



Editorial

Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy – Achieving global consensus and visibility for cellular host-directed therapies



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ABSTRACT

As of May 17th 2020, the novel coronavirus disease 2019 (COVID-19) pandemic has caused 307,395 deaths worldwide, out of 3,917,366 cases reported to the World Health Organization. No specific treatments for reducing mortality or morbidity are yet available. Deaths from COVID-19 will continue to rise globally until effective and appropriate treatments and/or vaccines are found. In search of effective treatments, the global medical, scientific, pharma and funding communities have rapidly initiated over 500 COVID-19 clinical trials on a range of antiviral drug regimens and repurposed drugs in various combinations. A paradigm shift is underway from the current focus of drug development targeting the pathogen, to advancing cellular Host-Directed Therapies (HDTs) for tackling the aberrant host immune and inflammatory responses which underlie the pathogenesis of SARS-CoV-2 and high COVID-19 mortality rates. We focus this editorial specifically on the background to, and the rationale for, the use and evaluation of mesenchymal stromal (Stem) cells (MSCs) in treatment trials of patients with severe COVID-19 disease. Currently, the ClinicalTrials.gov and the WHO Clinical Trials Registry Platform (WHO ICTRP) report a combined 28 trials exploring the potential of MSCs or their products for treatment of COVID-19. MSCs should also be trialed for treatment of other circulating WHO priority Blueprint pathogens such as MERS-CoV which causes upto 34% mortality rates. It's about time funding agencies invested more into development MSCs per se, and also for a range of other HDTs, in combination with other therapeutic interventions. MSC therapy could turn out to be an important contribution to bringing an end to the high COVID-19 death rates and preventing long-term functional disability in those who survive disease.

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Introduction – Coronavirus-2019 Disease (COVID-19) – a global pandemic

Since early January 2020, the world has witnessed unprecedented global scientific and political attention focused on the devastating coronavirus disease 2019 (COVID-19) pandemic, caused by the novel, highly contagious zoonotic pathogen, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Hui et al., 2020; Chen et al., 2020). By May 17th, 2020, there have been 307,395 deaths worldwide out of 3,917,366 (7% case fatality) confirmed COVID-19 cases reported from all continents to the World Health Organization (WHO, 2020). As with the two other novel coronavirus zoonotic diseases of humans, SARS and MERS, no specific treatments for reducing mortality or morbidity are yet available (Memish et al., 2020; Hui et al., 2020; Hui and Zumla, 2019). The management of COVID-19 patients remains largely symptomatic and supportive with organ support for severely ill

patients (Richardson et al., 2020; Guan et al., 2020). Deaths from COVID-19 will continue to rise globally until effective and appropriate treatments and vaccines are found.

Clinical trials of therapeutic interventions

With no specific treatments being available for treating COVID-19 patients, the global medical, scientific, pharma and funding communities have rapidly initiated over 500 COVID-19 related trials (https://clinicaltrials.gov/ct2/who_table). These clinical trials have been fast-tracked by ethical committees worldwide and a range of therapeutic interventions registered on clinical trials.gov are taking forward phase 1, 2 and 3 trials of antiviral drug regimens, biologics, repurposed drugs in various combinations, herbal remedies, nutritional supplements, and cellular therapies. A paradigm shift is underway from the current focus of drug treatment combinations targeting the pathogen, to advancing

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cellular Host-Directed Therapies (HDTs) for tackling the aberrant host immune and inflammatory responses, which underlie the pathogenesis of SARS-CoV-2 and the high COVID-19 death rates. This is an area, which has been eclipsed by the current emphasis the huge number of trials evaluating new anti-viral drugs, repurposed drugs and combinations thereof. We thus focus this editorial specifically on the background to, and the rationale for, the use and evaluation of mesenchymal stromal (Stem) cells (MSCs) in treatment trials of patients with severe COVID-19 disease. A paradigm shift is underway from the current focus of drug treatment combinations targeting the pathogen, to advancing cellular Host-Directed Therapies (HDTs) (Zumla et al., 2015; Zumla et al., 2020) for tackling the aberrant host immune and inflammatory responses, which underlie the pathogenesis of SARS-CoV-2 and the high COVID-19 death rates. This is an area, which has been eclipsed by the current emphasis the huge number of trials evaluating new anti-viral drugs, repurposed drugs and combinations thereof. We thus focus this editorial specifically on the background to, and the rationale for, the use and evaluation of mesenchymal stromal (Stem) cells (MSCs) in treatment trials of patients with severe COVID-19 disease.

