autologous BM-MSC and concluded that no toxicity associated with dose was found while 41,7 % of the patients presented clinical response 2 weeks after the treatment [119]. In the Phase II trial, allogeneic MSC were administered into patients with CD and reduced CD indexes of severity scores in patients presenting luminal CD not responding to biologic therapy [118]. In both studies, the serious adverse effects that were reported in 16,7 % and 6,3 % of patients respectively, were directly related with pre-existing complications in CD (2 dysplasia-associated lesions, need for surgery and risk of bacterial infections such as *C. difficile* that are known to be elevated in moderate to severe CD).

Therefore, pre-clinical and clinical studies show the feasibility and potential therapeutic effect of MSC treatment for GI inflammatory conditions. Importantly, these conditions are similar to the ones present in SARS-CoV-2 infected patients.

3.4. The brain, one of the most affected organs by SARS-CoV-2

The neuroinvasive role of SARS-CoV-2, also underestimated at the beginning of the pandemic, became evident when the loss of smell and taste in COVID-19 patients was first reported, implicating an involvement of neuronal circuits [120]. Ever since, several other symptoms such as headache, dizziness, depression, encephalitis, stroke, epileptic seizures, and Guillain-Barre syndrome have been reported, demonstrating that the central nervous system can be severely impaired in COVID-19 patients [22].

Two main hypotheses have been proposed for brain entry and propagation throughout the central nervous system: 1) via the bloodstream; 2) through the olfactory epithelium of the nasal cavity and olfactory bulb via retrograde transport along axons of olfactory sensory neurons [22,121,122]. On the other hand, recent evidences support the theory of direct neurotropism of SARS-CoV-2, as the RNA of this virus was detected in the cerebrospinal fluid of a patient with COVID-19 [22]. Moreover, sincethe ACE2 receptor is expressed in brain endothelium, SARS-CoV-2 can enter into the CNS by interacting with ACE-2 of the capillary endothelium leading to blood-brain-barrier (BBB) disruption. BBB can also be damaged by neuroinflammation as a result of the cytokine storm [122,123].

The BBB is affected in many viral infections, compromising the brain homeostasis and function [124–130]. If this is the case MSC can also help reducing viral invasion, as the capacity of MSC or their derived products to recover the BBB has been widely disclosed for different neurological contexts [131–135]. A pre-clinical study with mice intraperitoneally infected with Japanese Encephalitis Virus (JEV) evidenced that MSC can protect BBB, alleviate JEV-induced inflammation, reduce microglia activation and consequent neuronal damage. In fact, viral load was significantly decreased in this mouse model as well as mortality rate [136]. Furthermore, through *in vitro* co-culture experiments, the authors detected that the presence of MSC induced reprogramming of microglia from M1 to M2 and decreased viral load, while increasing the expression of INF-α/β in Neuro2a cells [136]. Another set of pre-clinical studies also evaluated the efficacy of MSC in reducing depression in mouse models for Malaria [137], major depressive disorder [138] and chronic mild stress [139], all showing that MSC were able to dimmish depressive-like behaviors in the respective models. Interestingly, these studies proposed a common action mechanism of MSC that correlated with the microglial polarization from M1 to M2 phenotype, and down-regulation of TNF-α, IL-1β, and IL-6 (and MCP-1 in the last study). Depression has been highly correlated with inflammatory processes. Thus, it makes sense that MSC can turn down depressive symptoms by normalizing the triggering pro-inflammatory effectors. Pre-clinical studies thus revealed that MSC can in fact lessen depression and encephalitis, two neurological symptoms of COVID-19.

Stroke is a relatively prevalent symptom among COVID-19 patients. A retrospective, observational study reported that of 219 patients with COVID-19, 10 developed acute ischaemic stroke (4.6 %) and 1 had intracerebral haemorrhage (0.5 %). These patients were older and were more likely to have cerebrovascular risk factors, such as hypertension, diabetes and medical history of cardiovascular disease [140]. Importantly, a few clinical studies have reported that MSC therapy for ischemic stroke is safe, feasible and demonstrated therapeutic efficacy to counteract neurological impairments driven by stroke. Namely, MSC induced immunomodulation, angiogenesis and both neuroprotection as well as the re-establishment of neural circuit. A summary of the reported clinical trials and a complete revision of the transplantation procedures, type MSC used, the most effective ways of administration and relevant therapeutic mechanisms can be found in [141].

