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Infusion of Mesenchymal Stem Cells: A Promising Treatment for Severe Covid-19

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Imtroduction

Over 8 million people around the world, to the present date, were reported to have the disease provoked by SARS-CoV-2 virus infection, COVID-19 [1]. This virus belongs to the same genus as SARS-CoV and MERS-CoV, Betacoronaviruses that have triggered previous epidemic outbreaks, causing respiratory infections. The most commonly reported symptoms of COVID-19 are fever, cough, and fatigue, shortness of breath, nausea and diarrhoea. Age has been identified as a major risk factor, as well as comorbidities, such as cardiovascular disease, diabetes, obesity and hypertension, disregard of age group [2]. The initial mechanism of infection occurs through the binding of the virus spike protein to the angiotensin-converting enzyme 2, which is present on the surface of several cell types, especially of epithelial cells [3].

A subgroup of COVID-19 patients develops the cytokine storm syndrome [4], which is associated with increased tissue and plasma content of cytokines, including interleukin (IL) -1, IL-10, IL-13, IL-17, macrophage inflammatory protein-1 α, interferon (IFN)-γ and tumour necrosis factor (TNF) -α. In the lungs, this results in alveolar oedema, oxygenation impairment and acute respiratory distress syndrome (ARDS), which may be lethal [3,5]. So far, despite all efforts, there is no stablished drug therapy capable of totally reverting the symptoms of COVID-19 [4].

About the Study

Mesenchymal stem cells (MSC) have shown safety and efficacy in clinical trials that include inflammatory conditions as Crohn's disease and cardiomyopathy [6] and in ARDS and sepsis treatment, in preclinical models [6], suggesting that these cells may be employed in the treatment ARDS, due to their ability to promote paracrine signalling [6,7]. MSCs are non-hematopoietic stromal precursor cells, considered to be multipotent, as they are able to differentiate into various cell types of mesodermal origin, depending on the stimulus received [8]. Moreover, MSCs can be isolated from several tissues, such as the bone marrow, adipose tissue, dental pulp, placenta, umbilical cord blood and matrix [9].

MSCs display several characteristics that render them excellent candidates for employment in the treatment of acute diseases. These cells can undergo extended expansion without detriment to their multipotency or self-renewal properties [10], and show low tumorigenicity [11], while being considered non-immunogenic, owing to low constitutive expression of the major histocompatibility complex (MHC) class I and to the absence of co-stimulatory molecules of MHC class II (allowing allogeneic transplantation without the need for human leukocyte antigen matching or immunosuppression) [9].

MSCs have immunomodulatory and anti-inflammatory effects on host tissue, partly through the release of paracrine factors [6]. Several preclinical studies, as reviewed by Johnson et al. [12], have demonstrated that in sepsis and acute lung injury/ARDS models, MSCs exposure resulted in a decline of the expression and secretion of pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, IFN-γ, and TNF-α, as well as an increase in the presence of anti-inflammatory cytokines such as IL-4, IL-5, IL-10 [12].

COVID-19 severe cases display a significantly lower number of total T cells, (both of T-helper and T regulatory lymphocytes, Treg) [4]. Local secretion of TGF-β by MSCs has been demonstrated impact regulatory T cells function [13]. Moreover, under inflammatory conditions, MSCs express indoleamine 2,3-dioxygenase, which modulates the generation of regulatory T cells [14].

The involvement of B lymphocytes in the context of COVID-19 immunopathology remains elusive. Since patients with agammaglobulinemia present a mild course of COVID-19, with a favourable outcome, a possible role of B lymphocytes in SARS-CoV-2–induced inflammation is suggested [15]. MSCs interact with B cells and can reduce plasma cell formation, along with promoting the induction of regulatory B cells (Bregs). Bregs show immunosuppressive properties, through which they contribute to immunological tolerance [16].

One possible mechanism through which B cells would induce inflammation might be related with activation of monocyte-derived macrophage through engagement of Fcγ receptors by anti-spike protein IgG immune complex, which would hence contribute to COVID-19-related cytokine storm with the release of massive amounts of pro-inflammatory cytokines [17]. Thus, it is possible to affirm that inflammatory macrophages play a relevant part in the immunopathogenesis of COVID-19. Moreover, in a mouse model of asthma, MSCs phagocytosis by pulmonary alveolar cells was shown to promote the polarisation of monocytes/macrophages toward an immunosuppressive phenotype with anti-inflammatory properties, which expresses IL-10 and of programmed death ligand-1 [18].

Currently, 40 registered clinical trials that aim to evaluate the adequation of stem cell employment in the treatment of patients affected by COVID-19 were identified [19]. From these, 15 trials with

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umbilical cord stem cells, 7 trials with adipose tissue stem cells, and 6 derived from bone marrow, 2 with dental pulp stem cells, 2 with placenta stem cells, and 1 derived from the olfactory epithelium. None of these clinical trial authors published the results so far.

A pilot study of intravenous transplantation of MSCs was performed in seven patients affected by COVID-19 pneumonia [3]. MSCs were applied to patients through intravenous drip ($1x10^6$ cells per kilogram of weight). Cell transplant was performed when symptoms were still deteriorating, even under the currently approved treatments. The administration of intravenous injection of MSCs yielded no side effects and all pulmonary and other symptoms disappeared in average 3 days post-treatment, with significant mitigation of the inflammatory status, characterised by a reduction in serum levels of the pro-inflammatory cytokines and chemokines. This resulted in consequent lower recruitment of mononuclear cells to the lungs, and at the same time, increased attraction of regulatory dendritic cells to the inflammatory tissue niche. Furthermore, there was an increase in IL-10 and vascular endothelial growth factor, promoting pulmonary repair [3]. These findings can be attributed to both the immunomodulatory and anti-inflammatory effects of MSCs [3].

MSCs intravenous infusion has been applied in a variety of clinical contexts, proving to be safe in patients, as well as effective in reverting the pro-inflammatory state in several diseases, including ARDS-associated infections. These findings strongly suggest MSCs potential for the treatment of severe COVID-19. Decreasing local and systemic inflammation present in the severe form of COVID-19 is crucial during the treatment time course. Although further studies are needed, it appears that employing MSCs in the context of SARS-CoV-2 infection is a safe and promising treatment strategy with minimal side effects.

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