Pathology and Autopsy studies of COVID-19 deaths

Defining the underlying pathogenesis and pathology of COVID-19 disease for developing appropriate therapeutic interventions may prevent end organ damage and long-term functional disability in those who survive severe disease. Autopsy and minimally invasive biopsy studies indicate that COVID-19 is a multi-system disease. The lungs in particular manifest significant pathological lesions, such as alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation and hyaline membrane formation (Menter et al., 2020; Tian et al., 2020). Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar and bronchial epithelia and hyaline membrane formation are seen (Xu et al., 2020); with predominantly macrophage and monocyte immune cell infiltration in alveoli with multinucleated giant cells; lymphocytes (mostly CD4-positive T cells), and some eosinophils and neutrophils. The blood vessels of alveolar septum were congested, edematous and widened, with modest infiltration of monocytes and lymphocytes. Hyaline thrombi in microvessels and focal hemorrhage in lung tissue, organization of exudates, and pulmonary interstitial fibrosis have been observed. Furthermore, degeneration and necrosis of parenchymal cells and formation of hyaline thrombus in small vessels were observed in other organs and tissues (Menter et al., 2020; Tian et al., 2020). Immunohistochemical staining showed alveolar epithelia and macrophages positive for SARS-CoV-2 antigen. Evidence of SARS-CoV-2 antigens in other organs and tissues has been detected which suggests that host immune responses evoked by SARS-CoV-2 infection are involved in the pathogenesis of multi-organ injury (Yao et al., 2020).

COVID-19 Pathogenesis and aberrant immune responses

SARS-CoV-2 enters the host cells via the cell surface angiotensin converting enzyme 2 (ACE2) receptor on the target cell surface (Zhang et al., 2020). ACE2 as a cardio-regulator, so there are numerous cells with ACE2 receptors in blood vessels, alveolar type II cells (AT2) in the lungs and several other organs, such as heart, kidneys. It appears that all three lethal zoonotic coronaviruses, MERS-CoV, SARS-CoV and SARS-CoV-2 seem to induce excessive and aberrant host immune responses which are associated with severe lung pathology leading to acute respiratory distress syndrome (ARDS) (Memish et al., 2020; Liu et al., 2020; Li et al., 2020a,b). Characteristic findings on chest imaging in COVID 19

include bilateral ground glass and consolidative changes (Shi et al., 2020). An associated cytokine storm may play a role in pathogenesis. Elevated proinflammatory cytokines and chemokines including tumour necrosis factor (TNF) α , interleukin 1 β (IL-1 β), IL-6, granulocyte-colony stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, and macrophage inflammatory proteins 1- α were significantly elevated in COVID-19 patients. (Huang et al., 2020; Liu et al., 2020; Ye et al., 2020; Zhou et al., 2020). Patients with evidence of hyperinflammation have an increased risk of mortality (Mehta et al., 2020; Ruan et al., 2020). In those who survive intensive care, the consequences of these aberrant and excessive immune responses may lead to long term pulmonary damage and fibrosis, with functional disability and reduction of quality of life (Batwai et al., 2019). It is important that therapeutic interventions which can dampen the excess inflammation, thus preventing end organ damage and long-term functional disability in those who survive severe disease.

Cellular based therapies to reduce excessive inflammation and immune-mediated tissue damage

For the past decade the medical and pharma communities have focused on developing therapeutics targeting the pathogen rather than on the role of underlying host factors (Zumla et al., 2015, 2020). Human immune defenses are dependent on a complex array of mechanical, innate and acquired immune mechanisms and any disturbance of this internal lung milieu results in serious and fatal consequences. Improved understanding of inflammatory and immune pathways governing protective or deleterious outcomes, provide novel opportunities to target specific pathways that mediate immune pathology (Figure 1). Advances in host-directed therapies (HDTs) now provide a range of options to enhance immune responses or reduce excessive inflammation. A range of HDTs with different mechanisms of action are under consideration from cellular therapy with mesenchymal stromal (stem) cells (MSCs), biologics, and repurposed drugs with HDT potential (Lérias et al., 2020; Hui et al., 2020).

