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Mesenchymal Stromal Cells in Novel COVID-19 Therapeutics

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) has already claimed over nine hundred thousand lives worldwide with more than twenty-eight million cases at present and increasing. Several research groups around the globe are working on developing therapeutics and vaccines to stall the pandemic. COVID-19 is caused by coronavirus SARS-CoV-2, and one of the major observations in COVID-19 patients is a drastic impact on the immune system, leading to various deleterious effects including cytokine storm that causes organ damage leading to death. Hence, immunomodulatory therapeutic interventions are one of the promising approaches to combat COVID-19. In this direction, Mesenchymal Stromal Cells (MSCs) provide a promising biological intervention to treat COVID-19. MSCs are adult precursor cells that have the potential to differentiate into diverse lineages, and such biological activity renders MSCs with immune-modulatory capabilities. Based on these characteristics, MSCs are implemented in clinical trials against immune disorders. The pathological manifestations of COVID-19 against which MSCs are implemented in clinical trials are highlighted here, along with a discussion on two phase 2 clinical trials involving MSCs against COVID-19 and associated lung disease.

Note: National Clinical Trial (NCT) Identifiers mentioned in parenthesis in the following text

INTRODUCTION

Mesenchymal Stromal Cells (MSCs) are multipotent, non-hematopoietic, self-renewing adult stromal cells found in various tissues, including umbilical cord, placenta, bone marrow and adipose tissue [1]. They have the potential to differentiate into diverse lineages like bone, cartilage, connective tissue, muscle and fat cells. The nomenclature for MSCs has been determined by the International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell (ISCT MSC) committee [2]. Through interference of proliferation, differentiation, and activation of various cells, MSCs regulate innate and adaptive immunity [3,4]. MSCs, by virtue of their multipotency and immunomodulatory characteristics, are widely used in clinical trials, and therapies against immune-mediated inflammatory diseases like Graft Versus-Host Disease (GVHD) and Systemic Lupus Erythematosus (SLE) [5-7]. Although Bone Marrow (BM)-derived MSCs were primarily used clinical applications until 2008, Adipose Tissue (AT) and Perinatal Tissue (PT)-derived MSCs are used as much as BM-derived MSCs thereafter to optimize clinical delivery based on the diverse tissue sources of MSCs [1].

Not surprisingly, under the current Coronavirus Disease 2019 (COVID-19) pandemic caused by coronavirus SARS-CoV-2, several clinical trials are actively trying to harvest the immense potential of MSCs for discovering novel therapeutics against COVID-19. Patients infected with COVID-19 manifest a broad range of predominantly respiratory symptoms including fever, dry cough and shortness of breath [8]. Systemic coagulopathy and thromboembolic damage in multiple organ systems are some of the other hallmarks of advanced COVID-19 [6,9]. Although most patients present with mild symptoms, severe respiratory symptoms occur in almost 5 % of the patients with COVID-19, and in almost 20 % of patients being hospitalized [8]. Therapeutic interventions for the latter group of patients are thus paramount and are the focus of several clinical trials with MSCs.

Clinical trials involving mesenchymal stromal cells against covid-19 and associated respiratory disease

Acute Respiratory Distress Syndrome (ARDS) has shown a surge for COVID-19 infected patients admitted in intensive care units globally and is the main cause of death from the same [10]. Many intervention trials currently use an intravenous infusion of umbilical cord, blood cell or adipose tissue- derived MSCs to study primary outcomes of improved respiratory and cardiac outputs. A compilation of primary and secondary clinical trials outcomes from clinical studies have been reported [11]. Other outcomes include survival of MSCs, adverse events and biochemical/ immunological changes. These clinical trials are in different phases, viz. early Phase 1 (NCT04456361, NCT04345601), Phase 1(NCT04390152, NCT04490486, NCT04447833, NCT04390139, NCT04333368), Phase 2 (NCT04416139, NCT04348461, NCT04390139, NCT04377334, NCT04537351, NCT04333368, NCT04466098).

Pneumonia is yet another common manifestation in patients requiring hospitalization due to COVID-19 infection [11]. Clinical trials are thus focussed on exploiting umbilical cord, placenta, adipose, olfactory or dental pulp derived MSCs for treating COVID-19 associated pneumonia. The primary outcomes of interest mostly include percentage of cure, clinical improvement, and safety and efficiency of administration of MSCs. Secondary outcomes include adverse events, change in symptoms and respiratory improvement. Trials currently active include those in early Phase 1 (NCT04371601, NCT04302519), Phase 1 (NCT04382547, NCT04366323, NCT04392778, NCT04522986, NCT04252118, NCT04339660, NCT04461925, NCT04276987) and Phase 2 (NCT04429763, NCT04315987, NCT04269525, NCT04361942, NCT04466098). Table 1 includes clinical trials mentioned above along with important parameters (Table 1).