There is also registration of a Phase I open-label clinical trial that evaluated the efficacy of MSC in reducing seizure frequency in epileptic patients [142] (Table 1). A total of 12 patients were recruited and all

received anti-epileptic drugs; from these, 10 were randomly treated with MSC. The authors reported that MSC injections were well tolerated and did not cause any severe adverse effects. Three out of 10 patients receiving MSC presented no seizures for more than one year and a higher percentage responded positively to anti-epileptic drugs than in the control group (5 out of 10 in treated group vs 2 out of 12 in controls, P = 0.0135).

Based on these studies, MSC can probably fight SARS-CoV-2 infection in the CNS and counteract its deleterious effects resembling what is here described for other neurological pathologies. However, clinical evidences in COVID-19 of this effect would be desired.

3.5. MSC: A pleiotropic effect?

As conclusion, we suggest that MSC may offer good supportive treatment to COVID-19 patients, by both inhibiting overactivation of the immune system and repairing not only the lungs but also other crucial organs. However, despite these meaningful comparative studies, very little is still known about the mechanisms of SARS-CoV-2 infection in each organ and more descriptive studies are required to better understand the behavior of the virus. On the other hand, clinical studies are extremely important as they will allow (or not) for translation.

4. Clinical trials with MSC in COVID-19 patients

Supporting the possible implementation of MSC treatment in COVID-19, since the beginning of the outbreak four clinical studies and four case reports investigating MSC's therapeutic potential (and their derived products) to treat COVID-19 patients have been performed and already published their results [5–12]. Moreover, several phase I or II clinical trials are currently ongoing (www.clinicaltrials.gov). Notably, there are also ongoing studies that will evaluate whether MSC-derived EVs or CM-MSC administration is safe and can ameliorate COVID-19 symptoms (NCT04276987, NCT04366063, NCT04398303, ChiCTR2000029569, ChiCTR2000030261). A concise review of both completed and ongoing clinical studies is given in Table 2.

To date, clinical trials and case reports showed that MSC use in COVID-19 is safe as no major adverse effects directly related to MSC transplantation were reported. Additionally, MSC treatment was shown to promote patient's recovery, even in critically ill elders with comorbidities [5–11]. In these studies, moderate to critically ill COVID-19 patients were infused with MSC after they failed to improve, and symptoms worsened, under standard [5,7] or other treatment conditions [6,8,6–11]. So far, MSC transplantation seem to lead to clinical recovery of patients in relatively short time, showing amelioration of COVID-19 symptoms few days after MSC treatment. Indeed, MSC treatment alone or its combination with other therapies improved respiratory function and increased oxygenation [5–11]. Sánchez-Guijo and colleges demonstrated the effectiveness of MSC administration in 13 patients under invasive mechanical ventilation, as they improved the clinical status for 70 % of infected individuals and lead to the extubation of 53 % of them [11]. Additionally, a study that compared the mortality rate of patients treated with MSC or treated with standard conditions showed that while the control group had a mortality rate of 10.34 % 28-days after treatment, none of the MSC-infused patients perished [7].

Importantly, these clinical studies underline MSC's modulation of the immune response as a key mechanism to avoid a cytokine storm which may be a crucial step in the treatment of COVID-19. Indeed, MSC reestablished the levels of lymphocytes counts [5–11], T and Natural killer cells [6] and increased migration of DC to the site of inflammation [5]. Moreover, treatment with MSC decreased the levels of C-reactive protein and of pro-inflammatory cytokines and chemokines, such as TNF-α and IL-6 [5,7,8,11]. In addition, MSC also lowered inflammation-induced lesion in the lungs [7–9] and promoted lung tissue repair with increased IL-10 and VEGF expression [5]. Notably, Leng and collaborators showed that MSC did not express ACE2 nor TMPRSS2, meaning they were naturally immune to SARS-CoV-2, reinforcing MSC as a feasible therapeutic agent [5].

Overall, the published clinical trials and case reports followed similar approaches for the administration of MSC as the main or adjuvant therapy. In most cases 1×10^6 cells/ kg of body weight (though it ranged from $0.3-2 \times 10^6$ cells/ kg) were IV delivered [5–8,10,11], with one exception in which the IV route was combined with intratracheal delivery [9]. From all the seven studies, four infused MSC derived from UC-MSC [6,7,9,10], one MSC derived from the AD-MSC [11], one BM-MSC [5] and another MSC from menstrual blood [8]. The frequency of administration varied from study to study, or depended on patients' clinical conditions, with MSC being delivered one [5,7,11], two [9,11] or three times [8,11].