Mesenchymal Stromal (Stem) Cells (MSCs)

Mesenchymal stromal cells (MSCs) are being widely used in basic research and clinical application (Pittinger et al., 2019; Galipeau and Sensebe, 2018; Yip et al., 2020; Wlatter et al., 2014). MSCs are non haemopoietic cells which are derived from bone marrow, adipose tissue, lung, umbilical cord tissue, dental pulp, and placenta. MSCs express certain markers such as CD73, CD90 and CD105 and test negative for CD14 (monocytes), CD19 (B-cells), CD34 (stem cells), CD11b (expressed on leukocytes including monocytes, neutrophils, natural killer cells, granulocytes and macrophages), and CD45 expressed on all leucocytes (Ullah et al., 2015; Dominici et al., 2006; Hoogduijn, 2015). They appear to exert anti-inflammatory and immunoregulatory functions, promote the regeneration of damaged tissues and inhibit tissue fibrosis. The immunomodulatory effects of MSCs involve direct and indirect effects on the host immune cells (Le Blanc and Mougiakakos, 2012). The use of MSCs have been approved as Advanced Therapy Medical Products (ATMP) and the guidelines from the Food and Drug Administration (FDA) require MSCs to be produced under good manufacturing Practice (GMP) with quality control measures, reproducibility and (Torre et al., 2015; Codinach et al., 2016). There have been FDA Regenerative Medicine Advanced Therapy (RMAT) designation to 42 products as of 6 May 2020, and 4/42 products are Mesenchymal stromal cells (MCS) (<https://ipsccell.com/rmat-list>). In 2018 the first allogeneic MSC product received marketing approval in the European Union. Since some commercial stem cell clinics

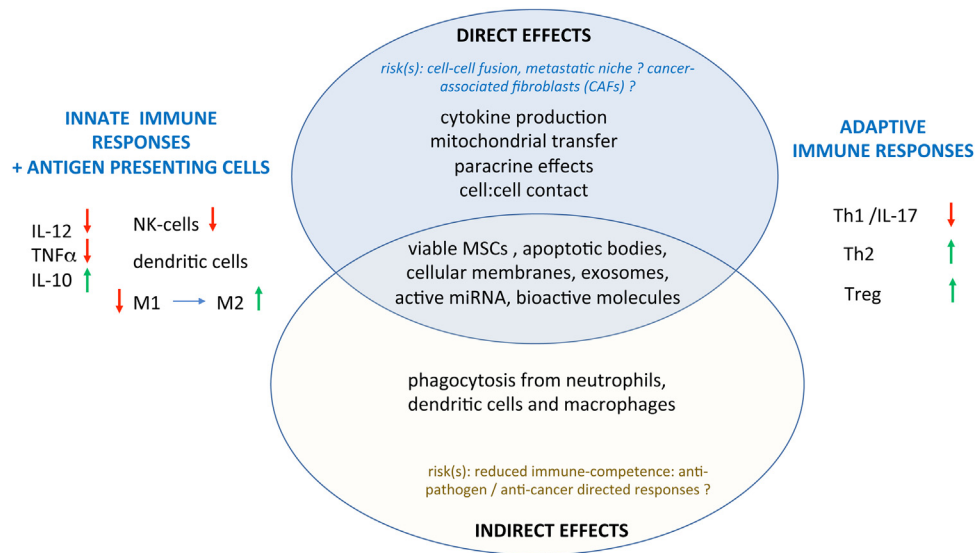


Figure 1. Overview of mechanisms of Action of Mesenchymal Stromal cells.

Viable MSCs rescue injured cells by mitochondrial transfer and produce a broad array of immuno-modulatory cytokines. MSCs may be taken up by phagocytic cells – that may prolong and augment their biological effect after intravenous delivery. Risks include generally reduced immune – competence including anti-viral/bacterial/fungal activity, as well as potential pro-tumorigenic effects. Beneficial reduction of pro-inflammatory cytokines, increased Treg and IL-10 production.

are marketing dubious therapies for cardiovascular disease and cancer (Sissung and Figg, 2020) there are FDA and CDC cautions regarding their use (<https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>) (<https://www.cdc.gov/hai/outbreaks/stem-cell-products.html>).

