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Journal of Controlled Release 325 (2020) 135–140

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Mesenchymal stromal cells and their secreted extracellular vesicles as therapeutic tools for COVID-19 pneumonia?☆

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A B S T R A C T

The COVID-19 epidemic represents an unprecedented global health emergency, further aggravated by the lack of effective therapies. For this reason, several clinical trials are testing different off-label drugs, already approved for other pathologies. Mesenchymal stem/stromal cells (MSCs) have been tested during the last two decades for the treatment of various pathologic conditions, including acute and chronic lung diseases, both in animal models and in patients. In particular, promising results have been obtained in the experimental therapy of acute respiratory distress syndrome, which represents the most threatening complication of COVID-19 infection. Furthermore, more recently, great interest has been devoted to the possible clinical applications of extracellular vesicles secreted by MSCs, nanoparticles that convey much of the biological effects and of the therapeutic efficacy of their cells of origin. This review summarizes the experimental evidence underlying the possible use of MSCs and of MSC-EVs in severe COVID-19 infection and underlines the need to evaluate the possible efficacy of these therapeutic approaches through controlled studies under the supervision of the Regulatory Authorities.

1. Introduction

The ongoing health emergency related to the COVID-19 epidemic is mainly due to the pulmonary complications of the disease, for which there are no proven effective therapies. According to recent studies, the cell entry receptors of the virus are represented by the angiotensin converting enzyme II ACE2 [1] and by the serine protease TMPRSS2 [2]. Both types of proteins are highly expressed on alveolar type II cells (AT2), while the ACE2 receptor is also widely distributed on several human cells, including cardiac and kidney cells, as well as endothelial and smooth muscle cells in several organs, explaining the ability of this virus to generate a systemic disease [3,4]. The binding of the SARS-CoV-2 spike protein to ACE2 has been suggested to cause the down-regulation of ACE2 from the cell membrane [5], resulting in an imbalance between ACE and ACE2 activity and contributing to acute lung injury [6]. Indeed, ACE2 has opposite effects to ACE [7]. ACE-catalyzed conversion of Angiotensin I to Angiotensin II promotes vasoconstriction, inflammation and oxidative stress, while ACE2 converts angiotensin II into angiotensin 1–7, a peptide inducing vasodilatation and exhibiting anti-oxidant and anti-inflammatory properties [6,8,9]. Acute respiratory distress syndrome (ARDS) and an exuberant inflammatory response characterized by high blood cytokine levels have been associated with critical and fatal illnesses [10]. ARDS is a devastating hypoxemic respiratory failure, characterized by disruption of the alveolar-capillary membrane barrier [11]. Despite decades of research, current management for ARDS remains supportive [11]. Several clinical trials are currently underway in a collective effort to fight COVID-19 pneumonia, including both new drugs and "off label" drugs, i.e. drugs

☆ This manuscript represents a consensus paper issued by the Scientific Board of STEMNET, a federation gathering the following four scientific societies devoted to stem cell research. • Italian Group for the Study of Mesenchymal Stem Cells (GISM): A. Pessina (President), E. Lucarelli, M. Muraca, M. Pozzobon. • Forum of Italian Researchers on Mesenchymal Stromal and Stem Cells (FIRST): L. Lazzari (President), M. Dominici. • Stem Cell Research Italy (SCRI): U. Galderisi (President) • International Placenta Stem Cell Society (IPLASS): O. Parolini (Past President).

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https://doi.org/10.1016/j.jconrel.2020.06.036
Received 21 April 2020; Received in revised form 12 June 2020; Accepted 29 June 2020
Available online 03 July 2020

that can be used in diseases other than those for which they have been authorized [12]. This is the case of some antivirals and some biological anti-cytokine drugs (such as anti-interleukin 6 and anti-TNF), tested on these patients based on their established mechanisms of action.

2. Mesenchymal stromal cells for the treatment of acute inflammatory lung diseases

A recent report described the possible therapeutic efficacy of mesenchymal stem/stromal cells (MSCs) in patients with severe COVID-19 pneumonia [13]. MSCs are a heterogeneous population containing stromal cells, progenitor cells, fibroblasts and stem cells [14,15]. They can be isolated from different tissues including bone marrow, adipose tissue, cord blood, Wharton jelly and placenta, and are currently being used to treat a number of clinical conditions, as well as being tested in several clinical trials around the world due to their immunomodulatory and tissue regenerative properties [16–21] together with their considerable safety [22].