Furthermore, a prospective nonrandomized open-label cohort study demonstrated that the IV administration of exosomes derived from BM-MSC (ExoFlo™) is safe (with no therapy-related adverse events observed) and may also improve COVID-19 patient's condition [12]. From 24 severe COVID-19 patients that showed moderate-to-severe ARDS, 71 % of the patients recovered and were discharged 5.6 days after ExoFlo treatment on average; 14 % remained critically ill, but stable; and 16 % deceased. Thus, the survival rate was 83 %, higher than that estimated for patients in the same condition. Moreover, treatment restored patient's oxygenation. Similar to MSC transplantation, treatment with ExoFlo also improved inflammation, promoting a decrease in neutrophil count and lymphopenia and a significant reduction in C-reactive protein, ferritin and D-dimer.

The results obtained in these initial studies were encouraging, and very important to design future clinical studies. However, more double-blind, placebo-controlled studies have to be performed to confirm MSC promising effects in COVID-19 treatment, and optimal therapeutic conditions have to be investigated. Importantly, large cohorts would be crucial to validate this therapeutic intervention in the future.

5. Challenges for the clinical application of MSC in COVID-19

There are still some concerns regarding MSC application for therapeutic purposes, namely: 1) the fact that the precise mechanisms of MSC in COVID-19 patients are unknown and there is no robust pre-clinical model for COVID-19 that could facilitate research. 2) limited number of clinical trials including a high number of COVID-19 patients; 3) different clinical presentations; 4) the diversity of genetics and the consequent immune response in COVID-19 patients, 5) the presence of other associated comorbidities, challenging the gathering of clear conclusions regarding MSC outcomes in patients suffering from COVID-19.

However, based on beneficial evidence highlighted by either pre-clinical or clinical studies performed in inflammatory conditions which affect the main organs disturbed by SARS-CoV-2, and due to the lack of so far efficient treatments, it is reasonable to consider MSC therapy a feasible treatment. In that line, their compassionate use was already approved by the FDA for patients presenting ARDS with very bad prognosis. Moreover, a high number of clinical studies involving the use of MSC or medicines derived from these cells are presently running with the aim of introducing this treatment to critically ill COVID-19 patients in which especially severe impairment of pulmonary function is present. It must though be kept in mind that other organs can be severely damaged. So, it should be considered to expand their application to Covid-19 patients with other severe symptoms.

Accordingly, a high-grade clinical study, placebo-controlled, and ideally including patients from different countries would be crucial and should hence be performed. The highest well tolerated dose tested for ARDS could be used to treat COVID-19 patients [63,143]. Regarding the type of cells, though UC-MSC or BM-MSC are the main sources used so far in clinical studies (www.clinicaltrials.gov), there is a lack of consensus on which source is more appropriate for the different conditions herein referred. Indeed, MSC from different sources may exhibit different therapeutic potentials. For example, UC-MSC are usually

Table 2
Concise information of the clinical trials and case reports performed with MSC or MSC-derived products in patients with COVID-19.

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
NCT03042143	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19)	I/II	Ireland	CD362 enriched UC-MSC	400×10^6 cells/Kg	1	IV	70	Active, recruiting
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	I	China	MSC	3×10^7 cells/Kg	3	IV	20	Active, recruiting
NCT04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	II	China	UC-MSC	9.9×10^7	4	IV	10	Active, recruiting A control group was not included
NCT04273646	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	NA	China	UC-MSC	0.5×10^6 cells/Kg	4	IV	48	Active, not yet recruiting
NCT04276987	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	I	China	Exo from AD-MSC	2×10^8 vesicles	5	AI	30	Active, recruitment complete A control group was not included
NCT04288102	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19)	II	China	MSC	4×10^7 cells/Kg	3	IV	90	Active, recruitment completed
NCT04302519	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	I	China	DP-MSC	1×10^6 cells/Kg	3	IV	24	Active, not yet recruiting A control group was not included
NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	I	Jordan	WJ-MSC	1×10^6 cells/Kg	3	IV	5	Active, recruiting A control group was not included
NCT04315987	NestCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	I/II	Brasil	NestCell®	1×10^6 cells/Kg	3	IV	66	Active, not yet recruiting
NCT04333368	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS (STROMA-CoV2)	I/II	France	WJ-MSC	1×10^6 cells/Kg	1	IV	60	Active, recruiting
NCT04336254 ChiCTR2000031319	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	I/II	China	DP-MSC	3×10^7	3	IV	20	Active, recruiting
NCT04339660	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	I/II	China	UC-MSC	1×10^6 cells/Kg	1	IV	30	Active, recruiting
NCT04345601	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	I	U.S.	MSC	1×10^8	1	IV	30	Active, not yet recruiting A control group was not included
NCT04346368	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With	I/II	China	BM-MSC	1×10^6 cells/Kg	1	IV	20	Active, not yet recruiting

