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**A current update in COVID-19 associated acute respiratory distress syndrome:  
Focus on mesenchymal stem cell therapy**

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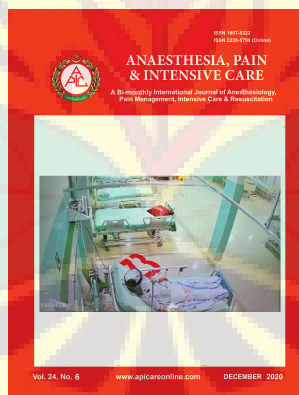
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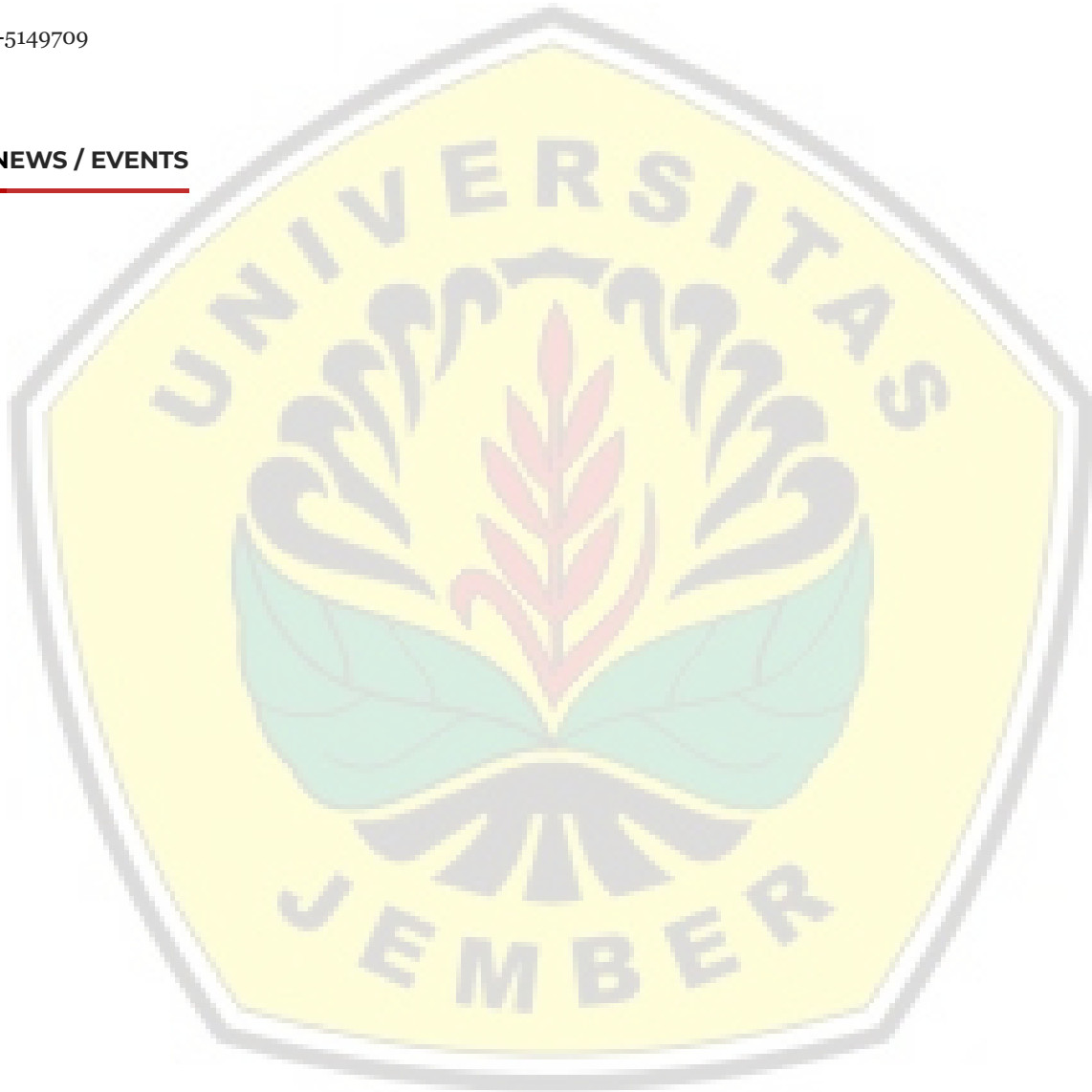
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## NARRATIVE REVIEW

