MESENCHYMAL STEM (STROMAL) CELLS

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Introduction

Mesenchymal stem cells (MSC) are non-hematopoietic, multipotent stem cells with the capacity to differentiate into mesodermal lineage such as osteocytes, adipocytes and chondrocytes as well ectodermal and endodermal lineages. The International Society for Cellular Therapy (ISCT) states that MSC must express CD29, CD44, CD73, CD90, CD105 and lack expression of CD14, CD19, CD45, CD79, or HLA-DR surface molecules.[1]

Mechanism of Action

MSC may have beneficial effects for preventing or attenuating the cytokine storm. MSCs play a positive role mainly in two ways: immunomodulatory effects and differentiation abilities. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells including T cells, B cells, dendritic cells, macrophages and natural killer cells leading to immunomodulation. Immunomodulatory effects are attained through the following possible mechanisms through the release of transforming growth factor alpha (TGF-alpha), hepatocyte growth factor (HGF), nitric oxide, indoleamine 2,3-dioxygenase (IDO), intracellular adhesion molecule 1 (ICAM 1), vascular cell adhesion molecule 1 (VCAM 1) and others. It may also inhibit proliferation of T-cells in reaction to alloantigens and mitogens.[2,3,4]

MSC have also been shown to improve the lung microenvironment, pulmonary fibrosis, and lung function, probably due to the regulation of the inflammatory response and the promotion of tissue repair and regeneration.[5]

Clinical Studies

The pilot trial published using intravenous umbilical cord (UC)-derived MSC was done in 7 patients with COVID-19 infected pneumonia who received one dose of stem cell therapy, compared to 3 patients in the control group (3 serious). Results showed improved pulmonary function, but no clear general trend in terms of inflammatory cytokines and T-regulatory cells. Limitations of this study include the small sample size and short-term follow-up.[5]

Since then, there have been 3 other published reports. Umbillical cord derived mesenchymal stem cells (UC-MSC) was used for the treatment of 31 patients with severe COVID-19 pneumonia at Taikangtongji Hospital in Wuhan, China. This demonstrated that the treatment could restore oxygenation and downregulate cytokine without any infusion reaction.[6]

A non-randomized open-label cohort study addressed the safety and efficacy of exosomes (ExoFlo™) derived from allogeneic bone marrow mesenchymal stem cells as treatment for 24 patients with severe COVID-19 and moderate-to-severe acute respiratory distress syndrome at a single hospital center. They reported a survival rate of 83%. And overall, there was improvement of clinical status, immune reconstitution and downregulation of cytokine storm.[7]

A clinical pilot study used menstrual blood-derived MSCs for the treatment of 2 patients with severe COVID-19 in Wuhan. It reported improvement in oxygenation, increase in immune indicators and decrease in inflammatory indicators after treatment.[8]

There are 55 other studies listed in ClinicalTrials.gov using MSC for COVID-19 that are either in the process of gathering data, recruiting subjects or have not yet started.[9]

Adverse Reactions

Safety and effectiveness of MSCs have been documented in several clinical trials.[10,11] However, numerous complications have been reported from improper application of stem cells.[12] Therefore, quality preparation of the stem cells is of paramount importance. Assurance for safety should include: (1) source should be from legitimate labs compliant with the FDA standards; (2) strict screening of donors, (3) product must be analyzed for cell viability, quality and sterility and must meet the highest standards, (4) cell passage numbers should be limited to increase potency and decrease cell size.[13]

Also, during IV infusion, all precautions should be taken to prevent pulmonary or other organ embolization. Patients should be monitored for allergic reactions especially when using allogeneic products.[13]

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy of MSC to treat COVID-19 infection. MSC appear to be relatively safe. One of the main restrictions in this approach is obtaining the source of clinical-grade MSCs and subsequently the speed of preparation for clinical usage.

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