Although MSCs show promise the clinical applications, it is important to note that MSCs originating from various tissue sources have different safety profiles during systemic infusion, because of different quantity in expression of highly pro coagulant tissue factor TF/CD142 on their cell surfaces [1,6,12]. The above difference casts significant influence on the safety profiles of cells for intravenous delivery and triggers an effect termed as Instant-Blood-Mediated Inflammatory Reaction (IBMIR) that is crucial to the safety and efficacy profiles of cells [13].

Mesenchymal stromal cells in clinical trial against covid-19 with ARDS and pneumonia

In one of the above Phase 2 interventional clinical trials (NCT04466098) based in the University of Minnesota, USA, patients of COVID-19 with associated pneumonia and ARDS are randomly assigned to receive either MSCs or vehicle placebo control (Figure 1). The randomization is based on stratification by risk i.e. high risk versus standard risk depending on the event of pre-existing co-morbidities.

Rationale: MSCs secrete paracrine factors for epithelial and endothelial permeability of lungs, growth factors, cytokines causing anti-inflammation, and peptides with antimicrobial activities. Through the above secretions, MSCs improve the condition of injured lungs in preclinical models. Moreover, MSCs have an established safety profile. Hence, MSCs are administered to rescue injured lungs of patients having COVID-19 with associated pneumonia and ARDS.

Dosage: Three doses of MSCs or placebo (ineffective drug) are planned to be given to patients in one week, but with a gap of 2 days between successive doses. Standard of care treatments for ARDS will also be provided. The dosage for MSCs involves a thawed product containing 300 × 106 cells in DMSO (dimethyl sulfoxide) resuspended 1:1 with Dextran 40 and 5% human serum albumin, at a total volume of 60

millilitres. The placebo consists of Dextran 40 and 5% human serum albumin, at a total volume of 60 millilitres.

Table 1: Some of the clinical trials for COVID-19 using mesenchymal stem and stromal cells.

NCT#	Title	Intervention/Treatment	Patients number, conditions
04456361	Use of Mesenchymal Stem Cells in ARDS (Acute Respiratory Distress Syndrome) Caused by COVID-19	Biological: Mesenchymal Stem Cells derived from Wharton Jelly of Umbilical cords – Early Phase I	9, ARDS, HumanCovid-19
04345601	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	Biological: Mesenchymal Stromal Cells Other: Supportive Care –Early Phase I	30, ARDS, Human Covid-19
04390152	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	Drug: Wharton's jelly derived Mesenchymal stem cells – Phase IDrug: Hydroxychloroquine, lopinavir/ritonavir or azithromycin, placebo standard therapy – Phase II	40, ARDS
04490486	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 (COVID-19)	Biological: UCMSCs Other: Placebo – Phase I	21, COVID-19, ARDS
04333368	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS (STROMA-CoV2)	Biological: Umbilical cord Wharton's jelly-derived human – Phase I Other: NaCl 0.9% – Phase II	40, Severe Acute Respiratory Syndrome Coronavirus 2, Severe ARDS
04466098	Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19)	Biological: Mesenchymal stromal cells Other: Placebo – Phase II	30, ARDS, COVID-19 Pneumonia
04302519	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	Biological: Dental pulp mesenchymal stem cells – Early Phase I	24, COVID-19
04276987	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	Biological: MSCs-derived exosomes – Phase I	24, severe patients with novel coronavirus pneumonia (NCP)
04429763	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMA)	Biological: Umbilical cord derived mesenchymal stem cellsBiological: Placebo – Phase II	30, COVID-19
04315987	NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	Biological: NestaCell®Biological: Placebo– Phase II	90, COVID-19 Pneumonia
04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia	Biological: UC-MSCs – Phase II	16, 2019-nCOV infection Pneumonia
04361942	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (COVID_MSV)	Biological: Mesenchymal Stromal CellsOther: Placebo – Phase II	24, severe COVID-19 pneumonia