## CORONA EXPERIENCE

# A current update in COVID-19 associated acute respiratory distress syndrome: Focus on mesenchymal stem cell therapy

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## Abstract

Indonesia has been fighting the COVID-19 pandemic since the beginning of March 2020, and it doesn't look that the situation is getting better any soon. Besides the country's current strategies to minimize the rising mortality rate, a novel therapeutic intervention is required. After a thorough search in several databases, we found stem cells to be a likely candidate. Regardless of the general use of stem cells, studies showed positive results regarding the efficacy of using these in lung injuries. Especially, mesenchymal stem cells (MSCs) are known for their easy accessibility and their diverse mechanisms of action, including MSCs immunomodulatory antiviral effect, and its ability to improve lung function. Moreover, some researches perceived these components to be applicable in COVID-19 patients with end stage acute respiratory distress syndrome (ARDS). While randomized clinical trials are still in progress, many case reports show MSCs to be an advantageous alternative to suppress the cytokine storm and help regulate the immune system. This review summarizes the common functions of MSCs and highlights its therapeutic assets to fully tackle this global pandemic.

**Key word:** Mesenchymal Stem Cells; Cell Therapy; COVID-19; SARS-CoV-2; ARDS

**Abbreviations:** COVID-19 – Coronavirus Disease; MSC – Mesenchymal Stem Cell; ARDS – Acute Respiratory Distress Syndrome

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## 1. Introduction

Since August 7, 2020, Indonesia's COVID-19 cases have set a new record. Indonesia has surpassed Peoples Republic of China with the total of 121,226 cases, 5,593 deaths, and 77,557 recovered.<sup>1</sup> Adapting WHO's six prioritized strategies, Indonesia has adopted several strategies to suppress the spread of COVID-19.<sup>2</sup> Ever since the first case

was confirmed to be positive, measures taken included large scale social restrictions, strict stay-at-home orders, improvement in healthcare services, and provision of personal protective equipment (PPEs) to healthcare workers across the country.<sup>3,4</sup> Nevertheless, the virus is still circulating among the community with over 1000 new cases per day.<sup>1</sup> There have been reports that hospitals taking care of

COVID-19 patients have reached their total capacity.<sup>5</sup>

Aside from restraining virus transmission, a novel treatment plan is required to lessen the growing number of deaths caused by COVID-19. One of the suggested measure is the use of stem cells. Stem cells have been widely used in auto-immune and transplantation medicine, and can also be used in lung injuries.<sup>6,7</sup> As the development of cell therapy grows, the researchers all around the world are now constantly trying to apply novel stem cell treatment in COVID-19 patients, particularly mesenchymal stem cells (MSCs). MSCs have attracted much attention due to their readily accessible source, their ability to easily expand to a large numbers, capability to repetitive therapeutic usage, and being without any known adverse events reported. It is compulsory to understand better the rationale and potential mechanisms of MSCs actions towards respiratory viral infections.<sup>8</sup> This review aims to present an overview of the MSCs and their potential implication in treating COVID-19 infection.

This literature review was constructed by comprehensive data searching in several databases such as PubMed, Science Direct, Scopus, The Cochrane Library, and other websites. We searched all relevant related articles with keywords such as cell therapy, mesenchymal stem cells, COVID-19, SARS-CoV-2, ARDS, and its synonym during the search strategy. Boolean operators (AND, OR, NOT) were applied to broaden and narrow the search results with the following combination ((Cell therapy OR Mesenchymal Stem Cell) AND ((COVID-19 OR SARS-CoV2) AND ARDS)). Subsequently, we included all articles including comprehensive cohort studies, case reports, randomized controlled trials, and systematic reviews, as well as meta-analyses regarding MSCs therapy in COVID-19 patients until August 2020. The search was limited to articles published in the past ten years with language restriction to English and Bahasa Indonesia, as convenient to the reviewers. Some data regarding COVID-19 infection in Indonesia were also taken from acknowledged authorized websites.

## 2. COVID-19 Overview

Ever since the early 2000s, coronavirus (Co-V) has invaded the world as one of its most significant health problems. In 2002 SARS-Co-V (Severe Acute Respiratory Syndrome-Co-V) was first found

in China and it brought upon an outbreak until 2004. In 2012 MERS (Middle East Respiratory Syndrome) Co-V was detected in Saudi Arabia in patients suffering from flu-like symptoms.<sup>9</sup> In the late 2019, China discovered a new kind of pneumonia caused by the novel coronavirus, which has been labeled as corona virus disease-2019 (COVID-19) by WHO. The virus was first confirmed in Indonesia on 2 March 2020.<sup>2</sup> Later on 11th March, WHO declared COVID-19 as a global pandemic.

