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REVIEW

Cellular therapies in ARDS

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Abstract

Acute respiratory distress syndrome (ARDS) is a critical illness characterized by a severe hypoxemic respiratory failure, caused by an inflammatory response which results in diffuse lung damage. Despite decades of research, the treatment of ARDS remains supportive. However, in recent years, cell-based therapies have been the subject of intensive ongoing research efforts, showing relevant therapeutic potential in preclinical ARDS models. Among all the different cells that have been identified as suitable candidates for use, mesenchymal stromal cells (MSCs) have been the most attractive candidates and have generated significant interest. MSCs are multipotent adult stem/stromal cells that can modulate the immune response and enhance repair of damaged tissue in multiple in vivo models. Their promising effect seems to be not primarily mediated by MSCs differentiation and engraftment but more by the paracrine release of different soluble mediators and cellular components such as extracellular vesicles (EVs). Preclinical experiments have provided encouraging evidence for the therapeutic potential of MSCs, leading to the launch of several phase I and II clinical trials that have shown safety of MSCs in ARDS, which became very common nowadays due to the Coronavirus disease (COVID-19) pandemic. However, some translational challenges have yet to be solved, such as the reproducibility of cell harvest, storage, reconstitution, and administration of cells/cell-products, before the therapeutic potential of stem cells therapies can be realized.

Keywords

ARDS; Cell therapy; MSCs; EVs

1. Introduction

Acute respiratory distress syndrome (ARDS) constitutes a condition of progressive acute hypoxic respiratory failure characterized by the dysfunction of alveolar-capillary barrier and by rapid onset of inflammation in the lungs, leading to diffuse alveolar damage [1]. In 2012, a panel of experts developed the Berlin definition for ARDS that comprised three severity levels (mild, moderate and severe) based on degree of hypoxemia that are associated with progressively increased mortality [2]. ARDS can be caused by a number of clinical disorders, predominantly bacterial and viral infection and/or sepsis, with other common causes including aspiration of gastric contents and major trauma, but it can be also triggered by less common events as severe acute pancreatitis, shock, drug overdose or devastating neurologic injury [3]. Recently, the Covid-19 pandemic added a new viral cause of ARDS with a huge impact on Intensive Care Units (ICUs) around the world [4, 5].

It is clear that ARDS is a complex clinical syndrome with distinct clinicopathological characteristics [6]. The reported incidence appears to vary widely, although this is likely due to differences in clinical recognition of the syndrome, and variable ICU bed availability [7]. Despite this, there is no doubt that ARDS is common in critically ill patients and represents one of the leading causes of death in intensive care units. It is important to note that, despite decades of study on the pathogenesis of ARDS, the transfer of this knowledge to discovering new therapies for ARDS has been disappointing. Currently treatment is still limited to assisted ventilation and other life support techniques such as fluid management, antimicrobial therapies and nutritional supplementation. Increases in survival rates in recent years are mainly related to improvements in these life support techniques [8–11]. Unfortunately, at present no effective pharmacological treatment is available for the treatment of ARDS. The consequence is that mortality remains unacceptably high, ranging from 35% in patients with mild ARDS to 46% in cases of severe ARDS [7].

This situation highlights the need to explore new therapeutic strategies for ARDS. In this regard, cell therapies have exhibited promising therapeutic potential in preclinical and clinical studies [12], but also they have a number of challenges to solve. The advantage of cell therapies is that their effects are exerted at different levels, from the regulation at molecular level to the structural regeneration of tissue. This offers remarkable therapeutic potential in conditions such as ARDS with a complex pathogenesis in which acting on individual pathways is often ineffective. Different cells [13] and cell products

have been used as potential therapeutic agents, including embryonic stem cells, induced pluripotent stem cells (iPSC), Endothelial progenitor cells (EnPC) or epithelial Progenitor cells (EpPC) stromal or mesenchymal stromal cells (MSC), and also products released by the cells [14], as conditioned media or extracellular vesicles [15], in particular exosomes. The ethical issues associated with embryonic stem cells as well as difficulties in obtaining and standardizing progenitor cells led most researchers to focus on adult stem cells, especially mesenchymal stem cells, which also have low immunogenicity and high capacity for expansion.