The study of Leng et al. [13] enrolled seven confirmed COVID-19 patients, including one critically severe type, four severe types and two common types in the MSC-treated group, while three severe type patients were enrolled in the placebo control group. Of note, "standard" treatment in the placebo group was not specified. Treated patients received 1×10^6 MSCs per Kg body wt. intravenously. No adverse effects were observed. The pulmonary function and symptoms of treated patients were significantly improved within 2 days after MSC transplantation. Chest CT imaging also showed significant improvement. In this group, three patients (two common and one severe type) recovered and were discharged within 10 days. In the placebo group, one patient died and two were reported to worsen, although their outcome is not described. MSC infusion was associated with increased peripheral lymphocyte count and with decreased systemic markers of inflammation compared to the placebo group.

Clearly, it is premature to draw any conclusion based on a single study with a limited number of patients likely receiving multiple treatments, as warned by scientific societies in the field [23–25]. On the other hand, more rigorous studies excluding possible confounding treatments in the placebo group could raise serious ethical concerns. Due to the complexity of the disease, a large sample size will probably be required to reach statistical significance, and it could be difficult to meet such a requirement with a decreasing prevalence of the infection. However, it is reasonable to put forward some considerations based on the knowledge accumulated over twenty years of experience with the use of these cells in various autoimmune, inflammatory and degenerative diseases. Indeed, the rationale for the use of MSCs in COVID-19 associated pneumonia is manifold.

The anti-inflammatory and immune modulatory properties of MSCs are well established and have been exploited in a large number of both preclinical and clinical studies [16,26,27]. Moreover, MSCs behave as tissue-protecting agents, inhibiting apoptosis, limiting oxidative injury and enhancing regeneration [18]. MSCs are massively retained in the lung following intravenous infusion [28] and they have been successfully tested in several animal models of acute and chronic lung injury such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, obstructive bronchiolitis, and bronchopulmonary dysplasia [29–35].

Documented biological activities supporting the use of MSCs/MSC-EVs as therapeutic agents in COVID-19 pneumonia include immune modulation, tissue protection and anti-bacterial/antiviral activity.

As stated above, the cytokine release syndrome (CRS) characterized by fever and multiple organ dysfunction is a major cause of death in COVID-19 patients. Data from recent studies suggest that SARS-CoV-2 infection can lead to a complex immune dysregulation affecting different subsets of immune cells [11]. This is probably the reason why targeting specific immune pathways has so far brought only partially beneficial effects to severe COVID-19 patient [36]. For instance, although Interleukin 6 (IL-6) seems to hold a key role in CRS pathophysiology, treatment with selective inhibitors such as Tocilizumab, a blocker of IL-6R that can effectively block IL-6 signal transduction pathway, did not reduce mortality in COVID-19 patients. The beneficial effects of MSCs in different models of lung injury and fibrosis are associated with a reduction in proinflammatory cytokines such as tumor necrosis factor-α and IL-6 and an increase in anti-inflammatory cytokines such as IL-10. Alveolar macrophages are crucial in orchestrating the initiation and resolution of lung inflammation, first by polarizing toward the M1 phenotype releasing pro-inflammatory cytokines and then by switching to the alternative M2 phenotype, releasing IL-10 and promoting the resolution of inflammation [37]. MSCs (activated by LPS or TNF-a via Toll-like receptor 4) can reprogram macrophages to an alternative phenotype by releasing prostaglandin E2 [38]. More recently, Lv et al. have demonstrated in an animal model of acute lung injury that the stress response protein stanniocalcin-2 can have a central role in MSC immunomodulation [39]. These results were obtained in animal models of toxic or LPS-mediated lung injury that could elicit different responses by MSCs when compared to SARS-CoV-2 infection. Interestingly, however, the clinical study by Leng et al. reported that the levels of TNF-α was significantly decreased, while IL-10 increased in COVID patients treated with MSCs compared to the placebo control group. These findings suggest that MSCs might help re-equilibrating the dysregulated immune response observed in these patients.

Lung pathology of COVID-19 pneumonia in critically ill patients include exudative and proliferative phases of diffuse alveolar damage and microvessel thrombosis suggestive of early ARDS [40,41], whose pathogenesis include altered alveolar permeability and neutrophil infiltration [42]. Administration of MSC-EVs was found to reduce protein permeability and to increase alveolar fluid clearance in an ex vivo model of human perfused lung injured with severe *E. coli* pneumonia [28,43,44]. These functional improvements were associated with decreased neutrophil infiltration. The MSC therapeutic potential was correlated with the secretion of cytoprotective agents such as keratinocyte growth factor (KGF), anti-inflammatory products such as PGE2 or lipoxin A4, anti-permeability factors such as angiopoietin-1 (Ang1). Interestingly, culture media of bacteria-stimulated MSCs were found to contain antimicrobial products [45], and in murine sepsis models treatment with MSCs increased bacterial clearance, in part due to enhanced phagocytotic activity of the host immune cells [46]. Moreover, MSC-EVs exhibited antiviral activity, both by suppressing influenza virus replication after virus entry in lung epithelial cells in vitro and by decreasing viral load in a pig model of influenza virus-induced lung injury [47].