Mechanism of action of Mesenchymal Stromal Cells

Mesenchymal stromal cells interact with most of the cell types of the innate and acquired immune system, including B cells, T cells, dendritic cells (DCs), natural killer (NK) cells, neutrophils, and macrophages, moderating their response to pathogens (deWitte et al., 2018; Dominici et al., 2006; Hoogdujin and Lombardo, 2019; Jiang et al., 2020; Le Blanc and Mougiakakos, 2012). MSCs also play a role in the control of tissue inflammation (Jiang et al., 2004). The therapeutic effects of MSCs have largely been attributed to their secretion of immunomodulatory and regenerative factors, and some of the effects may be mediated through host phagocytic cells which clear administered MSCs and in the process adapt an immunoregulatory and regeneration supporting function (Weiss and Dahlke, 2019; Walter et al., 2014; Wang et al., 2018). In response to inflammatory factors such as Interferon (IFN γ) and Tumour Necrosis Factor (TNF α) secreted by activated immune cells and tissue cells, MSCs can adopt an immunoregulatory phenotype (Ankrum et al., 2014). They increase the expression of anti-inflammatory factors including programmed death ligand 1 and prostaglandin E2 and inhibit immune cell activity and proliferation through metabolic regulation, such as via indoleamine 2,3-dioxygenase-dependent catabolism of tryptophan (Weiss and Dahlke, 2019). MSCs also express ATPases and possess ecto-nucleotidase activity through CD73 expression, through which they have the capacity to deplete ATP. The immunomodulatory effects of MSCs may also be triggered further by the activation of TLR receptor in MSCs, which is stimulated by pathogen-associated molecules such as LPS. Importantly, MSCs do not have an ACE2 receptor, which makes them immune to SARS-CoV-2.

Human therapeutic Trials of Mesenchymal stromal cells- safety, efficacy and regulatory approval

Whilst generally regarded as safe (Editorial, 2019), MSCs are not immunologically inert as previously thought (Lohan et al., 2017; Ankrum et al., 2014). A recent systematic review and meta-analysis of intravascular MSC therapy reviewed 55 randomised controlled trials of MSC therapy compared to controls (Thompson et al., 2020), MSCs compared to controls were associated with an increased risk of fever but not non-fever acute infusional toxicity, infection, thrombotic/embolic events or malignancy.

In ARDS, MSCs have been evaluated in several Phase 1 and Phase 2 trials. Wilson et al. (2015) reported the results of the phase-I Stem cells for ARDS Treatment (START) study. Patients with moderate-to-severe ARDS received a single intravenous administration of allogeneic bone marrow derived MSCs at either a low-dose [10e6 MSCs/kg predicted body weight (PBW)], intermediate-dose (5 \times 10e6 MSCs/kg PBW), or high-dose (10e7 MSCs/kg PBW) (n = 3/dose). No adverse events or toxicity was observed at any of the doses tested. High-dose MSCs improved daily SOFA score compared to lower doses. In the Phase 2 START trial, a randomized placebo controlled evaluating a single intravenous infusion of allogeneic bone marrow derived MSCs (107 cells/PBW) compared with placebo (2:1 ratio), with primary outcome of safety and secondary clinical outcomes including all-cause mortality at day 28 and day 60, no adverse respiratory or haemodynamic events were observed (Matthay et al., 2019). The 'MUST-ARDS' clinical trial (<https://clinicaltrials.gov/ct2/show/NCT02611609>) tested safety of MultiStem (multi-potent adult progenitor cells, related to MSCs) cells in patients with ARDS. The results have been published in abstract form (Bellington et al., 2020) and results of 1 year followup are awaited. 30 patients with moderate to severe ARDS were recruited: 20 randomised to MultiStem cell therapy (at a dose of 900 million cells) and 10 to placebo. The therapy was well tolerated, and the authors reported trends to improvement in mortality in the MultiStem treated group, although the study was not powered for mortality.

Additionally Phase 1 studies of MSCs in ARDS have been conducted by investigators in China and Taiwan. Zheng et al. (2014) investigated allogeneic adipose derived MSCs in a randomized,

placebo-controlled study (total recruitment n = 12, randomized 1:1). No serious adverse events related to MSC administration were reported. Yip et al. investigated UC derived MSCs in a dose escalation study (1, 5 and 10 × 10⁶ cells/kg) recruiting a total of 9 patients (3 patients per dose cohort). MSC infusion was associated with mild adverse reactions in 3 patients however no serious treatment related adverse events were identified.

The use of MSCs for treatment of COVID-19 patients

MSCs are now being used as a potential therapy for treating COVID-19 patients in order to reduce mortality. Although the use of MSCs has been found to be safe when used for treatment of other diseases, it is important to evaluate whether they are safe to use specifically in COVID-19 patients. There have been reports of early Phase studies in COVID-19 patients from China (NCT04252118 and NCT04288102). Leng et al. (2020) investigated the use of MSCs in hospitalized patients with COVID 19 who were not improving despite standard therapy. Seven patients were administered intravenous MSCs at a dose of 1 × 10⁶ cells per kg. MSC infusion was well tolerated in all patients with no acute infusion related reactions. A study published in Aging and Disease claimed the effectiveness of MSCs therapy was safe and attributed the recovery of all 7 patients who were administered MSCs. This was led by researchers from Shanghai University and Peking Union Medical College (PUMC) and Chinese Academy of