2. Mesenchymal Stromal Cells

Of all the options, the cells that have probably generated the most interest and in which there are the most studies underway are the MSCs [16, 17]. These multipotent adult stem cells can be obtained from the bone marrow, umbilical cord, or peripheral blood and can be maintained without losing their ability to differentiate into mesodermal lineages. In addition, they have low immunogenicity and possess anti-inflammatory, angiogenic, antifibrotic and immunomodulatory activities [18]. All these properties have potential to attenuate ARDS severity and/or promote recovery and tissue repair. Ideally, MSC administration may reprogram the immune response, decrease inflammation, and promote regeneration of damaged lung areas (Fig. 1). In addition, its antifibrotic potential could also prevent the appearance of foci of fibrosis that would compromise the proper exchange of gases [19]. Initially it was also considered that MSC grafting, differentiation and multiplication potential could facilitate the reconstruction of overly damaged tissue areas, but later it has been seen that this effect is very limited [20]. Finally, it has been observed that the therapeutic potential of MSC could be enhanced by stimulating them prior to administration. Exposure to hypoxia, lipopolysaccharide (LPS), different cytokine combinations and other stressful stimuli trigger survival genetic programs that strengthen the regenerative activity of MSCs [21].

2.1 Epithelial repair

Alveolar epithelial cell damage is one of the typical features of ARDS. In cases of severe ARDS, the damage can affect both type II and I alveolar cells, generating focal areas of destruction and exposing the basement membrane. All this increases lung permeability, triggers processes of fibrosis and coagulation and, obviously, dramatically affects lung function [22, 23]. Consequently, for the treatment of ARDS, it is essential to improve and accelerate the processes of epithelial regeneration to restore the functionality of the alveolar wall. Without this fundamental step, the effectiveness of supportive care, such as assisted ventilation, is relatively limited.

MSC administration had been demonstrated to enhance the regeneration of the pulmonary epithelium [24], via multiple mechanisms, including Keratinocyte Growth Factor (KGF) secretion [25], Matrix Metalloproteinase-8 (MMP-8) expression [26], β-catenin activation [27], NF-κB inhibition [28] and the induction of a reparative M2 phenotype in macrophages [29]. These effects are potentiated when MSCs are pre-treated with stimulating inflammatory agents as LPS or cytokines [21].

2.2 Alveolar fluid clearance

Fluid accumulation inside the alveoli is a consequence of the loss of endothelial integrity during ARDS and strongly contributes to lung edema and hypoxemia [30]. Several studies demonstrate that MSC treatments can enhance clearance of alveolar fluid reducing the amount of lung water contents in both *in vivo* and *ex vivo* models of lung injury [31, 32]. The mechanisms proposed includes the restoration of sodium equilibrium by acting on the sodium channels in a mechanism mediated by KGF [33] or by miRNA-34c [34]. Angiopoietin-1 appears to be also involved in the protective mechanism of MSC via stabilization of endothelial permeability [24].

2.3 Immune response modulation

MSCs have been reported to exert a number of effects in both adaptive and innate immune system [35]. The release of paracrine factors and extracellular vesicles modulate the phenotype and/or function of macrophages, neutrophils, T cells and B cells [29, 36–39]. Changes in the phenotype of these cells results in additional release of anti-inflammatory and immunosuppressive mediators, as Interleukin 10 (IL-10) or prostaglandin-E2, that reduces lung damage associated with the inflammatory response [40]. In particular, exposure of MSCs to an inflammatory microenvironment causes changes in the expression of genes that modulate the inflammatory response and the activation of different lymphocyte populations [41–43]. These effects of MSCs are of particular relevance given the role of the immune response in the pathogenesis of ARDS.

3. MSCs Engraftment

While engraftment and trans-differentiation of MSCs to replace damaged host tissue was initially considered an important potential mechanisms of action, it is now known that this is not the case. In fact, experimental data indicate that less than 1% of the administered cells will end up grafting into the damaged tissue [44, 45]. This amount is too small to justify the observed protective effects. This fact does not change the potential of MSC based therapies for controlling the progression of ARDS but open the door to additional treatments based on paracrine factors released by the MSCs. This is why, in addition to the administration of MSCs, studies have also been carried out to investigate the effect of treatment with conditioned medium, secretome and, in particular, extracellular vesicles (EVs) [33, 46–49].