Coronavirus is a single strand, positive RNA genome with 26-32kb, and is labeled as the largest RNA virus.<sup>9,10</sup> Similar to SARS-CoV, COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptor to enter the host's cells.<sup>10,11</sup> Coronavirus will use the S protein on its surface to bind with the ACE2 receptor and inserts virus particles into host cells.<sup>10</sup> ACE2 receptors are highly expressed in the lung, especially in the apical region within the alveolar space, but can also be found in other organs such as the heart, kidney and intestine.<sup>12,13</sup> Additionally, studies also found protease activators such as TMPRSS2 and lysosomal proteases in cell entry.<sup>14</sup> The host immune reaction is also similar to common acute viral infections. Immunoglobulin-M (Ig-M) antibodies of SARS-CoV can last upto 12 weeks, while IgG antibodies can last for a very long time. Although it is not confirmed yet, an animal experiment with rhesus macaques showed neutralizing antibodies of COVID-19 is enough to prevent reinfection in the first few days of recovery.<sup>15</sup>

The most common clinical features of COVID-19 are fever, cough and myalgia. There are also cases where patients showed congestion, sore throat, rhinorrhea, and diarrhea. Nonetheless, all COVID-19 patients exhibit bilateral ground-glass opacities in their radiographic images of the chest. Laboratory abnormalities that are frequently seen are lower lymphocyte count, higher lactate dehydrogenase, C-reactive protein and creatine kinase.<sup>16,17</sup> Reports from immunological assessment stated that interleukin (IL)-6 was higher in patients in critical condition. IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1- $\alpha$ , and tumor necrosis factor (TNF- $\alpha$ ) also increase in severe infections.<sup>12</sup> From these rising cytokine levels, the uncontrolled systemic pro-inflammatory response could then trigger ARDS, thus leading to multiple organ failure, ultimately ending into death. Patients with ARDS showed a

disturbance in homeostasis with elevating pro-inflammatory cytokines such as IFN- $\alpha$ , IFN- $\gamma$ , IL-1- $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF- $\beta$  and chemokines.<sup>11</sup>

Although the number of cases of SARS-CoV2-induced pneumonia patients is continuously increasing, there is no specific therapy. The current treatment has a limited effect on lung inflammation and regeneration. Considering the over-reactivity inflammatory state of SARS-CoV2, agents that modulate the immune response are being explored as alternative treatments for the management of moderate to critical COVID-19.<sup>18</sup> Choices for treatment can be classified into RNA-dependent RNA polymerase inhibitors (remdesivir, favipiravir, ribavirin); interferons; protease inhibitors (lopinavir/ritonavir, chloroquine, hydroxychloroquine, azithromycin, teicoplanin, monoclonal antibodies); convalescent plasma; herbal medications and other considerations namely corticosteroids. Patients are given supportive treatment to maintain hydration and nutrition.<sup>19</sup> Antipyretic, antimicrobial agents, and oxygen therapy are also prescribed as required.<sup>20,21</sup> Corticosteroids are the most commonly prescribed medication. However, the associated adverse effect need to be monitored attentively.<sup>21</sup> In India, hydroxychloroquine is now recommended for prophylactic use and recommended for healthcare personnel taking care of COVID-19 patients.<sup>22</sup> Immunoglobulin from healed patients (convalescent plasma) is also deemed to be safe and effective, but it is prioritized for critically ill patients.<sup>23</sup>

### *MSCs Potential Clinical Applications as an Alternative Yet Promising Choice*

Stem cells are the origin of all different types of cells in the human body. There are five types of stem cells: totipotent or omnipotent, which is the beginning of all life forms (zygote); pluripotent is usually known as the embryonic stem cells which will differentiate into the germinal layers (mesoderm, endoderm and ectoderm); multipotent are limited to a specific germ layer such as hematopoietic stem cell in the bone marrow; oligopotent or somatic stem cells can only differentiate into a more specific line, for instance myeloid stem cells; and lastly unipotent which can only multiply into one kind of cell type (muscle cell).<sup>7,24</sup> Therapies involving stem cells are being used in many diseases. From preclinical and clinical trials stem cells are shown to have a positive effect

on auto-immune diseases (type 1 diabetes mellitus), chronic myeloid leukemia, cirrhosis, pulmonary fibrosis, Crohn's disease, cardiovascular diseases (heart failure), as well as neurodegenerative diseases.<sup>24,25</sup> Nevertheless, among other stem cells, MSCs are seen as a rising star in cell therapy. MSCs are distinguished from others by their surface expressions. For instance, surface markers are CD73, CD90, CD105, human leukocyte antigen (HLA) Class I, etc. They also secrete various growth factors, cytokines, and immunomodulatory molecules.<sup>26,27</sup> MSCs are mainly collected from the bone marrow, but can be found in adipose tissue, synovial tissue, lung, umbilical cord, and peripheral blood.<sup>26</sup> Furthermore, MSCs are easy to isolate because they can maintain their characteristics for a long term.<sup>25</sup> Due to MSCs chemotactic ability to migrate towards the damaged tissue, they are preferable to be administered through intravenous injection. This mechanism is similar to leukocytes, where some suggested that MSCs were also attracted to chemoattractants released by the injured site. Studies hypothesized that MSCs used a proteolytic enzyme called matrix metalloproteinase (MMPs) to move and attach to endothelial cells.<sup>28</sup>

