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Review

Promising role for mesenchymal stromal cells in coronavirus infectious disease-19 (COVID-19)-related severe acute respiratory syndrome?

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ABSTRACT

Mesenchymal stromal cells (MSC) have immune regulatory and tissue regenerative properties. MSCs are being studied as a therapy option for many inflammatory and immune disorders and are approved to treat acute graft-versus-host disease (GvHD). The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic and associated coronavirus infectious disease-19 (COVID-19) has claimed many lives. Innovative therapies are needed. Preliminary data using MSCs in the setting of acute respiratory distress syndrome (ARDS) in COVID-19 are emerging. We review mechanisms of action of MSCs in inflammatory and immune conditions and discuss a potential role in persons with COVID-19.

1. Introduction

Mesenchymal stromal cells (MSCs) are a promising therapy of inflammatory and immune disorders because of their immune modulatory properties [1,2]. MSCs, by interacting with the innate immune system, sense inflammatory signals and exert anti- and pro-inflammatory roles making them an option to treat auto- and allo-immune processes [3,4]. MSCs are used to treat some diseases with promising results [5–7]. There are recent reports of therapy of COVID-19-related severe acute respiratory syndrome (ARDS) with MSCs [8,9]. ARDS is the leading cause of death in COVID-19. It is characterized by acute onset with bilateral lung infiltrates, no evidence of elevated left atrial pressure and arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) < 200 mmHg [10]. The cytokine storm caused by the viral infection probably precipitates COVID-19-associated ARDS. Avoiding this storm using the anti-inflammatory properties of MSCs may be effective [9,11,12]. We review data on anti-inflammatory activity of MSCs and discuss mouse and human studies in COVID-19.

2. Mechanism of action of MSCs in inflammatory conditions

Accurate identification of MSCs is challenging and imprecise [13,14]. Homing of MSCs to different tissues or organs may lead to different effects [15]. Cell source, surface markers and cytokine profile in the cell culture can influence the behavior and activity of MSCs [15–18]. Also, the cell and molecular mechanisms how MSCs interact and modulate other immune cells are complex and incompletely understood [15]. These prevent accurate understanding of their mechanism of action. MSCs express several adhesion molecules, endopeptidases and growth factors which facilitate migration to different tissues. They modulate several immune cells including regulatory T-cells (T-regs), conventional T-cells (T-cons), B-cells, natural killer (NK)-cells, monocytes, macrophages, and dendritic cells via direct interactions and via secretion of diverse cytokines [15,19]. Fig. 1 shows interactions between MSCs and immune cells. MSCs promote anti-inflammatory response by promoting monocytes and macrophages polarization toward a type II phenotype and by inhibiting differentiation toward a type I phenotype [20,21]. MSCs-produced interleukin-6 (IL-6)

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and hepatocyte growth factor (HGF) stimulate monocytes to secrete interleukin-10 (IL-10) at high concentrations. These effects reduce IL-12p70, tumor necrosis factor-alpha (TNF-a), interleukin-17 (IL-17), high levels of major histocompatibility complex (MHC) class II antigens, CD45R and CD11b which suppress T-cells. This action of MSCs is independent of FoxP3+ Tregs and inhibits differentiation of dendritic cells (DCs) to a type I phenotype [15,22–24]. Also, Tregs are stimulated by MSCs and achieve immune homeostasis by suppressing auto-immunity [25,26]. In preclinical models, treatment of MSCs with interferon-gamma (IFN-γ) enhances their anti-inflammatory effects. Incubation with muramyl dipeptide (MDP) increases their ability to suppress mononuclear cell proliferation and reduce inflammation [27,28]. Additionally, MSCs produce LL37 (a 37 amino acid cathelicidin anti-microbial peptide), a potent anti-microbial that kills bacteria and viruses [18]. As such MSCs inhibit dendritic cells maturation, suppress T- and NK-cells and promote regulatory T-cells resulting in anti-inflammatory effects in diverse models of acute inflammation in different tissues and organs [29–36].

Toll-like Receptors (TLR) are the main sensors of viral presence and involved in many immune responses during infection. Inflammation caused by direct viral injury results in TLR-priming (TLR-agonist engagement) which can affect MSC phenotype, multi-lineage potential and their immune-modulatory capacity. TLR activation in response to viral infection modulates expression of HLA-antigens and other co-stimulatory molecules resulting in impaired function of some immune cells. Because MSC exposed to TLR ligands up-regulate expression of HLA—I, HLA-II and costimulatory molecules (CD40, CD80, CD86) it is important to consider this when giving allogeneic MSCs [37,38].. Additionally, pre-stimulation of MSCs with specific TLR-ligands could be a priming step to modulate their function to achieve a desired effect in specific viral infections such as with SARS-CoV-2.

