

## A Perspective on UC-MSC Treatment in Severe and Critically Severe Covid-19 Patients

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### Abstract

*The covid-19 disease is characterized by cytokine storm and severe pneumonia causing pulmonary edema and acute respiratory distress syndrome. This is followed by an overactive immune response that can cause severe multiple organ failure. Millions of people have died since then, and many more are still suffering from the disease's consequences. Studies have been published to develop strategies for effective treatments as still there is no effective treatment for the disease. In the last decade, there are significant results about mesenchymal stem cells (MSCs) having the unique potential to modulate the immune system. To improve therapeutic benefit and design more effective treatments for Covid-19 disease with MSCs, several issues were covered in this commentary: MSC-derived products, MSC administration routes, and the ideal time and dose for MSC administration. Since, there is no unanimity in the literature as to which MSCs will provide more effective healing when administered by which route, in what amount, and at what time. This commentary will have provided inferences that can contribute to developing innovative treatments for patients suffering from Covid-19.*

**Keywords:** ARDS; Covid-19; MSCs treatment; UC-MSC

### Introduction

In the perspective of our study titled "Clinical experience on umbilical cord mesenchymal stem cell treatment in 210 severe and critical Covid-19 cases in Turkey, we would like to comment on the proceeding articles as follows [1]. In particular, Mesenchymal Stem Cells (MSCs) may be effective against coronavirus due to their robust immunomodulatory capabilities and may also offer beneficial effects to mitigate the cytokine storm by secreting potent anti-inflammatory molecules [2]. According to the literature, MSCs are recognized to make a significant contribution to immune regulation by either releasing cytokines or by having contact with target tissues. In a clinical investigation, IV transplantation of MSCs was reported to be safe and efficacious in patients with Covid-19, especially in seriously unwell patients with pneumonia [3]. Immunomodulatory effects and differentiation capabilities are two ways in which MSCs function. To ensure immunomodulation, MSCs can either produce a variety of cytokines in a paracrine manner or interact directly with immune cells. MSCs' immunomodulatory actions are prompted when they are induced by viruses or infections [4]. Growth factors, exosomes, chemokines, and apoptotic cells are all

factors that influence MSCs' immunosuppressive mechanisms. The frequency and diversity of inflammatory responses affect the plasticity of MSC immunoregulation. MSCs can prevent macrophages, monocytes, and neutrophils from infiltrating inflammatory areas, and this process is crucial for MSCs' ability to treat acute lung injury [5]. MSC activation is facilitated by pro-inflammatory mediators such as IL-1, IFN, and TNF-. By triggering an inflammatory response, MSC activation promotes tissue healing. T cell proliferation is suppressed by IDO, which is produced by MSCs. With cytokines, growth factors, and exosomes, MSCs regulate the immune system. MSCs respond to their environment by releasing growth and differentiation factors, and they help with tissue remodeling following transplantation [5]. Despite the short half-life of intravenously transplanted cells, their cellular remnants can be phagocytosed and distributed throughout the body via the bloodstream. It is stated that MSCs are eliminated from the body within 24 hours after being injected intravenously. However, phagocytosis allows lysed transplanted cells to enter the bloodstream and be transmitted to various parts of the body via signaling pathways, possibly paracrine signals and provides immunomodulation with a systemic effect due to macrophage polarization via cytokines [6, 7]. Also, it has been

reported that the source of MSCs is important in regulating the cytokine storm caused by the COVID-19 infection [8]. The aforementioned study demonstrated that Umbilical Cord – Mesenchymal Stem Cells (UC-MSCs) can be used to treat critical Covid-19 patients by immune regulation and reducing the cytokine storm as to prevent systemic multiorgan failure. In preclinical research, MSCs were found to be beneficial in a variety of respiratory disorders. MSCs have been examined especially in acute respiratory distress syndrome (ARDS) for their impact on epithelial cells, improving epithelial barrier function, clearance function, and reducing inflammation with immunomodulatory effects [9]. From fundamental research to clinical trials, MSCs have been widely used in stem cell treatment studies. It has been indicated by both preclinical and clinical studies that MSC-mediated therapies are safe and effective (2) [10]. Furthermore, in Covid-19 patients, MSCs not only helps to cure the lung injury but also enhance to improve the patient's overall condition via immunomodulatory effects [11].

## Discussion

The tissue from which MSC is derived, route of administration, dose, and the number of injections are all aspects that determine MSC therapy's performance [12, 13]. The promising role of UC-MSC therapy in curing Covid-19 disease is discussed in three parts in terms of treatment outcomes, in light of current advancements and novel therapeutic possibilities.

### 1. MSC Derived Products

MSCs systemic treatment has shown promising outcomes in Covid-19 patients [1, 14]. Hence, due to FDA regulation, bone marrow MSCs are dominantly used, adipose stem cells, amniotic stem cells, menstrual blood derived MSCs, and umbilical cord stem cells are used in clinical applications more frequently in recent studies [15]. UC-MSCs can be obtained in a non-invasive manner with a high concentration and have faster doubling time and high plasticity capacity. Therefore UC-MSCs appear to be the most attractive. It is also critical that they are non-tumorigenic [2]. According to recent studies, in severe or mild Covid-19 sufferers, UC-MSC intravenous (IV) transplantation has been shown to be safe and effective [10, 11 and 16]. In addition, the safety and efficacy of UC-MSC infusions were investigated in a randomized controlled clinical trial conducted in 2020. In patients with Covid-19 ARDS, UC-MSC infusions have been demonstrated to be safe, and the therapy has been shown to be successful in terms of patient survival, with a significant reduction in inflammatory cytokines [16]. However, inconsistency in cell outcomes and engraftment, as well as a lack of guideline standardization in cell management, the use of UC-MSCs is limited in terms of patient safety. In addition, urgent Covid-19 treatment in a new, complex, and unknown disease will exacerbate the problem [17]. Adipose-Derived Stem Cells (ASCs) are another important source of stem cell; they play a key role in regenerative medicine due