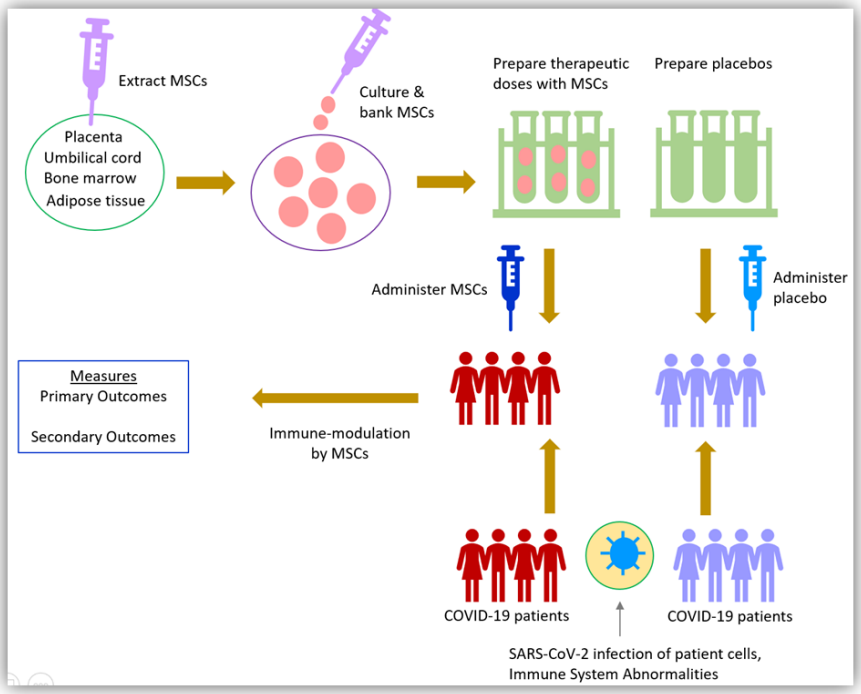

Figure 1: Workflow of clinical trials administering mesenchymal stem cells to patients of COVID-19 and associated diseases affecting the lung.

In order to evaluate the effect of an intervention/treatment, primary and secondary outcome measures are determined, based on more and less importance of planned outcome measures, respectively. For this clinical trial, primary outcome measures will be based on grade 3-5 infusional toxicities, and inadvertent hemodynamic or respiratory occurrences which are predefined, and observed within 6 hours of infusion. As secondary outcome measures, reduction of one or more biomarkers of inflammation within one week of first infusion will be assayed. Several parameters related to air pressure-mediated changes will also be monitored, along with mortality, days without ventilator and oxygen support, and other conditions.

Mesenchymal stromal cells in clinical trial against severe covid-19 pneumonia

Severe COVID-19 pneumonia is another condition which is targeted in clinical trials by MSCs because of their immunomodulatory properties. Several phase I/II, placebo-controlled, randomized clinical trials against the above condition are harnessing the potential of MSCs. In one such interventional clinical trial based in Hospital Universitario Rio Hortega in Spain (NCT04361942), mesenchymal stromal cells are administered to patients of severe COVID-19 pneumonia.

Rationale: Preclinical studies show that acute lung injury by H9N2 and H5N1 viruses are ameliorated by MSCs, along with reduction in pro inflammatory cytokines and inflammatory cells in the lungs (Khoury et al., 2020). Hence, the immune-modulatory effects of MSCs are being tested against SARS-CoV-2 infection in this clinical trial.

Dosage: Patients with severe COVID-19 pneumonia are planned to be given intravenous injection of MSCs at a concentration of 1 million cells/kg diluted in 100 ml saline, or a placebo of 100 ml saline containing no cells. The injection is to be administered only once.

Primary outcome measures for this clinical trial will consist of assaying mortality and withdrawal of invasive ventilation within four weeks and one week of treatment, respectively. Secondary outcome measures will be based on haemoglobin saturation, air pressure-mediated changes, fever, and other criteria.

DISCUSSION AND FUTURE PERSPECTIVES

To combat the rising death toll and infection rate of COVID-19, several approaches are currently being pursued to combat the pandemic through pharmacological and non-pharmacological methods, which are in various phases of clinical trials. Since COVID-19 severely impacts the immune system, therapeutic targeting of immune components is a popular mode of intervention that is being developed by several groups worldwide. In this direction, numerous clinical trials at various phases across the globe are administering MSCs to patients of COVID-19 with associated conditions that are detrimental to the lungs. This is because MSCs are known for their immune-modulatory benefits in preclinical studies against other viruses that are detrimental to the lungs, similar to SARS-CoV-2 infection [14-19]. Numerous clinical trials are testing the effect of MSCs on COVID-19 patients with associated ARDS and pneumonia, which are two very common conditions that lead to lung damage. Based on past preclinical studies using MSCs against lung damage by viral infection, it is expected that MSCs will show promise in these clinical trials. In addition to lungs, several other organs including the heart are also damaged upon SARS-CoV-2 infection [20]. If MSCs succeed in clinical trials for treating COVID-19 through amelioration of lung damage, then their therapeutic potential can be extended in the future to other damaged organs as well.

However, there are disadvantages to using MSCs because of costs, viability, and accessibility at remote and disadvantaged sections of the world, which need to be collectively addressed by administrations around the globe. Further, in addition to various therapeutic interventions against SARS-CoV-2 infection and severe immune response, underlying comorbidities associated with COVID-19 in various populations also need to be addressed. Two major comorbidities for COVID-19 are diabetes and obesity, which result from various causes including ill health, genetic and epigenetic abnormalities, and nutritional causes. Among the various causes of diabetes and obesity, the nutritional a spectis the easiest to take care of through improved nourishment and food processing procedures [21]. Hence, a concerted effort through affordable and accessible therapeutic interventions and nutritional improvements will be helpful in combating this pandemic. Despite the hurdles, over 60 clinical trials worldwide are using MSCs against COVID-19

which indicates towards the promise of this biological intervention against the ongoing pandemic, and the therapeutic potential of MSCs can be hoped to be further manifested with time.

CONFLICTS OF INTEREST

None

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