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Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
	Coronavirus Disease 2019 (COVID-19)								
NCT04348435	A Randomized, Double-Blind, Single Center, Efficacy and Safety Study of Allogeneic HB-adMSCs to Provide Immune Support Against COVID-19	II	U.S.	AD-MSC	G1: 2×10^8 G2: 1×10^8 G1: 5×10^7	5	IV	100	Active, enrolling by invitation
NCT04348461	BAttLe Against COVID-19 Using MesenchYmal Stromal Cells	II	Spain	AD-MSC	1.5×10^6 cells/Kg	3	IV	100	Active, not yet recruiting
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	II	U.S.	AD-MSC #	NR	5	IV	56	Active, enrolling by invitation A control group was not included
NCT04352803	Adipose Mesenchymal Cells for Abatement of SARS CoV-2 Respiratory Compromise in COVID-19 Disease	I	U.S.	AD-MSC #	5×10^5 cells/Kg	1	IV	20	Active, not yet recruiting
NCT04355728	Use of UC-MSCs for COVID-19 Patients	I/II	U.S.	UC-MSC	1×10^8	2	IV	24	Active, not recruiting
NCT04361942	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (COVID_MSV)	II	Spain	MSC / MSV	1×10^6 cells/Kg	1	IV	24	Active, recruiting
NCT04362189	Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	II	U.S.	AD-MSC	1×10^8	4	IV	110	Active, not recruiting
NCT04366063	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	II/III	Iran	MSC EVs from MSC	G1: 1×10^8 MSC G2: 1×10^8 MSC + EVs	2	IV	60	Active, recruiting
NCT04366271	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 (MESCEL-COVID19)	II	Spain	UC-MSC	NR	1	NR	106	Active, recruiting
NCT04366323	Clinical Trial 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	I/II	Spain	AD-MSC	8×10^7	2	IV	26	Active, recruiting
NCT04366830	Intermediate-size Expanded Access Program (EAP), Mesenchymal Stromal Cells (MSC) for Acute Respiratory Distress Syndrome (ARDS) Due to COVID-19 Infection	NR	U.S.	Remestemcel-L	2×10^6 cells/Kg	2	IV	NR	Active, expanded access no longer available A control group was not included
NCT04371393	MSCs in COVID-19 ARDS	III	U.S.	Remestemcel-L®	2×10^6 cells/Kg	2	IV	300	Active, recruiting
NCT04371601	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	I	China	UC-MSC	1×10^6 cells/Kg	4	IV	60	Active, not recruiting Patients were also treated with antiviral oseltamivir and hormones
NCT04377334		II	Germany	BM-MSC	NR	NR	NR	40	Active, not yet recruiting