What makes MSCs so promising are the end product of their interaction with the immune system. MSCs will interact with monocytes/macrophages, dendritic cells (DCs), T cells, B cells, and natural killer (NK) cells. MSCs are known to have at least five capacities (Figure 1) namely trophic/anti-apoptotic, anti-inflammatory, anti-bacterial, antiviral, and improving lung function.<sup>29-31</sup> The anti-apoptotic properties of MSCs are believed to be mediated by production of growth factor and other chemokines to induce cell proliferation and angiogenesis.<sup>31</sup> These molecules comprise of vascular endothelial growth factor (VEGF), insulin growth factor (IGF), hepatocyte growth factor (HGF), fibroblast growth factor-7 (FGF7), and interleukin-6 (IL-6).<sup>30-32</sup> Besides anti-apoptotic properties, MSCs will stimulate paracrine factors as well as modulate the balance of pro and anti-inflammation. Paracrine mechanism took place when MSCs are directly in contact with the immune cells, thus cytokines such as TGF-beta, IL-10, and IL-1RA, nitric oxide, and indoleamine 2,3 dioxygenase (IDO) are released from MSCs. These cytokines will then affect the proliferation and activation of naive and effector T cells.<sup>6</sup> In addition, IDO has the potential to inhibit viral replication and reduce viral load.<sup>33</sup>

In response to inflammatory stimuli, MSCs secrete growth factor and key immunomodulatory anti-inflammatory cytokines such as PGE2, TGF- $\beta$ 1, HGF, SDF-1, NO, indoleamine 2,3-dioxygenase, IL-4, IL-6, IL-10, etc.<sup>31,34</sup> In addition, MSCs indirectly induce the transition of T helper-1 (T<sub>H</sub>1) cells to T helper-2 (T<sub>H</sub>2) and shift macrophages from M1 to anti-inflammatory, tissue healing M2 state induced by directly secretes PGE2 and finally M2 will increase IL-4 and IL-10 production.<sup>29,30,35</sup> Development of Th-17 pro-inflammatory cells is also suppressed by secreting anti-inflammatory cytokines.<sup>6,28</sup> Studies suggested that monocyte differentiation into DCs are disturbed, as well as of DCs role as antigen presenting cells. Additionally, B cells proliferation, differentiation, and chemotaxis are also impeded by MSCs. Nevertheless, since MSCs help to regulate the immune system, they are not affected by the cytotoxic effect of other immune cells.<sup>28</sup>

Several anti-bacterial substrates secreted by MSCs have been identified. MSCs promote bacterial clearance directly by secreting lipocalin-2, LL-37, beta defensin-2, toll-like receptor (TLR4). MSCs will indirectly activate the phagocytic ability of neutrophils and alveolar macrophages when reprogramming them to an anti-inflammatory phenotype.<sup>30,36</sup> There are also reports stating that LL-37 has the ability as an antiviral by degrading viral membrane.<sup>37</sup>

In the case of respiratory viral infections (SARS CoV-2), MSCs had two different potential antiviral mechanisms. First is by constitutively increasing levels of MSC-specific interferon-stimulated genes (ISGs) that has antiviral protection role, and secondly in response to interferon makes broad viral resistance by ISG induction.<sup>38,39</sup> Furthermore, MSCs may interact with immune cells and promote T-regulatory cells (Tregs), which enhances virus clearance.<sup>29</sup> MSCs could serve as an integrated innate antiviral defense that could lead to therapeutic advantages in COVID-19 patients. In these patients, ARDS may manifest itself as impaired alveolar fluid clearance, which is associated with higher morbidity and mortality. The secretion of keratinocyte growth factor (KGF) and angiotensin-1 (Ang-1) by MSCs essentially contribute to the restoration of alveolar-capillary barriers disrupted as part of ARDS pathogenesis.<sup>38</sup> Beside KGF and Ang-1, FGF7 secreted by MSCs is also taking a significant role to