Medical Sciences (CAMS). Seven COVID-19 patients aged between 45 to 65 (four severe cases, one critically severe case) received with allogenic MSC therapy and three were in the control group. Since the study had several limitations, no conclusions on efficacy can be drawn. It was a small study with 7 patients with no blinding or randomization, and the control group of 3 patients was selected after all MSC patients were treated. The Chinese Medical Association has issued guidelines to standardize stem cell treatment for COVID-19. On April 5, 2020, the US-FDA approved MSC treatment for use in seriously ill COVID-19 patients under what is known as 'expanded access compassionate use'.

Ongoing trials of Mesenchymal stromal (stem) Cell Therapies for COVID-19

The excessive host response seen in patients with COVID-19 appears to have induced a paradigm shift in longstanding focus of drug treatment interventions targeting the pathogen (SARS-CoV-2 in this case) to targeting the host response. Currently, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) report a combined 28 trials exploring the potential of MSCs and their products for treatment or prevention of COVID-19.

Table 1 lists clinical trials of MSCs or their products which have been registered on clinicaltrials.gov. Not all of the registered trials

Table 1
Mesenchymal stromal (Stem) cell trials registered on ClinicalTrials.Gov related to treatment of COVID-19 Disease – Trial number, source of MSCs, Dose, route of administration and Primary endpoints.

Trial ID No	Responsible institution	Patient population	Source of MSCs	Dose of MSCs	Route of administration Number of treatments	Primary endpoint(s)
NCT04315987	Azidus Brasil	COVID 19 pneumonia	NestCell [®]	2 × 10 ⁷ cells/dose	IV 3/4 (days 1, 3, 5; day 7 optional)	Change in clinical condition (WHO ordinal scale) (day 10)
NCT04288102	Beijing 302 Hospital	COVID 19 pneumonia	Human MSCs	4 × 10 ⁷ cells/dose	IV 3 (days 0, 3 and 6)	Size of lesion area and severity of pulmonary fibrosis by chest CT (day 6, 10, 14, 28 and 90)
NCT04313322	Stem Cells Arabia	COVID 19	Wharton's Jelly-MSCs	1 × 10 ⁶ cells/kg/dose	IV 3 (3 days apart from each other)	Clinical Outcome CT Scan changes RT-PCR results (All at 3 weeks)
NCT04336254	Renmin Hospital of Wuhan University	COVID 19 pneumonia	Allogeneic Human Dental Pulp MSCs	3 × 10 ⁷ cells/dose	IV 3 (days 1, 4 and 7)	Time to Clinical Improvement (day 1 to 28)
NCT04302519	CAR-T (Shanghai) Biotechnology Co., Ltd.	COVID 19 pneumonia	Dental Pulp MSCs	1 × 10 ⁶ cells/kg/dose	IV 3 (days 1, 3 and 7)	Disappearance time of ground-glass shadow in the lungs (day 14)
NCT04339660	Puren Hospital Affiliated to Wuhan University of Science and Technology	COVID 19 pneumonia	Umbilical cord derived MSCs	1 × 10 ⁶ cells/kg/dose	IV 1/2 (Second infusion after 1 week optional)	Immune function (TNF-α, IL-1β, IL-6, TGF-β, IL-8, PCT, CRP) (within 4 weeks) Blood oxygen saturation (within 4 weeks)
NCT04252118	Beijing 302 Hospital	COVID 19 pneumonia	Human MSCs	3 × 10 ⁷ cells/dose	IV 3 (Days 0, 3 and 6).	Size of lesion area by chest radiograph or CT (day 3, 6, 10, 14, 21 and 28) Side effects in the MSCs treatment group (indicated by treatment related adverse events) (day 3, 6, 10, 14, 21, 28, 90 and 180)
NCT04333368	Assistance Publique - Hôpitaux de Paris	COVID 19 -ARDS	Umbilical Cord-Wharton's Jelly derived MSCs	1 × 10 ⁶ cells/kg/dose	IV 3 (Days 1, 3 and 5)	PaO ₂ /FiO ₂ ratio (baseline to day 7)
NCT04273646	Wuhan Union Hospital, China	COVID 19 pneumonia	Umbilical Cord-derived MSCs	0.5 × 10 ⁶ cells/kg/dose	IV 4 (Days 1, 3, 5 and 7)	Pneumonia severity index (baseline to week 12) Oxygenation index (PaO ₂ /FiO ₂) (baseline to week 12)
NCT04341610	Rigshospitalet, Denmark	COVID 19 pneumonia	Adipose derived MSCs	100 × 10 ⁶ cells/dose	IV 1	Changes in clinical critical treatment index (at day 7)