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Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)								
NCT04382547	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	I/II	Belarus	OM-MSC	NR	NR	IV	40	Active, enrolling by invitation
NCT04389450	Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX PAD for the Treatment of COVID-19	II	U.S.	PLX-PAD $	G1: high dose G2: low dose + placebo G3: placebo G4: high dose G5: placebo	G1: 2 of cells G2: 1 of cells + 1 of placebo G3: 2 of placebo G4: 1 of cells G5: 1 of placebo	IM	140	Active, recruiting
NCT04390139	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (COVIDMES)	I/II	Spain	WJ-MSC (XCEL-UMC-BETA)	1×10^6 cells/Kg	2	IV	30	Active, recruiting
NCT04390152	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	I/II	U.S.	WJ-MSC	5×10^7	2	IV	40	Active, not yet recruiting Patients were also treated with hydroxychloroquine + Lopinavir/Ritonavir or Azithromycin
NCT04392778	Clinical Use of Stem Cells for the Treatment of Covid-19	I/II	Turkey	UC-MSC	3×10^6 cells/Kg	3	IV	30	Active, recruiting
NCT04397796	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	I	U.S.	BM-MSC	NR	NR	NR	45	Active, recruiting
NCT04398303	ACT-20 in Patients With Severe COVID-19 Pneumonia	I/II	U.S.	ACT-20-MSC (UC-MSC) ACT-20-CM (UC-MSC-CM)	G1: 1×10^6 cells in 100 mL CM G2: 100 ml CM	1	IV	70	Active, not yet recruiting
NCT04399889	hCT-MSCs for COVID19 ARDS	I/II	U.S.	hCT-MSC	1×10^6 cells/Kg	3	IV	30	Active, recruiting
NCT04400032	Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard (CIRCA-19)	I	Canada	BM-MSC	G1: 2.5×10^7 G2: 5×10^7 G3: 9×10^7	3	IV	9	Active, recruiting A control group was not included
NCT04416139	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19)	II	Mexico	UC-MSC	1×10^6 cells/Kg	1	IV	10	Active, recruiting
NCT04428801	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	II	U.S.	AD-MSC	2×10^8 #	3	IV	200	Active, not yet recruiting
NCT04429763	Safety and Efficacy of Mesenchymal Stem Cells in the Management of	II	Colombia	UC-MSC	1×10^6 cells/Kg	1	NR	30	Active, not yet recruiting

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Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
	Severe COVID-19 Pneumonia (CELMA)								
NCT04437823	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	II	Pakistan	UC-MSC	5×10^5 cells/Kg	3	IV	20	Active, recruiting
NCT04444271	Mesenchymal Stem Cell Infusion for COVID-19 Infection	I	Pakistan	BM-MSC	2×10^6 cells/Kg	2	IV	20	Active, recruiting
NCT04445220	A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	I/II	U.S.	SBI-101	G1: 2.5×10^8 G2: 7.5×10^8	NA	NA	24	Active, not yet recruiting SBI-101 is combination of a sham device with MSC
NCT04445454	Mesenchymal Stromal Cell Therapy for Severe Covid-19 Infection	I/II	Belgium	BM-MSC	$1.5-3 \times 10^6$ cells/Kg	3	IV	20	Active, recruiting A control group was not included
NCT04447833	Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome (ARDS-MSC-205)	I	Sweden	KI-MSC-PL-205 (BM-MSC)	$1-2 \times 10^6$ cells/Kg	1	IV	9	Active, recruiting
NCT04452097	Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS	I	U.S.	UC-MSC	G1: 0.5×10^6 G2: 1×10^6 G3: 1.5×10^6 cells/Kg	1	IV	9	Active, not yet recruiting
NCT04456361	Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19	I	Mexico	WJ-MSC	1×10^8	1	IV	9	Active, not recruiting A control group was not included
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)	NA	U.S.	Remestemcel-L	2×10^6	2	IV	50	Active, expanded access available Patients will receive diphenhydramine 30 min prior to the infusion of remestemcel-L, plus patients not taking a corticosteroid will receive hydrocortisone A control group was not included
NCT04457609	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients	I	Indonesia	UC-MSC	1×10^6 cells/Kg	1	IV	40	Active, recruiting Patients from both control and experimental groups were also treated with Oseltamivir and AZ
NCT04461925	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs	I/II	Ukraine	P-MSC +	1×10^6 cells/Kg	3	IV	30	Active, recruiting Patients from both control and experimental groups were also treated with ceftriaxone, AZ, dexamethasone and Enoxaparin
NCT04466098	Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19)	II	U.S.	MSC	3×10^8	3	IV	30	Active, recruiting
NCT04467047	Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19 (COVID19)	I	Brazil	MSC	1×10^6 cells/Kg	1	IV	10	Active, not yet recruiting
NCT04482699	RAPA-501-Allo Off-the-Shelf Therapy of COVID-19	I/II	U.S.	RAPA-501 ALLO	G1: 4×10^7 G2: 1.6×10^8			88	Active, not yet recruiting
NCT04490486	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary	I	U.S.	UC-MSC	1×10^8	2	IV	21	Active, not yet recruiting