4. MSC Secretome and EVs

The advantage of using elements of MSC secretome is that they avoid some of the potential problems associated with the use of whole MSCs as a therapy. This includes the difference in therapeutic efficacy between different batches of cells, the control of apoptosis and other ways of cell clearance including phagocytosis by macrophages, the potential toxicity of different agents required in the process of MSCs culture

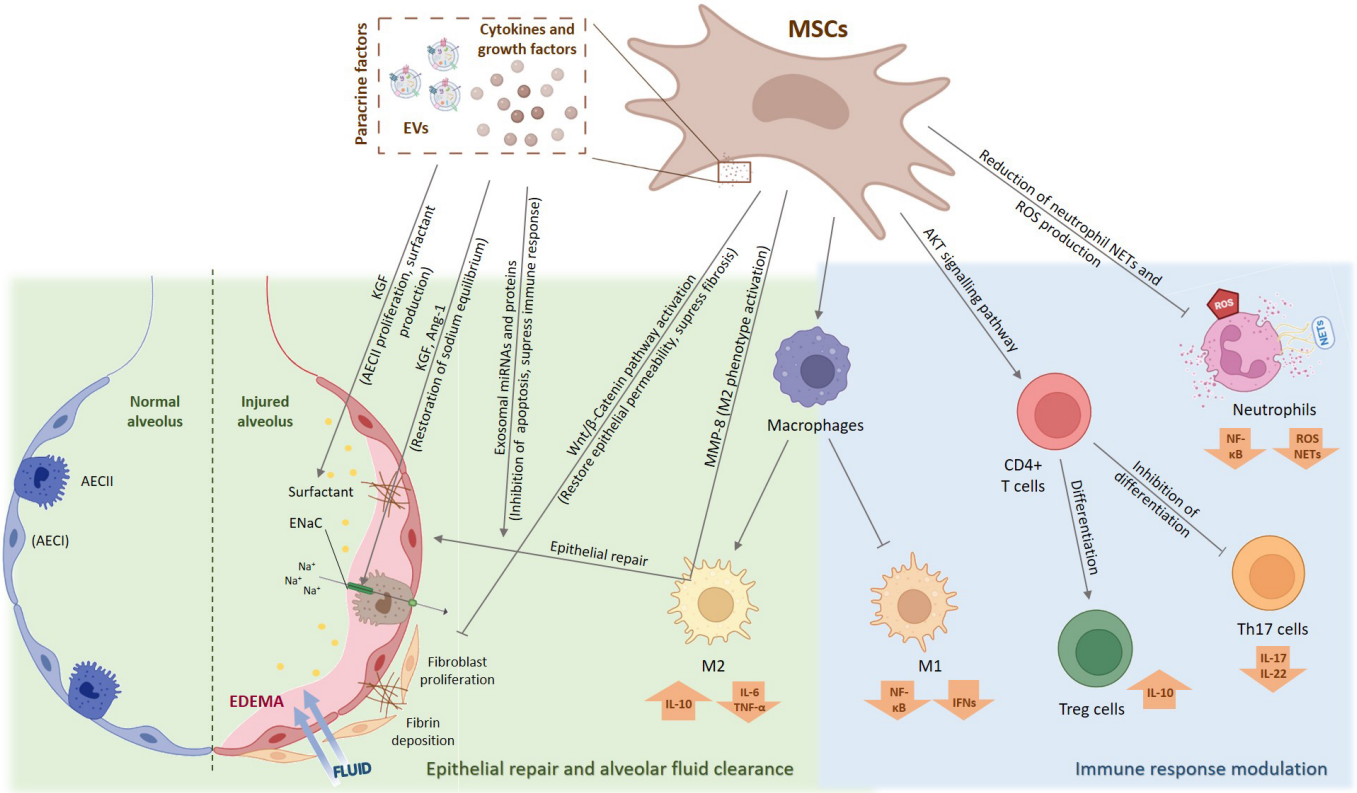

FIGURE 1. MSCs mechanisms for ARDS treatment. ROS: reactive oxygen species; NETs: neutrophil extracellular traps; Th17: T helper 17; Treg cells: regulatory T cells; M1: M1 macrophage phenotype; M2: M2 macrophage phenotype; KGF: keratinocyte growth factor; Ang-1: angiopoietin-1; AEC I: type I alveolar epithelial cells; AEC II: type II alveolar epithelial cells; ENaC: epithelial sodium channel; MMP-8: matrix metalloproteinase-8; EVs: extracellular vesicles; MSCs: mesenchymal stromal cells.

and preservation, the potential risk associated to the use of heterologous cells and the logistical problems linked to the use of cells in the clinical practice [50]. Although most of these drawbacks can be controlled or have not been found to be as significant as expected [51], the use of exosomes allows them to be avoided while maintaining much of the therapeutic potential of the cells themselves. In some ways exosomes can be seen as a delivery system for regenerative and anti-inflammatory proteins and microRNAs to damaged epithelial cells or, alternatively, activated inflammatory cells in lung.

However, some challenges have yet to be solved. For example, as with MSCs, there are also differences in the content, and therefore in the therapeutic activity, between the different batches of exosomes. Storage and reconstitution have been also challenging since exosomes could form aggregates during the process of freezing and thawing [52]. The standardization of methods for determining the therapeutic potential of exosomes in a homogeneous manner is also proving difficult to establish [53].

5. Route of Administration

5.1 MSC routes of Delivery

The optimal route of administration for MSCs remains under debate. It can be delivered either by intravenous or intratracheal routes, and for exosomes or paracrine mediators, delivered as an aerosol using a nebulizer. Intravenous use currently remains the preferred route due to its greater feasibility in clinical practice. However, this way makes it difficult to control the amount of MSCs that effectively reach the lung and are retained