Currently, there are several ongoing clinical trials on the use of MSCs in the treatment of several pulmonary diseases including idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, obstructive bronchiolitis and bronchopneumodysplasia [19] as well as for the treatment of ARDS [48] and of septic shock [49]. Interestingly, Leng et al. also showed that MSCs do not express ACE2 and TMPRSS2 receptors, suggesting that the virus should not infect this cell population. Moreover, it was shown that MSC administration to a rat model of hyperoxia-induced lung injury reduced to normal level the hyperoxia-induced overexpression of angiotensin II, angiotensin II type 1 receptor, and of angiotensin-converting enzyme [50]. Very recently, Simonson et al. [51] reported a long-term follow up of two patients with the most severe form of ARDS that in the acute phase needed ECMO support in combination with mechanical ventilation and at the same time were treated with a single systemic infusion of allogeneic MSCs. Remarkably, 5 years after the treatment both patients had fully recovered their physical and mental capacities, which is unusual for ARDS survivors. Moreover, the patient that had the most severe form of ARDS and was on ECMO support for 28 days before the MSC-infusion, had no signs of pulmonary fibrosis five years after the MSC treatment as demonstrated using CT scan with dual energy.

As mentioned above, no firm conclusion can be drawn by the study of Leng et al., but both the reported preliminary results and the scientific background should encourage further investigation on MSC treatment for COVID-19 pneumonia with well-designed clinical trials under the control of Regulatory Authorities.

3. The new therapeutic potential of extracellular vesicles

The provision of large amounts of MSCs at affordable cost is however an issue. Industrial GMP production of clinical-grade MSCs is both cumbersome and expensive [52]. To date, MSCs have been authorized by Regulatory Authorities for diseases involving a limited number of patients, such as GVHD in pediatric patients or anal fistulas resistant to conventional therapy in Crohn's disease. Clearly, the use of MSCs in a large number of patients such as the one encountered in a pandemic disease would require a significant cost reduction, also considering the relatively high dose used in the study of Leng et al.

MSCs exert most of their therapeutic effect via paracrine mechanisms [53–56], including the secretion of extracellular vesicles (EVs). EVs, including exosomes and microvesicles, are complex biological machines secreted by all cell types and ranging from 0.03 to 1 μm in size. EVs carry.

a variety of proteins, lipids and nucleic acids, with profound effects on target cells [57–59]. In the case of MSC-derived EVs, both others and we have demonstrated their immunomodulatory effects in vitro [60–64] and revealed a remarkable anti-inflammatory and pro-regenerative capacity in several animal models of disease [65,66]. More specifically, both others and we demonstrated that MSC-EV administration shows therapeutic effects in animal models of lung injury, including hyperoxia [67–69], severe bacterial pneumonia [70] and viral pneumoni [47]. Moreover, administration of MSC-EVs showed beneficial effects in ex vivo perfused human lungs injured with severe *E. coli* pneumonia [71]. Finally, MSC-EVs were effective in rehabilitating marginal donor human lungs, by increasing alveolar fluid clearance in a dose-dependent manner, decreasing lung weight gain following perfusion and ventilation, and improving both airway and hemodynamic parameter [59]. Based on these promising data, the role of MSC-EVs in mitigation and repair of lung injury in ARDS is being increasingly recognized [54,70,72,73]. Finally yet importantly, MSC-EVs can prevent the development of fibrosis following experimental lung injury, similarly to their cells of origin [34,74]. Of note, anecdotic descriptions of fibrotic sequelae with reduced lung function in patients recovered from COVID-19 pneumonia are being reported [75]. Indeed, the risk of developing idiopathic pulmonary fibrosis in increased following viral infections [76], and this long term complication was also reported in some patients following SARS infection [77]. Actually, there is growing interest in the potential use of EVs as therapeutic tools (see graphical abstract for a proposed effect of MSC/ MSC-EVs on COVID-19 mediated tissue injury). EVs are considered safer than their cells of origin, and are easier and cheaper to produce, isolate, store and administer [78], which should result in reduced cost and larger availability of the product. It should be mentioned that EVs seem to be extremely versatile products that can be engineered by various techniques, such as manipulation of their parent cells through genetic engineering, by introducing exogenous material that is subsequently incorporated into secreted EV [79–81]. A similar strategy has been used to deliver exogenous microRNA-let7c via MSC-EVs to attenuate renal fibrosis in mice with unilateral ureteral obstruction [82]. EVs can also be loaded with therapeutic molecules to improve targeting to the desired site of action [81,83–85].