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Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	N° of cells	N° of infusions	Delivery route	N° of patients	Status/Observations/ Outcomes
	Inflammation Due to COVID-19 (COVID-19)								
NCT04491240	Evaluation of safety and efficiency of method of exosome inhalation in sars-cov-2 associated pneumonia. (covid-19exo)	I/II	Russian	Exo from MSC (2 types of exo)	$0.5-2 \times 10^{10}$ nanoparticles	20 (2 a day for 10 days)	AI	90	Active, recruitment completed No advers events were observed
NCT04492501	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan	NA	Pakistan	BM-MSC	2×10^6 cells/Kg	1		600	Active, recruitment completed Patients were divided in 4 groups: G1 received standard protocol Plus, patients of Cytokine release storm (CRS) received either Methylprednisolone or Dexamethasone G2: Therapeutic Plasma exchange G3: Therapeutic Plasma exchange in combination with Tocilizumab, Remdesivir and MSC G4: alone or combination of MSC, Remdesivir and Tocilizumab
NCT04493242 [12]	Extracellular Vesicle Infusion Therapy for Severe COVID-19 (EXIT COVID-19)	II	U.S.	DB-001/ Exo flo (EVs from MSC)	NR	NR	IV	60	Active, not yet recruiting A prospective study showed that from 24 patients 71 % recovered, 14 % remained critically and 16 % deceased with the overall survival rate of 83 %. ExoFlo were able to modulate inflammation and restore oxygenation. No major adverse effects were observed
NCT04494386	Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS (ULSC)	I/II	U.S.	UC-MSC	1×10^7	1 or 2	IV	60	Active, recruiting
NCT04522986	An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection (COVID-19)	I	Japan	ADR-001 (AD-MSC)	1×10^8	4	IV	6	Active, not yet recruiting A control group was not included
NCT04524962	Study of Descartes-30 in Acute Respiratory Distress Syndrome	I/II	U.S.	Descartes 30 (MSC ou MSC secreting combination of DNases	NR	NR	NR	30	Active, not yet recruiting
NCT04525378	MSC-based Therapy in COVID-19-associated Acute Respiratory Distress Syndrome	I	Brazil	MSC	G1: 2.5×10^7 G2: 5×10^7 G3: 10×10^7	1 or 2	IV	20	Active, recruiting
NCT04527224	Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia	I/II	U.S.	Astrostem-V (AD-MSC)	NR	NR	NR	10	Active, not yet recruiting A control group was not included
NCT04537351	The MEseNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19 (MEND)	I/II	Australia	CYP-001 (Cymerus™ MSC)	2×10^6 cells/Kg	2	IV	24	Active, recruiting
NCT04535856	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in	I	Indonesia	DW-MSC	G1: 5×10^7 * G2: 10×10^7*	1	IV	9	Active, not yet recruiting

(*continued on next page*)

Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	N° of cells	N° of infusions	Delivery route	N° of patients	Status/Observations/ Outcomes
	COVID-19 Patients (DW-MSC)								
NCT04565665	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	I	U.S.	UC-MSC	NR	1 or 2	IV	70	Active, recruiting
NCT04573270	Mesenchymal Stem Cells for the Treatment of COVID-19	I	U.S.	PrimePro (UC-MSC)	NR	NR	IV	40	Active, recruitment completed
NCT04602442	Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia (COVID-19EXO2)	II	Russia	Exo from MSC (2 types of exo)	$0.5-2 \times 10^{10}$	20 (2 a day for 10 days)	AI	90	Active, enrolling by invitation
NCT04611256	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19	I	Mexico	AD-MSC	1×10^6 cells/Kg	2	IV	20	Active, recruiting
NCT04614025	Open-label Multicenter Study to Evaluate the Efficacy of PLX-PAD for the Treatment of COVID-19	II	Germany/ Israel	PLX-PAD (MSC-like)	3×10^8	15	IM	40	Active, recruiting
NCT04615429	Clinical Trial to Assess the Efficacy of MSC in Patients With ARDS Due to COVID-19	II	Spain	MSC	1×10^6 cells/Kg	1	IV	20	Active, recruiting
NCT04625738	Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome (MSC-COVID19)	IIa	France	WJ-MSC	2×10^6 cells/Kg	3	IV	30	Active, not yet recruiting
NCT04629105	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER) (RECOVER)	I	U.S.	LMSC	1×10^8	3	IV	70	Active, recruiting
ChiCTR2000029606 [8]	Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	0	China	MB-MSC	1×10^6 cells/Kg	3	IV	60	Active, recruiting A case report with two of the patients showed that MSC along with antiviral treatment were able to modulate inflammation and improved respiratory function. No major adverse effects were observed A control group was not included
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	0	China	CM from UC-MSC	NR	NR	NR	30	Active, not yet recruiting
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	0	China	NR	NR	NR	NR	35	Active, recruiting
ChiCTR2000029990 [5]	Transplantation of ACE2- Mesenchymal	I/II	China	BM-MSC	1×10^6 cells/Kg	1	IV	7	All 7 patients recovered showing no symptoms