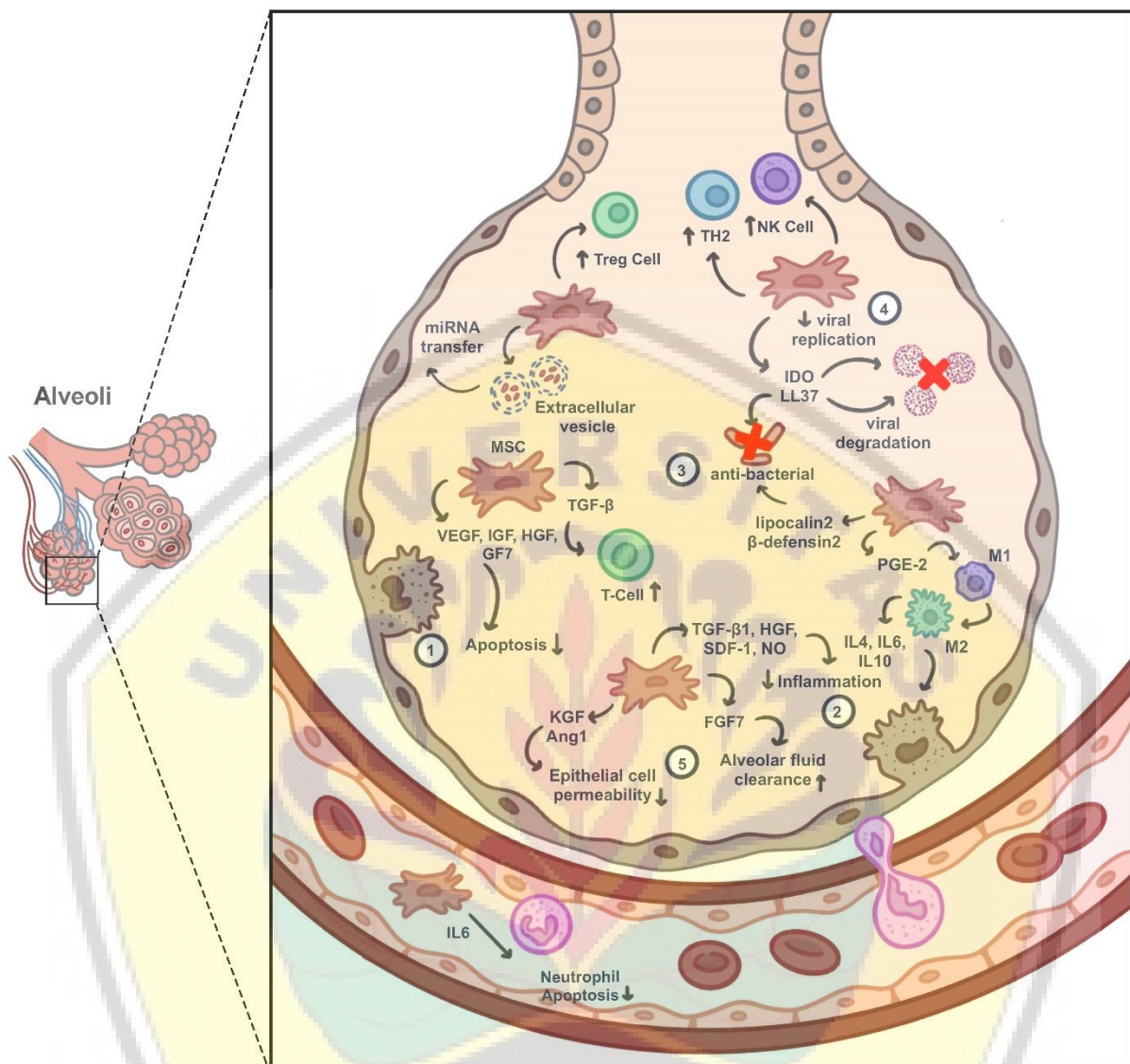
improve alveolar fluid clearance.<sup>30</sup> To sum up, a pro-inflammatory environment like IFN-gamma can trigger immunomodulatory aspects of MSCs, and a higher level of an anti-inflammatory agent will terminate MSCs immunosuppressive mechanism.