to their ability to self-renewal, differentiation into tissue-specific progenitors, migration to wounded areas, movement through autocrine and paracrine mechanisms, and cell regeneration. Due to, they include a higher number of cells than MSCs from other sources, ASCs are indicated as a therapeutic alternative for the therapy of Covid-19. However, when compared to non-invasively obtained allogeneic UC-MSCs, the fact that ASCs are obtained through a minimally invasive lipoaspiration method may be regarded as a disadvantage [18].

### 2. MSC Administration Route

The most preferable method of delivery of UC-MSCs is IV infusion since it is less invasive. Although IV injected UC-MSCs have a shorter half-life as they are degraded within 24 hours in the lungs, this can be beneficial as the lungs are the most affected by the coronavirus [2]. IV infusion of MSCs has some disadvantages as well. MSCs can be given intravenously easily, but they are also unable to cross the blood-brain barrier at the cellular level like other stem cells [9]. However, UC-MSCs can reach distant organs with a systemic effect through paracrine signaling, cell-cell interaction, and signaling pathways, and thus it is likely to provide recovery in distant organs [2]. In a phase I trial published in 2020, it was notified that IV MSC treatment might enhance Covid-19 patients' clinical results and indicate good immunological tolerance, particularly in critical patients [4]. A clinical trial in 2021 established the long-term safety and efficacy of IV delivery of UC-MSCs in patients with severe Covid-19. UC-MSC treatment yields a long-term improvement in the amelioration of lung lesions and symptoms in Covid-19 patients. According to this 1-year follow-up study, MSC therapy may be a promising treatment for chronic patients with severe pneumonia [19]. After IV injection, MSCs become trapped in the affected lung. As In way, MSCs can be stated to be successful in coping with one of Covid-19's most lethal consequences, cytokine storm, and acute respiratory distress, both of which generate an overwhelming immune response. Even though intrathecal injection is expected to produce better results, the safety and efficacy of MSC administration via intrathecal injection are yet unknown, as most research utilizes the IV approach until today [20]. Inhalation is another route of drug delivery that has been utilized extensively since ancient times and is currently preferred for numerous lung disorders, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and pneumonia. Besides, there are many FDA-authorized inhaled medications for influenza and respiratory syncytial virus infection. Also, many antibacterial, antiviral, and steroidal inhaler drugs have been developed and others are under development to treat Covid-19 patients who have pneumonia. Although inhalation of therapeutics and vaccines against Covid-19 is a potential, non-invasive method of administration with distinct advantages, employing inhalers in infectious disorders can be hazardous due to contamination. In this context, additional investigation into alternative methods of

administration routes to reduce healthcare risks is crucial [21]. An advantage of inhalation delivery is difficult to pinpoint, as there are much different research involving variances in the production process, changes between patients and disease phases, and uncertainties about administration [9]. In the light of recent results, since the lung is the tissue that will be directly affected, IV infusion may be preferable in the treatment of acute coronavirus because it is less invasive and has a lower risk of contamination.

### 3. The Appropriate Time and Dose for MSC

In preclinical investigations, mesenchymal stem cells have been demonstrated to be useful in the treatment of lung damage and ARDS, because of their restorative and immunomodulatory characteristics to prevent or cure injured alveoli and fibrosis [20]. The scheduling and ideal dose of MSC administration are the two difficult aspects of its therapeutic application [13]. It has been stated in the clinical studies that a single dose of MSC infusion is enough for therapeutic efficacy in acute respiratory disease, and repeated applications are not required for recovery [12]. In fact, since different stem cell sources and different administration routes are used, there is no agreement in the literature on the optimal dose of MSCs [13]. Nonetheless, a recent phase 1 study in moderate to critically severe ARDS patients no dose-limiting toxicity was detected in any dose cohort (100-200-400 x 10<sup>6</sup>), and a dose of 400 x 10<sup>6</sup> cells was found to be the highest tolerated dose for the phase 2 study [22]. But repeated doses of MSC administration may be needed for chronic respiratory distress. So, UC-MSC IV infusion is recommended mostly in case of acute respiratory distress as in Covid-19 disease [1]. According to a study investigating the immunomodulatory effects of MSCs in acute and chronic animal models with emphysema, and atherosclerosis, MSCs inhibited the pulmonary inflammation in the acute stage, which is caused by lipopolysaccharide, while MSC treatment has less influence on the progression of inflammation, emphysema, and atherosclerosis in the chronic stage [1, 23].

### Conclusion

This commentary considered several aspects of MSCs transplantation for Covid-19 treatment. To achieve the best treatment outcome in Covid-19 patients, the results of the recent studies were evaluated that IV allogeneic therapy is a powerful and safe therapeutic agent in the treatment of Covid-19 as an acute autoimmune disease.

One of the most significant challenges of MSC treatment is the requirement of validation for its efficacy in randomized, controlled, multicentre research with a consistent follow-up period.

### Authors' Contributions

Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration,

Visualization, Writing - original draft: NE. Writing - review & editing: NK, NE

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### Declaration of Competing Interest

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