Exosomes, apoptotic bodies and micro-vesicles, are formed by budding from the endosomes and other membranes of MSCs and released into the extra-cellular space [39,40]. Considerable data indicate MSC-exosomes contain molecules (tetraspanins, heat shock protein, phosphatidylserine, annexins, MHC class I and II, etc.) released in response to diverse stimuli. These molecules interact with target cells resulting in similar therapeutic benefits as intact cells [15,41–44].

3. MSCs in human disease

Immune modulatory effects of MSCs offer an attractive potential therapy for several reasons including safety, availability, ex vivo expandability, and ease of in vitro modification to produce diverse effects. However, there are many unanswered questions such as best tissue source of MSCs (bone marrow, fat, placenta, dental pulp, etc.), best dose, route, frequency, recipient age-dependency groups, interaction with other therapies and the long term effects [45–51].

There are few data of safety and efficacy of MSCs in humans [52]. In a transplant study investigator infused culture-expanded MSCs with HLA-identical sibling-matched hematopoietic stem cells in 46 subjects with hematologic cancers. There were no adverse effects [53]. A phase-3 trial comparing MSCs or placebo in subjects with corticosteroid refractory acute GvHD showed no benefit [54,55]. A single arm trial of ex vivo expanded MSCs for corticosteroid refractory acute GvHD in children had a 70% overall response rate compared with a pre-specified target of 45% [56]. These trials were neither blinded nor placebo-controlled. A meta-analysis suggested safety and efficacy of MSCs in acute GvHD [57]. Based on these data MSCs were approved to treat gastro-intestinal GvHD in children in Canada and New Zealand but not in the US or EU [58]. Studies using MSCs for ARDS report safety but little efficacy [59,60]. A meta-analysis suggested efficacy of MSCs in inflammatory bowel disease [61]. A search of *ClinicalTrials.gov* identified 282 studies of MSCs in diverse settings. Table 1 summarizes these data.

4. MSCs for inflammatory lung injury in mice

Precisely how SARS-CoV-2-infection causes COVID-19 including ARDS is unknown, some data indicate high plasma concentrations of inducible protein-10 (IP10), monocyte chemoattractant protein 1 (MCP-1), macrophage Inflammatory protein 1A (MIP1A), IL-6, granulocyte colony stimulating factor (G-CSF) and tumor necrosis factor α (TNF α). These molecules may be responsible for an exaggerated systemic immune inflammatory state with resultant ARDS [11]. MSCs are a potential intervention in this setting. In animal models of viral infections many chemokines cause an exaggerated inflammatory response and lung injury. In some but not all studies lung injury was reduced by giving MSCs [44,62]. Additionally, MSCs are effective in several mouse models