### 3. MSCs Therapy for ARDS

Acute lung injury (ALI) is a disease characterized by capillary membrane injury, causing pulmonary edema and atelectasis.<sup>40</sup> The main clinical manifestation is an acute onset of hypoxic respiratory failure, which can subsequently trigger a cascade of profound complications and even death. ALI is an old terminology which previously used to describe mild acute respiratory distress syndrome (ARDS) with PaO<sub>2</sub>/FiO<sub>2</sub> (PF) ratio of 200-300.<sup>29</sup> The current definition of ARDS is clinical, based on measurement of hypoxemia, the initial occurrence of injury, and bilateral infiltrates finding on chest x-ray without any cardiogenic cause.<sup>29</sup> ARDS develops most commonly in the setting of pneumonia (bacterial and viral being more common than fungal), non-pulmonary sepsis, aspiration of gastric and/or oral and esophageal contents and major trauma such as blunt or penetrating injuries as well as burns.<sup>41</sup>

Most of the COVID-19 patients suffer from ARDS. A single-centered retrospective study in Wuhan, China reported that approximately 67% of critically ill COVID-19 patients develop ARDS with considerable mortality rate.<sup>42</sup> This respiratory distress peaks at 7 to 10 days with manifestations of immune dysregulation, including cytokine storm with the rise of cytokine levels (IL-6, IL-8, IL-1, IL2R, IL-10, and TNF- $\alpha$ ), lymphopenia (in CD4+ and CD8+ T cells), and decreases in IFN- $\gamma$  expression in CD4+ T cells.<sup>17</sup> To date, many therapeutics efforts have been proposed regarding ARDS management, yet none have proven to be effective, and thus supportive strategies including low tidal volume mechanical ventilation, the institution of antibiotics, and fluid restriction remain the mainstay of therapy.<sup>43</sup> Nevertheless, an increasing number of clinical investigations of cell-based therapies, primarily MSCs has been conducted. Recent data in models of respiratory virus-associated ARDS with MSCs administration showed promising results.





**Figure 1: MSC potential therapeutic effects in ARDS**

Mesenchymal stem cell (MSC) has five potential roles, which makes MSCs so promising. First, they secrete several growth factors and chemokines like vascular endothelial growth factor (VEGF), insulin growth factor (IGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF7). Second, MSC secretes key immunomodulatory anti-inflammatory cytokines such as PGE2, TGF- $\beta$ 1, HGF, SDF-1, NO, indoleamine 2,3-dioxygenase (IDO), IL-4, IL-6, IL-10. Third, lipocalin-2, LL-37, beta defensin-2 have an anti-bacterial effect. Fourth, IDO and LL-37 also have antiviral activity. Fifth, MSC enhances alveolar lung function through its paracrine factors like KGF, Ang-1, and FGF7.

A single-centered, open-label, randomized study, RUMCESS (NCT 01849237), reported that a group

treated with MSCs ( $1 \times 10^6$  MSC IV) showed a significant increase in 28-days survival rates (57% vs. 15%) and was associated with lower SOFA-scores.<sup>44</sup> Another study conducted by Simonson *et al.* reported that after being treated with  $2 \times 10^6$  cells/kg bone marrow stromal cells (BMSCs), their subjects showed a decrease in epithelial apoptosis markers, alveolar-capillary fluid leakage, miRNA, and chemokines in plasma and BAL fluid.<sup>45</sup> Following intravenous administration, the majority of MSCs will accumulate in the pulmonary vascular bed and interact with the capillary endothelial cells.<sup>38</sup> In the case of ARDS, this action may be a beneficial as this would facilitate a high local concentration of MSCs directly at the site of inflammation. MSCs will secrete several paracrine

signals that can play a significant role in protecting or recovering alveolar epithelial cells, enhance lung function, and reduce inflammation.<sup>46</sup>

### 4. Current Evidence on MSCs Treatment

Since the outbreak of SARS CoV-2 in December 2019, cell-based therapy, in particular MSCs, exhibits favorable results, as described earlier, to cure lung injuries. As of 31st July 2020, there are 52 COVID-19 clinical trial using various sources of MSCs registered on the NIH website

www.clinicaltrials.gov (Table 1). There are 23 trials using allogenic MSCs, while only three trials using autologous MSCs; the remaining trials were unspecified. Among these, 14 trials used UC-MSCs, seven trials used AD-MSCs, five trials used BMSCs, and four trials used WJ-MSCs. Autologous cells are used less often because it needs more time to be processed, thus it is not feasible for the deteriorating patient's condition.<sup>47</sup> Dental pulp MSCs were used in two studies, one trial used olfactory mucosa MSCs, the second trial used exosome derived MSCs. One study used core blood cell, while the remaining did not specify the type of MSCs.