there [54]. Depending on the patient's condition, the administered cells may be retained in different organs. In experimental studies it has been suggested that in non-injured animals, large amounts of administered cells are trapped in the liver, spleen or kidney while in injured animals, cells accumulate in the lungs [55, 56]. This adds a degree of uncertainty to the dose of cells that will actually reach the lung, particularly where there are multiple sites of injury, *e.g.*, multiple organ injury. The effects that cells retained in other tissues and organs have on these tissues is also uncertain, which adds to the complexity of using this therapy.

The alternative is direct administration into the lung. The intratracheal route, based on the administration of fluid-suspended cells using an intratracheal tube, has been extensively used in experimental models [57], but has many disadvantages in clinical application. It is an invasive delivery approach, associated with an irregular distribution of cells and, above all, adding fluid to lungs which, given their already increased water content, might worsen the pre-existing pathology. The alternative is the use of aerosols or nebulizers, that convert the liquid into aerosols that can be easily inhaled. This approach offers higher efficiency than the alternative ways but there are differences depending on the type of

TABLE 1. Clinical trials: registered MSC-based treatment in Covid-19-associated ARDS.

Identifier (status)	Clinical trial phase	Cell source	Dosage	Route	Enrolled number	Primary outcomes
NCT04525378 (Recruiting)	1	BM-MSCs	2.5, 5, 10 × 10^7 cells/kg	I.V	20	Intrahospital mortality at day 28
NCT04456361(Active)	1	WJ-MSCs	1 × 10^8 cells/kg	I.V	9	Oxygen saturation
CHICTR2000029990 (Recruiting)	1–2	BM-MSCs	1 × 10^6 cells/kg	I.V	60	Oxygen saturation
NCT04355728 (Recruiting)	1–2	UC-MSCs	1 × 10^8 cells/kg (2 times)	I.V	24	Adverse events
NCT03042143 (Active)	1–2	UC-MSCs	1, 2, 4 × 10^8 cells/kg	I.V	75	Oxygenation index, adverse events
NCT04390139 (Recruiting)	1–2	WJ-MSCs	1 × 10^6 cells/kg	I.V	30	All-cause mortality at day 28
NCT04416139 (Recruiting)	2	UC-MSCs	1 × 10^6 cells/kg	I.V	10	PaO_2/FiO_2 ratio, heart and respiratory rate, changes in body temperature
NCT04865107 (Recruiting)	2	UC-MSCs	2, 7 × 10^8 cells/kg	I.V	54	Number of days free of oxygen mechanical ventilation at Day 28
NCT04366063 (Recruiting)	2–3	BM-MSCs	1 × 10^8 cells/kg (2 times)	I.V	80	Adverse events, blood oxygen saturation
NCT04371393 (Recruiting)	3	BM-MSCs	2 × 10^6 cells/kg (2 times)	I.V	300	All-cause mortality at day 30