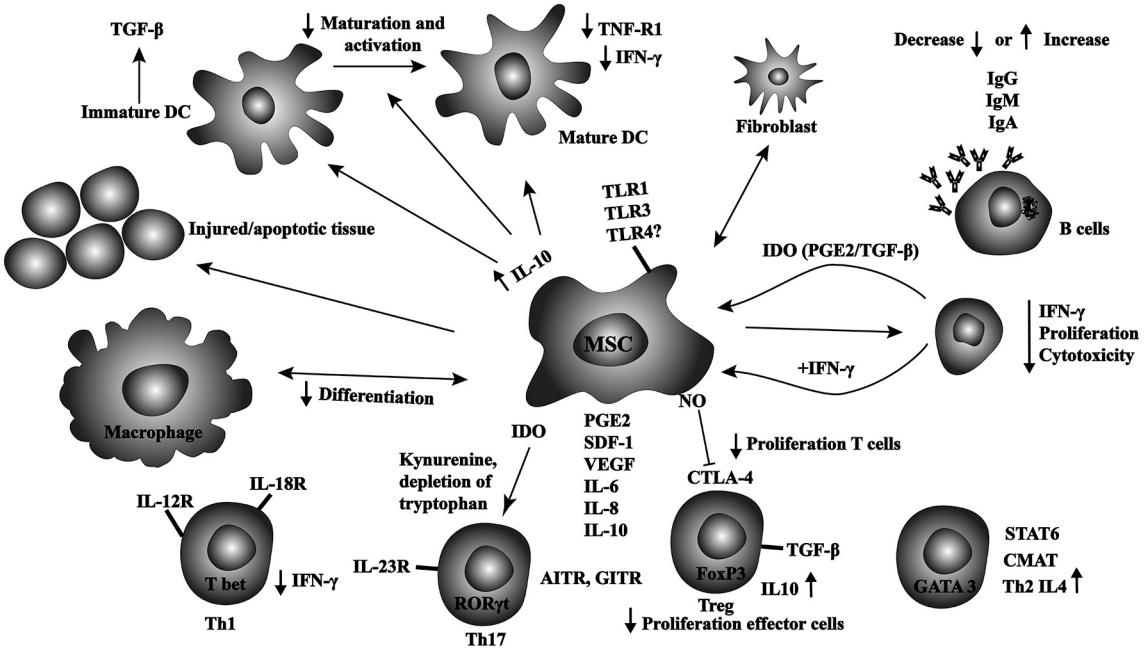

Fig. 1. Schematic overview of the complex interactions between MSCs and immune.

Table 1
Completed and recruiting studies of MSCs for diverse diseases.

Completed	
Condition	NCT number
Inflammatory bowel diseases	NCT01090817, NCT01915927, NCT03209700, NCT03555773, NCT01144962, NCT01659763
Neurologic diseases	NCT01051882, NCT02017912, NCT01777646, NCT03828123, NCT00395200, NCT00781872, NCT02495766, NCT02274428, NCT02165904
Degenerative and musculoskeletal diseases	NCT01038596, NCT03007576, NCT02580695, NCT01586312, NCT02351011, NCT01585857, NCT03810521, NCT01061099, NCT02033525, NCT01860417, NCT04210440
Respiratory distress syndrome	NCT02097641
Rheumatologic diseases	NCT03917797
Organ transplant	NCT02012153, NCT02057965, NCT02387151, NCT01175655
Graft versus host disease and hematopoietic cell transplant	NCT02336230, NCT00957931
Cardio-vascular diseases	NCT00644410, NCT01449032. NCT03651791, NCT00919958, NCT00951210
Others	(Autism) NCT03099239, (Emphysema) NCT01872624, NCT01306513, (Chronic kidney disease) NCT02195323, NCT02801890, (Surgical leak fistula) NCT02807389, NCT02589119, (Septic shock) NCT02421484, (Dental pulp regeneration) NCT03102879
Recruiting	
Diabetes	NCT03325322, NCT03840343, NCT03973827, NCT03406585, NCT02940418, NCT04126603, NCT03509870, NCT02585622
Inflammatory bowel diseases	NCT03449069
Neurologic diseases	NCT03268603
Degenerative and musculo-skeletal diseases	NCT02805855, NCT02838069, NCT02696876, NCT02805855
Respiratory distress syndrome	NCT03818854
Rheumatologic diseases	NCT03745417, NCT03392311, NCT04275024
Organ transplant	NCT03478215, NCT03504241, NCT02565459, NCT03015623, NCT02709343, NCT02260375
Graft-versus-host disease	NCT02359929, NCT02032446, NCT03389919, NCT04247945
Cardio-vascular diseases	NCT03794622, NCT03793530, NCT03792594, NCT03787329, NCT01071577, NCT02408432
Others	(Autism) NCT04089579, (Radiotherapy complications) NCT02814864, (Dysphonia) NCT04290182, (Xerostomia) NCT04007081, NCT03874572 (Autoimmune hepatitis) NCT02997878

such as endotoxin- and bleomycin-induced lung injury [63–65]. MSCs were ineffective in a mouse model of H1N1 influenza-induced lung injury [66] but effective in a model of a more virulent strain of influenza H5N1 [67]. Another preclinical study used intravenous MSCs combined with oseltamivir to prevent or treat mice inoculated with the 2009 pandemic H1N1. This strategy was ineffective [68].