So far, clinical experience is limited to a few trials on the use of EVs derived from dendritic cells in adoptive immune therapies for cancer [86] and to a single patient successfully treated with MSC-derived EVs for steroid-resistant GVHD [87]. A clinical trial on the use of MSC-EVs in premature neonates at high risk for bronchopulmonary dysplasia is currently recruiting [88].

However, there are still significant barriers in the development of MSC-EVs as therapeutic tool [89]. Some of these challenges are shared with their parent cells, including the variability in tissues of origin and culture conditions, [90,91]. Although MSCs from different sources exhibit different immune suppressive and differentiation capacity, the optimal source(s) of MSCs for immunomodulation have not been conclusively determined [92] and no comparative studies on MSC-EVs from different tissues are available. Large scale production of MSC-EVs suitable for clinical applications remains a major challenge. Refined isolation methods yielding EVs with a high degree of purity may not be applicable at industrial level [93]. Moreover, some “contaminants” co-isolating with EVs may contribute to their therapeutic efficacy [94]. The heterogeneity of EV subpopulations represents an additional challenge [95]. Indeed, so far all published studies have used a heterogeneous population of EVs, even if in some cases a partial size selection (“small” EVs <200 nm) is performed. Of note, it was shown that EV populations of different sizes secreted by dendritic cells can induced different patterns of polarization of activated T cells [96]. Quantifying EV preparations is also an unresolved problem, since accurate EV counting is hampered both by lack of standardization and by the inability of currently used devices to distinguish membrane- enclosed vesicles from non-vesicular particles [95]. The above issues highlight the need for reliable potency assays, which according to regulatory authorities should measure the biological activity of the product that mediates the therapeutic effect of a given drug [97]. Unfortunately, as stated above, the mechanism of action of MSC-EVs is complex and poorly understood, and potency assays for this therapeutic product are not validated and are still experimental [87]. It should be noticed that it took about two decades of preclinical and clinical tests before some MSC-based treatments were approved by Regulatory Authorities. Even if knowledge in the field has progressed fast, additional improvements in EV production and better understanding on their mechanisms of action will be required for EV-based treatments to become more clinically applicable. On the clinical side, little is known regarding optimal therapeutic doses and optimal route(s) of administration [89]. Regarding safety, MSC-EVs have been shown to exhibit procoagulant activity, similarly to their cells of origin [98], a property that could cause concern in patients prone to thrombotic events such as those with SARS-CoV-2 infection.

When this manuscript was under review, a first-in-man trial on 24 patients with severe COVID-19 pneumonia treated with MSC-EVs was published [99]. The study included both outpatients (cohort A) and hospitalized patients without (cohort B) or with (cohort C) artificial ventilation and a follow-up period of 14 days following MSC-EV administration. Associated treatments included hydroxychloroquine and azythromycin. The patients received a single IV dose of MSC-EVs over 60 min. Unfortunately, neither the origin of MSCs nor the EV dose were specified. The study met its primary safety endpoints, with no reported adverse events in the immediate (<24 h), intermediate (<72 h) or delayed (>72 h) period following EV infusion. Overall survival rate was 83% (4 deaths/24 patients, 2 in cohort B and 2 in cohort C), and 13% of the patients (3/24) remained critically ill, still requiring mechanical ventilation and intensive care at the end of the follow up period. Eighty percent of patients (20/24) exhibited improved PaO2/FiO2 ratio within 3 days of treatment. Again, no conclusion on efficacy can be driven from a small phase I study. Interestingly, however, inflammatory markers and absolute neutrophil count significantly decreased while total lymphocyte and CD8+ count significantly increased within 5 days following EV treatment. Moreover, D-dimer was significantly decreased, a reassuring finding in view both of the thromboembolic syndrome often associated with serious SARS-CoV-2 infection and of the above-cited potential procoagulant activity of MSC-EVs.

In conclusion, MSC-EVs should also be considered in parallel with MSCs as an experimental therapeutic tool in seriously compromised patients at the risk of life and/or for the prevention of fibrotic complications after the acute phase, following the current regulations of the phase I / II clinical trials or for compassionate use.

Authors contributions

Each author has approved the submitted version and agrees to be personally accountable for the author's own contributions and for

ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Funding

This work received no external funding.

Declaration of Competing Interest

None.

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