Table 1 (Continued)

Trial ID No	Responsible institution	Patient population	Source of MSCs	Dose of MSCs	Route of administration Number of treatments	Primary endpoint(s)
NCT04269525	Zhongnan Hospital	COVID 19 pneumonia in ICU	Umbilical Cord-derived MSCs	9.9×10^7 cells/dose	IV 4 (days 1, 3, 5 and 7)	Oxygenation index (PaO ₂ /FiO ₂) (day 14)
NCT04299152	Tianhe Stem Cell Biotechnologies Inc.	Symptomatic COVID 19 patients	'Educated' autologous immune cells	SCE therapy circulates a patient's blood through a blood cell separator, briefly cocultures the patient's immune cells with adherent cord-blood stem cells (CB-SC) in vitro, and returns the "educated" autologous immune cells to the patient's circulation.		Determine the number of Covid-19 patients who were unable to complete SCE Therapy
NCT04276987	Ruijin Hospital	COVID 19 pneumonia	Exosomes Derived from Allogenic Adipose MSCs	2×10^8 nano vesicles/3 mL	Inhalational 5 (days 1, 2, 3, 4 and 5)	Adverse reaction and severe adverse reaction (day 28) Time to clinical improvement (day 28)
NCT03042143 COVID 19 REALIST	Belfast Health and Social Care Trust	COVID 19 - ARDS	REALIST Orbcel-C Human umbilical cord derived CD362 enriched MSCs	400×10^6 cells/dose	IV 1	Oxygenation index at day 7 (defined as (Mean Airway Pressure*FiO ₂ *100)/PaO ₂) Incidence of Serious Adverse Events (day 28)
NCT04345601	Baylor College of Medicine	COVID 19 ARDS	Bone marrow derived MSCs	1×10^8 cells/dose	IV 1	Incidence of unexpected adverse events (day 28) Improved oxygen saturations $\geq 93\%$ (day 7)
NCT04362189	Hope Biosciences	Hospitalised COVID 19	Allogeneic Adipose derived MSCs	100×10^6 /dose	IV Day 0, 3, 7, and 10.	Mortality rate (day 28) Need for Invasive mechanical ventilation (day 0, 3, 7, 10 and 28) All-cause mortality (day 30)
NCT04371393	Icahn School of Medicine at Mount Sinai	COVID 19 ARDS	Mesoblast Remestemcel-L Bone marrow derived MSCs	2×10^6 cells/kg/dose	IV 2 (day 1 and 4 days following first infusion ± 1 day)	
NCT04371601	Fuzhou General Hospital	COVID 19 pneumonia	Umbilical cord derived MSCs	10×10^6 cells/kg/dose	IV 4 (once every 4 days)	Oxygenation index (PaO ₂ /FiO ₂) (12 months)
NCT04377334	University Hospital Tuebingen	COVID 19 ARDS	Allogeneic bone marrow derived MSCs	Not specified	Not specified	Lung injury score (day 10)
NCT04355728	University of Miami	COVID 19 ARDS	Umbilical cord derived MSCs	100×10^6 cells/dose	IV 2 (day 1 and 3)	Incidence of pre-specified infusion associated adverse events (day 5) Incidence of Severe Adverse Events (day 90)
NCT04349631	Hope Biosciences	Risk of occupational exposure COVID 19 No signs or symptoms of COVID 19	Autologous Adipose derived MSCs	Not specified	IV 5 (time points not specified)	Incidence of hospitalization for COVID-19 (week 26) Incidence of symptoms for COVID-19 (week 26)
NCT04348435	Hope Biosciences	Risk of occupational exposure COVID 19 No signs or symptoms of COVID 19	Allogeneic Adipose derived MSCs	50, 100 or 200×10^6 cells/dose	IV 5 (0, 2, 6, 10 and 14 weeks)	Incidence of hospitalization for COVID-19 (week 26) Incidence of symptoms associated with COVID-19 (week 26)
NCT04366063	Royan Institute	COVID 19 ARDS	MSCs (source not specified) MSC derived extracellular vesicles	MSCs – 100×10^6 cells/dose EVs – dose not specified	IV 2 (days 0 and 2) ± 2 EV infusions (on day 4 and 6)	Adverse events assessment (day 28) Blood oxygen saturation (day 14)
NCT04346368	Guangzhou Institute of Respiratory Disease	COVID 19 pneumonia	Bone marrow derived MSCs	1×10^6 cells/kg/dose	IV 1	Oxygenation index (PaO ₂ /FiO ₂) (baseline, 6 h, Day 1 and 3, Week 1, 2, 4 and 6 months) Side effects (treatment related adverse events) (6 months)
NCT04348461	Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz	COVID 19 ARDS	Allogeneic Adipose derived MSCs	1.5×10^6 cells/kg/dose	IV 2	Survival rate (day 28) Adverse event rate (day 28)
NCT04366271 MESCEL- COVID19	Hospital Infantil Universitario Niño Jesús, Madrid, Spain	COVID 19 pneumonia	Umbilical cord derived MSCs	Not specified	IV 1	Mortality rate (day 28)
NCT04361942	Red de Terapia Celular	COVID 19 pneumonia in ICU	Allogeneic MSCs (source not specified)	1×10^6 /kg/dose	IV 1	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation (day 7) Mortality rate (day 28)