5. MSCs in COVID-19-related ARDS

Because ARDS in persons with COVID-19 is thought to result from cytokine release syndrome (CRS) studies of interventions to moderate this response seem reasonable. Corticosteroids were used in several uncontrolled studies but a recent meta-analysis reported them ineffective with prolonged virus clearing and other adverse events in severe coronavirus infections [69]. MSCs in the lung release anti-inflammatory mediators responsible for ameliorating respiratory viral-induced lung injuries [70,71]. In an uncontrolled study investigators gave MSCs to 7 subjects with COVID-19-related pneumonia and results compared with 3 non-randomized, non-concurrent controls [9]. MSCs recipients had decreased plasma concentrations of C-reactive protein (CRP), TNF-α (tumor necrosis factor), and increased IL-10. Blood lymphocyte concentrations increased and cytokine-secreting cells including CXCR3 + CD4+ T-cells, CXCR3 + CD8+ T-cells, and CXCR3+ NK-cells decreased. CD14 + CD11c + $CD11b^{mid}$ regulatory DCs also increased. There were no adverse events. Because MSCs have no ACE2 or TMPRSS2 receptors they are likely protected from infection by SARS-CoV-2. However, there are some methodological issues with this study and the above observations require confirmation. In another uncontrolled phase-2 study, 7 subjects with COVID-19-related ARDS received allogeneic placenta-derived MSCs. Four improved but there were no controls and investigators were not blinded (https://www.hospimedica.com/covid-19/articles/294781654/pluristem-reports-preliminary-data-from-its-covid-19-compassionate-use-program.html). Recently, Mesoblast Ltd. announced its allogeneic MSC therapy showed an 83% survival rate in ventilator-dependent COVID-19 patients with moderate to severe ARDS. (https://www.bioworld.com/articles/434640-mesoblast-reports-83-survival-in-ventilator-dependent-covid-19-patients-following-stem-cell-therapy). Nine of 12 subjects were weaned off the ventilator support within 10 days following two infusions of MSCs. A recent meta-analysis of cell based therapies for COVID-19 identified 200 subjects receiving allogeneic MSCs intra-tracheally or intravenously [72]. There were no adverse events and authors reported a non-statistically-significant improvement in mortality, pulmonary function, oxygenation and inflammatory markers. Exosomes derived from allogeneic bone marrow-derived MSCs were given to 24 subjects with severe COVID-19 in an uncontrolled study [73]. There were no adverse events. The authors reported improvement in oxygenation and acute phase reactants. Four subjects died, 3 remained critically ill and 17 recovered. Without controls it is impossible to critically analyze these data. These studies are uncontrolled and critical interpretation of these data is impossible.

Many questions regarding the use of MSCs in COVID-19 remain unanswered including best source, dose, route of administration etc. Because MSCs take 3–4 weeks to expand, the use of autologous MSCs in COVID-19 related ARDS is impractical. Data using MSCs in persons with COVID-19-related ARDS are encouraging but not convincing. Studies were small, none were randomized, there were no placebo-treated controls and investigators were not blinded. Based on these data we conclude it is reasonable to study MSCs in COVID-19-related ARDS but only in the context of appropriately designed and controlled clinical trial with blinded investigators. Because single arm trials report few adverse events we suggest the next step should be evaluating MSCs in randomized phase trials with appropriate endpoints.

6. MSCs safety profile

Giving MSCs to humans seems safe [8,9,54,56,61,72]. A meta-analysis with data of >1000 subjects reported only transient fever [74]. Reports of using MSCs for diverse setting including heart failure, kidney transplant and multiple sclerosis report few adverse events [75–78]. MSCs products are diverse with multiple potential sources, production methods and delivery routes complicating critical analyses of safety. Serious adverse events including thrombosis, embolization and death are reported with some products in animals and humans but at a low frequency [79–83].

7. Conclusion and future directions

MSCs are an attractive potential therapy of diverse diseases including ARDS in persons with COVID-19. Several trials of MSCs are ongoing. Preliminary studies report favorable effects but have severe methodological limitations precluding critical analyses (Table 2). There are several unanswered questions: (1) the best donor; (2) source; (3) dose, route and frequency; (4) fresh or cryopreserved; (5) expanded or not; (6)

Table 2
Active trials of MSCs in the setting of COVID-19 infection.