BM-MSCs: bone marrow-derived mesenchymal stem cells; I.V.: intravenous; WJ-MSCs: Wharton-Jelly mesenchymal stromal cells; UC-MSCs: umbilical cord-derived mesenchymal stem cells.

nebulizer used and there is still much research that need to be done before cell product nebulization become routine in clinical practice. Specifically, the administration of intact cells by nebulizers needs to be optimized, although there is great potential for administering MSCs-derived EVs or the whole secretome this way [12].

5.2 Clinical Trials

Preclinical experiments have provided encouraging evidence for the therapeutic potential of MSCs in a variety of diseases, including ARDS [18]. This led to the launch of several phase I and II clinical trials which have demonstrated the safety and feasibility of these treatments [58–60]. Relevant issues that remain to be determined include the need to establish the appropriate dose of cells administered, and the most effective dose regimen. Lower doses could be ineffective while the administration of an excessive number of cells could result in complications associated to thromboembolic risk. It should be noted that the selected route of administration is in almost all cases intravenous. Only in a few Covid-19 trials the inhaled route of administration has been selected [61], showing that, despite its advantages, the aerosolized and nebulized routes require additional improvements before moving on to a clinical application.

5.3 COVID-19-related ARDS

The number of studies increased dramatically during 2020 due to the arrival of the Covid-19 pandemic. In just one year, a substantial number of phase I and II clinical trials focused on controlling Covid-19-associated ARDS were initiated, mostly in China [62] (Table 1). Predictably, there is a huge variation in the origin of MSCs, the number of patients recruited, or the administration protocols. There are also a number of studies administering MSCs-derived EVs [63]. Despite these differences, these studies consistently demonstrated that the administration of MSCs is, as expected, safe and. In some studies, patients have shown improvement in some clinical parameters. For instance, in a phase IIa clinical trial conducted in the USA, in which patients received a high dose level of allogeneic Bone Marrow-MSC (BM-MSC) (10 × 106 cells/kg), no predefined MSC-related haemodynamic or respiratory adverse effects were observed. Besides, infusioned patients showed an improvement in the oxygenation index and a reduced level of Angiopoietin 2 (ANG-2) in plasma, demonstrating that the MSC administration improved endothelial injury [64].

One of the factors that facilitated the application of MSCs in therapies for Covid-19-ARDS is the fact that these cells are highly resistant to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, as they do not express either angiotensin-converting enzyme 2 (ACE2) or transmembrane protease serine subtype 2 (TMPRSS2) on its surface

[65]. Importantly, this low expression is observed also in inflammatory situations [66].

6. Conclusions

The development of new and effective therapies for ARDS is a key objective of biomedical research and the therapies based on MSCs are among the approaches with the greatest potential. The potential suggested by preclinical studies has been extended in clinical studies which have shown that, in the treatment of ARDS, MSCs were safe and well tolerated. This impression has been reinforced by the large number of studies initiated in response to the Covid-19 pandemic. However, mechanistic studies will still be needed to fully understand the mechanisms of action so that these therapies can be optimized.

AUTHOR CONTRIBUTIONS

AAB, DC contributed in the design of the review, searched the literature, designed and elaborated the figure and wrote the manuscript. JGL and AA critically revised the manuscript for important intellectual content and accurate English language. All authors approved the last version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Antonio Artigas is serving as one of the Guest editors of this journal. We declare that Antonio Artigas had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to TCS.

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