**Table 1 : Ongoing MSCs clinical trials for COVID-19**

No	NCT	Status	Phase	Conditions	Type of Stem Cell	Locations
1	NCT04444271	Recruiting	2	C-19	MSCs	Pakistan
2	NCT04416139	Recruiting	2	C-19	MSCs	Mexico
3	NCT04429763	NYR	2	C-19	UC-MSCs	N/A
4	NCT04315987	NYR	2	C-19 Pneumonia	MSCs	Brazil
	NCT04456361	Active, not recruiting	1	C-19 ARDS	WJ-MSCs	Mexico
6	NCT04252118	Recruiting	1	C-19	MSCs	China
7	NCT04366271	Recruiting	2	C-19	MSCs	Spain
8	NCT04366323	Recruiting	2	C-19	Allogenic AD-MSCs	Spain
9	NCT04313322	Recruiting	1	C-19	WJ-MSCs	Jordan
10	NCT04336254	Recruiting	1	C-19	Allogeneic dental pulp stem cells	China
11	NCT04346368	NYR	1	C-19	BM-MSCs	China
12	NCT04288102	Active, not recruiting	2	C-19	UC-MSCs	China
13	NCT04273646	NYR	N/A	Pneumonia, C-19	UC-MSCs	China
14	NCT04348435	Enrolling by invitation	2	C-19	AD-MSCs	USA
15	NCT04382547	Enrolling by invitation	1	Pneumonia, C-19	Allogenic pooled olfactory mucosa-derived MSCs	Belarus
16	NCT04366063	Recruiting	3	C-19	MSCs	Iran
17	NCT04339660	Recruiting	1	C-19	UC-MSCs	China
18	NCT04428801	NYR	2	C-19	Autologous AD-MSCs	N/A
19	NCT04349631	Enrolling by invitation	2	C-19	AD-MSCs	USA
20	NCT04457609	Recruiting	1	C-19	UC-MSCs	Indonesia
21	NCT04352803	NYR	1	Pneumonia, C-19	autologous AD-MSCs	N/A
22	NCT04302519	NYR	1	C-19	Dental pulp MSCs	N/A
23	NCT04490486	NYR	1	ARDS, C-19	UC-MSCs	USA
24	NCT04355728	Recruiting	1	ARDS, C-19	UC-MSCs	USA
25	NCT04461925	Recruiting	1	Pneumonia, C-19	Placenta-Derived MSCs	Ukraine
26	NCT04371601	Active, not recruiting	1	Pneumonia, C-19	MSCs	China

27	NCT04348461	NYR	2	ARDS, C-19	Allogeneic AD-MSCs	N/A
28	NCT04362189	Recruiting	2	C-19	AD-MSCs	USA
29	NCT04390152	NYR	1	ARDS, C-19	WJ-MSCs	Colombia
30	NCT04452097	NYR	1	ARDS, C-19	UC-MSCs	N/A
31	NCT04371393	Recruiting	3	ARDS, C-19	MSCs	USA
32	NCT04397796	NYR	1	C-19	Bone Marrow derived MSCs	N/A
33	NCT04494386	Recruiting	1	ARDS, C-19	Umbilical Cord Lining Stem Cells	USA
34	NCT04377334	NYR	2	ARDS, C-19	MSCs	Germany
35	NCT04345601	NYR	1	ARDS, C-19	MSCs	USA
36	NCT04390139	Recruiting	2	ARDS, C-19	WJ-MSCs	Spain
37	NCT04392778	Recruiting	1	Pneumonia, C-19, MOF	MSCs	Turkey
38	NCT04467047	NYR	1	C-19	MSCs	N/A
39	NCT04398303	NYR	1	Pneumonia, C-19	UC-MSCs	N/A
40	NCT04361942	Recruiting	2	Pneumonia, C-19	MSCs	Spain
41	NCT03042143	Recruiting	1	ARDS, C-19	UC-MSCs	UK
42	NCT04269525	Recruiting	2	Pneumonia, C-19	UC-MSCs	China
43	NCT04389450	Recruiting	2	ARDS, C-19	MSCs	USA
44	NCT04447833	Recruiting	1	ARDS, C-19	MSCs	Sweden
45	NCT04437823	Recruiting	2	C-19	UC-MSCs	Pakistan
46	NCT04491240	Enrolling by invitation	2	Pneumonia, C-19	MSCs-derived exosomes	Russia
47	NCT04333368	Recruiting	1	ARDS, C-19	WJ-MSCs	France
48	NCT04299152	NYR	2	Pneumonia, C-19	Cord blood stem cell	N/A
49	NCT04466098	NYR	2	Pneumonia, ARDS, C-19	MSCs	USA
50	NCT04445220	NYR	1	C-19, Acute kidney injury	Allogenic MSCs	N/A
51	NCT04400032	NYR	1	ARDS, C-19	MSCs	Canada
52	NCT04276987	NYR	1	C-19	MSCs-derived exosomes	N/A