(*continued on next page*)

Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
	Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia								2~4 days after treatment. MSC were able to modulate inflammation and promote tissue repair No major adverse effects were observed
ChiCTR2000030020	The clinical application and basic research related to mesenchymal stem cells to treat novel coronavirus pneumonia (COVID-19)	NA	China	MSC	NR	NR	NR	20	Active, recruiting A control group was not included
ChiCTR2000030088	Umbilical cord Wharton's Jelly derived mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	0	China	UC-MSC	1×10^6 cells/Kg	1	IV	40	Active, not yet recruiting
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)	NA	China	UC-MSC	NR	NR	NR	16	Active, recruiting A control group was not included
ChiCTR2000030138	Clinical Trial for Human Mesenchymal Stem Cells in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	2	China	UC-MSC	NR	NR	IV	60	Active, not yet recruiting
ChiCTR2000030173	Key techniques of umbilical cord mesenchymal stem cells for the treatment of novel coronavirus pneumonia (COVID-19) and clinical application demonstration	0	China	UC-MSC	NR	NR	NR	60	Active, not yet recruiting
ChiCTR2000030261	A study for the key technology of mesenchymal stem cells exosomes atomization in the treatment of novel coronavirus pneumonia (COVID-19)	0	China	EXO from MSC	NR	NR	AI	26	Active, not yet recruiting
ChiCTR2000030484	HUMSCs and Exosomes Treating Patients with Lung Injury following Novel Coronavirus Pneumonia (COVID-19)	NA	China	UC-MSC	5×10^7	2	IV	90	Active, not yet recruiting
ChiCTR2000030835	Clinical study for the efficacy of Mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19)	NR	China	UC-MSC	G1: 2×10^6 G2: 1×10^6 cells/Kg	3	IV	20	Active, recruiting
ChiCTR2000030866	Open-label, observational study of human umbilical cord derived mesenchymal stem cells in the treatment of severe and critical patients with novel coronavirus pneumonia (COVID-19)	0	China	UC-MSC	NR	NR	IV	30	Active, recruiting A control group was not included
ChiCTR2000030944	Clinical study of human NK cells and MSCs transplantation for severe novel coronavirus pneumonia (COVID-19)	I	China	UC-MSC + NK	NR	NR	NR	20	Active, not yet recruiting
ChiCTR2000031430		II	China	UC-MSC		3	IV	200	Active, recruiting

(*continued on next page*)

Table 2 (*continued*)

Trail Identification	Title	Phase	Country	Cells/ product	Nº of cells	Nº of infusions	Delivery route	Nº of patients	Status/Observations/ Outcomes
	Clinical study of human umbilical cord mesenchymal stem cells in the treatment of novel coronavirus pneumonia (COVID-19) induced pulmonary fibrosis				4×10^6 cells/Kg				
ChiCTR2000031494 [7]	Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells	I	China	UC-MSC	2×10^6 cells/Kg	1	IV	41	No MSC treated patients progressed from severe to critical states while 4 of the control patients did. The mortality rate of MST treated patients was 0 at 28-day, contrary to the 10.34 % rate in the control group Time to clinical improvement was shorter in patients treated with MSC MSC were able to modulate inflammation
[6]	Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells	NA	China	UC-MSC	5×10^7	3	IV	1	The patient completely recovered Clinical ameliorations and decreased inflammation were observed soon after 2nd MSC transplantation No major adverse effects were observed A control group was not included
[9]	Mesenchymal stem cell treatment in a critically ill COVID-19 patient: a case report	NA	Turkey	UC-MSC	IV: 0.7×10^6 cells/kg + IT: 0.3×10^6 cells/kg	2	IV/IT	1	The patient requiring intubation was treated with MSC along with antivirals Clinical ameliorations and decrease inflammation were observed upon MSC transplantation. The patient was extubate 5 days after MSC infusion No major adverse effects were observed A control group was not included
[11]	Adipose-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation. A proof of concept study	NA	Spain	AD-MSC	$\sim 0.98 \times 10^6$ cells/kg	G1: 2 G2: 1 G3: 3	IV	G1: 10 G2: 2 G3: 1	Thirteen patient requiring intubation were treated with MSC and steroids 70 % of patients showed clinical ameliorations and 53 % were extubated MSC were able to modulate inflammation No major adverse effects were observed A control group was not included
[10]	Human Umbilical Cord Mesenchymal Stem Cells for Adjuvant Treatment of a Critically Ill COVID-19 Patient: A Case Report	NA	China	UC-MSC	1×10^6 cells/Kg	1	IV	1	Clinical ameliorations and decrease inflammation were observed upon MSC transplantation. No major adverse effects were observed A control group was not included