NCT number	Title	Phase	Condition	Intervention
NCT04313322	Treatment of COVID-19 Patients Using Wharton Jelly-Mesenchymal Stem Cells	I	Use of Stem Cells for COVID-19 Treatment	Wharton Jelly MSCs
NCT04288102	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	II	Corona Virus Disease 2019 (COVID-19)	MSCs
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	I	2019 Novel Coronavirus Pneumonia	MSCs
NCT04339660	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	I/II	COVID-19	MSCs
NCT04273646	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	NA	2019 Novel Coronavirus Pneumonia	MSCs
NCT04293692	Therapy for Pneumonia Patients infected by 2019 Novel Coronavirus	NA	COVID-19	MSCs
NCT04269525	Umbilical Cord (UC)- Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	II	Pneumonia, Viral Pneumonia, Ventilator-Associated	MSCs
NCT04333368	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	I/II	Severe Acute Respiratory Syndrome Coronavirus 2	Umbilical cord Wharton's jelly- derived human MSCs
NCT04276987	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cell Exosomes Treating Severe Novel Coronavirus Pneumonia	I	Coronavirus	MSCs- derived exosomes

when to begin therapy and others. These questions can only be answered in controlled trials. Table 3 summarizes our opinions regarding potential solutions to current methodological limitations and heterogeneity in MSCs trials. Although phase-3 studies may be impractical in the setting of the SARS-CoV-2 pandemic, randomized phase-2 studies with a placebo control and blinded investigators are possible. We hope societies such as the International Society of Cell Therapy (ISCT) and International Society for Stem Cell Research (ISSCR) update guidelines and recommendations to improve the quality and conduct of trials of MSCs in COVID-19.

Table 3
Authors' opinions regarding potential solutions to overcome current methodological limitations and heterogeneity in MSCs trials.

Current stance	Potential solutions
No prospective studies available evaluating autologous versus allogeneic source of MSC for infections	Allogeneic source can be utilized under clinical trial. Given the public health crises, an allogeneic source may be logistically easier and quicker
No randomized data available to differentiate between the various tissue sources for MSCs	A clinical trial may utilize any of the tissue sources for generation of MSCs. At least 3 culture passages should be undertaken the MSCs should fulfill at least the definition proposed by the ISCT [62]
No randomized data available evaluating the optimal route of delivery in human trials. Earlier data suggesting "lung trapping" of MSCs when given via intravenous route, however, other studies did not report a difference in outcomes (historic controls) based on the route of delivery	Intravenous systematic delivery of the MSCs has been the most common route evaluated in clinical trials, and is an acceptable and logistically feasible way to try MSC intervention for a COVID-19 infection complication, even when the target organ is the lung
No concrete data that the expanded MSC pool can improve clinical hard end points	Clinical trials can be conducted for COVID-19 complication treatment with or without culture expansion of MSCs
Various end-points have been used in different clinical trials which have utilized MSCs for different diseases. E.g. for GVHD, response rates have been the most common end-point reported in the clinical trials.	Given COVID-19 is a highly fatal disease, the primary outcome variable should focus on mortality. Proposed primary end-point for MSC trials in COVID-19 ARDS: All-cause hospital mortality Or A scale which encompasses mortality e.g. 7-point ordinal scale for COVID-19 severity

8. Practice points

- After licensing MSCs express HLA class I and can express HLA class II molecules. However, MSCs may have low immunogenicity.
- Allogeneic MSC source can be utilized for ARDS in COVID-19 infection. The allogeneic source provides an off the shelf quick option for these acutely ill patients in need for a quick intervention.
- MSC characterization should fulfill at least the definition proposed by the ISCT.
- Intravenous systematic delivery of the MSCs has been the most common route evaluated in clinical trials.
- Earlier data suggest lung trapping of MSCs, this may be advantageous for COVID-19 infection, however the optimal route of administration still has not been determined.
- Clinical trials can be conducted for COVID-19 complication treatment with or without culture expansion of MSCs.
- Given COVID-19 is a highly fatal disease therefore the primary outcome variable should focus on mortality. Proposed primary endpoint for MSC trials in COVID-19 trials may include: All-cause hospital mortality or a scale which encompasses mortality e.g. 7-point ordinal scale for COVID-19 severity.

9. Research agenda

- Optimum donor source of MSCs i.e. allogeneic versus autologous should be determined.
- Best tissue source for MSCs: adipose tissue, dental pulp, umbilical cord, bone marrow, etc. should be evaluated.
- Best route to administer MSCs: systemic or proximal should be studied.
- The role of expanded versus unmanipulated MSCs has to be explored.

- The optimal end point of the clinical trials of MSC usage for COVID-19 treatments must be determined.
- Microvesicles and exosomes efficacy and safety should be explored, as these can bypass a number of logistic issues with MSCs.

Declaration of Competing Interest

None.
cells.

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