Table 1 (Continued)

Trial ID No	Responsible institution	Patient population	Source of MSCs	Dose of MSCs	Route of administration Number of treatments	Primary endpoint(s)
NCT04366323	Andalusian Network for Design and Translation of Advanced Therapies	COVID 19 pneumonia	Allogeneic Adipose derived MSCs	80×10^6 cells/dose	IV 2	Adverse Event Rate (12 months) Survival Rate (day 28)
NCT04352803	Regeneris Medical	Hospitalized COVID 19	Autologous Adipose derived MSCs	0.5×10^6 cells/kg/dose	IV 1	Incidence of unexpected adverse events (day 28) Progression to mechanical ventilation (day 28) Length of mechanical ventilation (day 28) Length of weaning of mechanical ventilation (day 28) Length of hospital stay (day 28) Mortality rate (day 28)

will be pursued and in recent weeks, five trials registered on the Chinese Clinical Trial Register (“ChiCTR”) and one trial registered on ClinicalTrials.gov have been marked as “Cancelled by the Investigator”.

The registered trials are different in design, have different sources of MSCs, different dose administration schedules, selection of patients and primary outcomes highlighting the need for standardizing protocols through a global consortium network.

Table 2

Priority needs for advancing Mesenchymal Stromal Cell and Cellular therapies for COVID-19 and other infectious diseases.