Most clinical trials include a control/placebo group except for the ones were this absence is mentioned.

List of abbreviations: ACE2 - angiotensin-converting enzyme-2; AI - aerosol inhalation; AZ - Azithromycin; AD-MSC – adipose tissue-derived mesenchymal stromal cells; BM-MSC – bone marrow-derived mesenchymal stromal cells; hCT-MSC – human Cord Tissue-derived mesenchymal stromal cells; DP-MSC - dental pulp-derived

mesenchymal stromal cells; MB-MSC – menstrual blood-derived mesenchymal stromal cells; P-MSC - placenta-Derived MSC; OM-MSC - olfactory mucosa-derived mesenchymal stem cells; UC-MSC – umbilical cord-derived mesenchymal stromal cells; CM – conditioned media; ChiCTR - Chinese Clinical Trial Registry; EXO - exosomes; IV– Intravenous; IM – Intramuscular; HC - Hydroxychloroquine; NA - Not Applicable; NR – Not Reported; SP-D - surfactant protein D.
#Autologous cell infusion.
$Allogeneic ex vivo expanded placental mesenchymal-like adherent stromal cell.

associated with a greater immunomodulatory action [144]. Therefore, a clarification on the best cell source for each clinical case of COVID-19 could help improving therapeutic outcomes. Despite the fact that different administrations routes can offer advantages for specific organs, the systemic injection may be the most appropriate for COVID-19 patients since it allows MSC to spread throughout the whole body and target several affected organs. Indeed, Lu and colleagues showed that upon IV administration in ARDS mice, MSC tend to accumulate mainly in the lungs, but also reached the liver, kidney, spleen, heart, and brain [145]. Moreover, MSC administration may be combined with other drugs or therapeutic strategies in order to obtain a synergistic multidirectional effect in COVID-19 patients. This has been tested in some clinical trials (Table 2).

Because studies comparing the efficacy of MSC and their secretome/EVs are missing, it is not clear which kind of therapy should be used. However, as some studies reported the importance of direct cellular contact for therapeutic success [53,54,59,113,146], and given the urgent character of applicability of the treatment, it makes sense to start by directly using MSC. Notwithstanding, both kind of therapies can possibly be admitted, as was demonstrated by the clinical studies in COVID-19 patients.

6. Conclusion

The potential advantage of using MSC to treat SARS-CoV-2-infected patients is the fact that they can target different organs simultaneously and have a pleiotropic action aimed at counteracting infection, repairing damaged tissues and avoiding invasion from other opportunistic agents. When thinking of a therapy for COVID-19 we should not look into the human body as a compartmentalized structure; but as a whole instead, where every single structure is connected to each other strongly depending on their interplay.

In order to rationally improve therapies for COVID-19, more research is required aiming at characterizing the mechanisms underlining MSC immunomodulatory capacity and defining the microenvironment expressed in different SARS-CoV-2 *scenarios* [147]. Clinical studies that were reported so far are extremely important as they shed light on the possible future application of MSC to COVID-19 patients not only suffering from ARDS, but also from other organ failures. We expect that the presently undertaking clinical studies can also give a precious input into the field.

Authors' contributions

Maria Inês Barros - discussion and paper writing, figure design; António Dinis da Silva - discussion and paper writing; Luís Pereira de Almeida – paper discussion and reviewing; Catarina Oliveira Miranda – paper outline, discussion and paper writing, and reviewing.

Declaration of Competing Interest

The authors report no declarations of interest.

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