**Legend:** C-19 - Coronavirus disease; ARDS - Acute respiratory distress syndrome; MSC - Mesenchymal stem cell; UC-MSC - umbilical cord-derived mesenchymal stem cell; WJ-MSC - Wharton-Jelly derived mesenchymal stem cell; AD-MSC - Adipose-derived mesenchymal stem cell; NYR – Not yet recruiting

A prospective, non-randomized, open-label cohort study used exosome derived BMSCs in treating severe COVID-19 patients.<sup>48</sup> The cells were administered intravenously over 60 min, and the outcome was observed for the next five days. Overall, the survival rate was over 83%. 71% of the patients (17/24) recovered with no adverse events. The patients' clinical status and oxygenation (PaO<sub>2</sub>/FiO<sub>2</sub>) improved significantly as well as the laboratory findings, including lymphocyte and neutrophil counts, CRP, and D-Dimer levels. Additionally, it is widely accepted to use exosome derived MSCs. The exosome properties provide protective paracrine effects without having to inject

living cell; therefore it could prevent immunological adverse events.<sup>34,38</sup>

Another single-centered, open-label pilot study in Beijing, China, administered BMSCs into seven COVID-19 patients with various degrees of severity. One patient was categorized as critically ill, four with a severe condition, and two had mild symptoms. They injected 10<sup>6</sup> cells/kg BMSCs intravenously and followed them for 14 days. Neither toxicity or allergy, nor other adverse events were reported, and the patients displayed clinical improvement of their pulmonary function and symptoms after 2-4 days.<sup>49</sup> Along with this study, Rogers *et al.* showed that infused MSCs did not

interact with the ACE2 receptor and TMPRSS2, which implied that MSCs would not associate with SARS-CoV-2.<sup>29</sup>

A 65-year-old female critically ill COVID-19 patient indicated a good clinical remission after MSCs treatment.<sup>50</sup> After antiviral and glucocorticoid management failed to show any improvement, she received UC-MSCs ( $5 \times 10^7$  cells) intravenously. After the second administration, neutrophil count decreased, lymphocytes increased as well as CD3<sup>+</sup>T cell, CD4<sup>+</sup>T cell, and CD8<sup>+</sup>T cell back to normal. On the CT scan findings, it was reported that the pneumonia imaging greatly improved, and she was finally released from the hospital with a negative swab test. This finding suggested that MSCs could improve patient outcomes even in elderly. A meta-analysis revealed that MSCs treatment did decrease the mortality rate in COVID-19 patients.<sup>51</sup> From these reported cases, there were notable improvements in lung compliance and tidal volume in COVID-19-induced ARDS treated with MSCs.

## 5. Limitations in MSCs therapy

Before resolving the use of MSCs for the recommended therapy, several things need to be acknowledged. Stem cells therapy is a complicated one, and there are cases where unwanted side effects did occur. Even though MSCs are relatively safe, a study reported immunosuppression in some patients with injured lungs, causing secondary infection.<sup>52</sup> A similar case was also described in patients receiving MSCs as immunosuppressive after having hematopoietic stem cell transplantation.<sup>53</sup> More in-depth research in utilizing MSCs is needed to prevent unwanted differentiation of MSCs in local engrafted setting. Lastly, despite the positive impact of the paracrine and endocrine mechanism by MSCs, they may stimulate proangiogenic factors (VEGF, HGF, angiopoietin-1, platelet-derived growth factor, and placental growth factor) which is in line with augmenting tumor growth.<sup>28,52,53</sup> Long term use of MSCs could also cause the production of allo-antibodies, while single use of MSCs are harmless and did not cause any dangerous immune response.<sup>28</sup> More trials are necessary to know the side effects that MSCs may carry.

## 6. Conclusion and recommendation

In conclusion, although there is no standardized therapy for SARS Co-V2, MSC is a promising alternative treatment. Several studies, both pre-clinical and early clinical, have provided tantalizing clues that MSCs can provide a consistent therapeutic benefit. Moreover, the majority of previous results confirmed that MSCs are capable of dampening the over-reactivity inflammation cascade, decreasing infection, improving lung recovery, and increase the survival rate. It may take several months even years to develop a vaccine, and even if it's effective, it will not completely eradicate the ongoing infection. Further clinical trials regarding MSCs-based therapies in ARDS are urgently needed, including investigation regarding its safety.

## 7. Conflict of interest

No funding was used for the preparation of this review.

## 8. Authors' contribution

DN: concept, literature search, manuscript writing, figure illustration

NAK: concept, literature search, manuscript editing

RY: manuscript editing

AP: bibliography editing

HBH: concept, manuscript editing

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