- 1 Taking forward the Global Network for Cellular and other Host-Directed Therapies:** Advancing an international multidisciplinary, multi-continental consortium between clinical infectious disease and cancer research investigators with interested stakeholders for proactively defining the landscape, priorities for R&D, developing common protocols, and having regular ‘out of the box’ thinking exchanges’. (Website: <https://fchampalimaud.org/covid19/aci>). This consortium network is open to any interested party to join and help take forward the growing portfolio of cellular therapies for improving treatment outcomes for a range of acute and chronic infectious diseases. Current focus of the consortium is on HDTs for COVID-19.
- Opportunities for conduct of common scientific studies and defining unanswered questions regarding MSC therapy:
- 2 Omics approach:** RNAseq data/Proteomics shared or centrally conducted from MSCs products for better definition of: cellular products; differences in gene expression/proteomics in freshly prepared versus cryopreserved and subsequently thawed MSCs; microRNAs in MSCs; Investigator – initiated studies and commercial products; use different tissue origins and culture methods that may lead to different MSC phenotypes and gene expression patterns; difference of ‘edited’, e.g. cytokine-edited MSCs
- Host responses: RNAseq expression pattern, immuno-phenotyping and functional T-cells assays gauging immuno-competence (e.g. anti-CMV responses) in longitudinally sampled blood prior and after MSC infusion to gauge for systemic MSC effects
- Measuring CMV DNA in patients prior to MSC delivery and in the clinical followup after MSC infusion. Gauges immune-competence using CMV control as a biological readout.
- Tagging or barcoding MSCs. Better understanding of MSC-MoA, e.g. phagocytosis of MSCs by macrophages and systemic effects.
- Differences in Dendritic Cells and Macrophage responses in vitro and ex vivo using viable MSC or MSC-derived products (e.g. exosomes, apoptotic bodies). Gauging the most suitable and safest MSC profile for COVID-19 treatment.
- Better definition of MSC delivery and dosing
 - Smart clinical studies to address different modes of MSC delivery, e.g. single or repeated doses, escalating dosing? Improved clinical efficacy by repeated infusions? Role of identical MSC donor in repeated dosing? Increased efficacy and safety if MSCs are used from different donors in the case of repeated infusions?
 - *Conditioning’ patients prior to MSCs delivery. Can MSC-associated effects be improved by using repurposed drugs or biologicals that would augment the desired MSCs effects, e.g. decreasing damaging inflammation, while preserving pathogen directed immune responses?
- Better definition of selection of patients receiving MSCs
- Concise study design considering COVID pathophysiology. Which patients benefit most from MSC treatment? Concise clinical documentation needed concerning patients with COVID-19 that allows comparison of trials. Differences associated with MSC products (viable, MSC – apoptotic bodies, exosomes), (COVID-19), disease status or the patients ‘inflammatory phenotype’ (e.g. high IL-6 or IL-17 levels)? Role of lymphopenia in response to MSCs? Smarter patient selection associated with pathophysiology may aid to offer improved treatment modalities.
- Attracting pharma and funder attention: Convincing donors that cellular therapies are viable options for the adjunct treatment of patients with COVID-19 and other lethal infectious diseases
- Gathering trials evidence base on MSC therapy for COVID-19 (the Acronym ‘DOSES’: D = Donor, O = Origin, S = Separation Method, E = Exhibited Characteristics, S = Site of Delivery has been proposed to define optimal MSCs therapy (Murray et al., 2019)
- Adverse events monitoring and analysis: short term and long-term followup of patients, e.g. short term analysis of general immuno-competence (e.g. anti-CMV and anti-SARS-CoV-2 humoral and cellular responses, long term observation concerning infectious complications, increased premalignant or malignant diseases?
- Creation of Biobanks and Access to biological material from patients with COVID-19 infection: Creating repository of samples obtained during MSC trials e.g. blood samples (or BAL) for unbiased gene expression analysis, proteomics and molecular analysis of T-cell responses, e.g. defined by deep TCR sequencing to gauge for MSC effects, different reactivity and biology of neutrophils, macrophages and dendritic cells from patients with COVID-19 as compared to non-Covid-19 patients? Synoptic view with other, complementary assays gauging pulmonary recovery, immuno-competence and capacity to mount long-term anti-SARS-CoV immune responses.
- 9 Advancing HDT trial activities to application of MSCs or MSC-associated products with identical biological readouts, for other infectious diseases where the host response underlies end organ damage causing death or long term functional disability.** e.g. MERS, MDR-TB.

There is an urgent need for reaching global consensus on advancing Mesenchymal Stromal Cell and Cellular therapies for COVID-19 and other infectious diseases.

Advancing MSC therapeutics and achieving global consensus and visibility for cellular host-directed therapies

Table 2 highlights the priority needs for advancing Mesenchymal Stromal Cell and Cellular therapies for COVID-19 and other infectious diseases. We have created an international consortium between clinical cancer and infectious disease research investigators (Website: <https://www.fchampalimaud.org/covid19/aci>) is open to any interested parties to join us to help define optimal MSC therapy regimens and change the course of COVID-19 and sustain the growing portfolio of cellular therapies for a range of acute and chronic infectious diseases.

Conclusions

Despite intense research and pharma activity on developing effective antiviral drug and biologics treatments for the two previous novel lethal coronavirus infections of humans, SARS-CoV-1 and MERS-CoV, all efforts have been fruitless. Novel treatments which can save lives and prevent long-term functional disability in those who survive are urgently required. The COVID-19 pandemic has provided an opportunity for a paradigm shift in focus from targeting the pathogen to the tackling host immune and inflammatory responses which underlie the pathogenesis of SARS-CoV-2. The increasing interest in therapeutic use of MSCs is a promising sign that COVID-19 pandemic and the year 2020 may be the dawn of the new therapeutic era of MSCs treatment for lethal infectious and inflammatory diseases. MSCs should also be advanced and trialed for treatment of severe cases of MERS, where mortality rates are up to 34% since MERS-CoV remains a WHO priority Blueprint pathogen (Memish et al., 2020; Zumla et al., 2015; Azhar et al., 2017). It's about time funding agencies now invested more into accelerate trailing of MSC per se, and combinations of MSCs with other therapeutics. MSC therapy could turn out to be an important contribution to bringing an end to the high COVID-19 and MERS death rates.

Author declarations

All authors have a special interest in Host-Directed Therapies and are members of an International consortium involved in MSC trials for COVID-19, other infectious diseases and cancer.

Professor Fu-Sheng Wang and Professor Danny McAuley are PIs of clinical trials of MSCs in Covid-19 patients.

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