

Mesenchymal Stem Cells and Inflammaging

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Rapid growth of the geriatric population has been made possible with advancements in pharmaceutical and health sciences. Hence, age-associated diseases are becoming more common. Aging encompasses deterioration of the immune system, known as immunosenescence. Dysregulation of the immune cell production, differentiation, and functioning lead to a chronic subclinical inflammatory state termed inflammaging. The hallmarks of the aging immune system are decreased naïve cells, increased memory cells, and increased serum levels of pro-inflammatory cytokines. Mesenchymal stem cell (MSC) transplantation is a promising solution to halt immunosenescence as the cells have excellent immunomodulatory functions and low immunogenicity.

Keywords: mesenchymal stem cells ; aging ; inflammaging ; frailty ; immune system

1. Introduction

Frailty can be defined as a decline in physiological reserve across organ systems; it afflicts geriatric subjects above the age of 65. Immunosenescence is the term used to refer to profound changes in the immune system related to age. Immunosenescence involves dysregulation of the immune functions at both cellular and serological levels ^[1]. As a result of degenerating immunity, older age groups are more susceptible to severe infections with poor prognoses ^[2]. The risk of contracting community-acquired pneumonia increased by 21% in older adults of 65–74 years compared to younger patients, with an even higher incidence in older adults 85 years and above ^{[3][4]}. Bacteremia and sepsis are also more prevalent among older adults. More troubling—older adults have a higher risk of morbidity and developing cognitive decline post-infection ^{[5][6]}. Interestingly, older adults have higher autoimmunity, but not autoimmune disorders. The autoimmunity in older adults is associated with the high levels of circulating T-regulatory cells (Treg) and reduced CD4/CD8 ratio. Subsequently, this predisposes the aging host to infection and cancer ^[7]. The increasing age also hampers the effects of vaccination unless the vaccine is developed to bypass this concern, i.e., conjugating it with an adjuvant. Hence, immunization for the aging population is limited ^{[1][8][9][10]}.

As a direct result of senescence, the immune system is in a constant subclinical inflammatory state known as 'inflammaging'. Inflammaging is conjectured to be a consequence of activation of innate immunity and declination of adaptive immunity without exogenous stimuli. This state is associated with the cytokine's milieu that skews towards a pro-inflammatory phenotype. The exact relationship between inflammaging and the disease state is yet to be elucidated ^[11]. However, most age-related degenerative diseases share similar inflammatory pathogenesis to which inflammaging may further exacerbate the disease process and its morbidity. The common inflammatory disease includes cardiovascular disease (myocardial infarction, hypertension, atherosclerosis), cognitive impairments (Alzheimer's disease, Parkinson's disease), rheumatoid arthritis, and metabolic diseases (type II diabetes) ^{[11][12][13]}.

The population aging is rapidly accelerating. The United Nations speculates that the number of people aged 65 years old and older will double between 2019 and 2050. In 30 years, one out of six people worldwide will be categorized in the "older adult" age bracket ^[14]. The older adult population is accompanied by a state of physiological vulnerability and declining ability to maintain homeostasis and respond to stress. This clinical expression of age-related decline is also known as frailty. Frailty and inflammation are strongly correlated where the serum levels of inflammatory markers are significantly higher in the older age group compared to the younger age group ^[15]. Frailty includes functional and structural alterations in multiple organ systems and impaired immune responses, which predispose to a plethora of disorders ^{[16][17]}. Consequently, the older adult population is a significant financial burden to the healthcare system ^[18]. Although the presentation of diseases may be incited by other risk factors, aging is a significant contributing mechanism due to the inevitable frailty development.

Currently, there are a few measures that may delay frailty onset and improve the morbidity of age-associated disease. The management of geriatric patients includes implementing calorie restriction, exercise regimes, and hormonal supplementations ^{[12][19][20]}. Diets high in n-3 polyunsaturated fatty acids and vitamin D have positive outcomes in

reducing circulating levels of inflammatory molecules, namely C-reactive protein (CRP) and interleukin (IL)-6, as well as lower the mortality of the inflammatory diseases [21][22]. Zhang et al. showed that physical exercise can delay cognitive impairment while Ng et al. reported that cognitive training can improve physical mobility and strength [23][24]. The studies also showed that a mix of interventions (exercise and/or nutrition and/or cognitive training) would have better results than just either one [25]. Frailty is a complex condition that is unique to every individual; these clinical treatments require personalization to directly intercept immunological frailty. Moreover, Zhang et al. have found that the frailty index scoring system does not necessarily reflect the conditions the subject is facing. Some elderly may still be classified as pre-frail due to the cut-off score, but were experiencing frailty in different domains, be it cognitive or functional [23]. In the systemic review composed by Apostolo et al., the current personalized approach to manage disease-associated frailty has failed to produce consistent results [25]. Hence, there is yet an exact solution to frailty.

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can be isolated from the bone marrow, adipose tissue, dental tissues, skin, salivary gland, limb buds, menstrual blood, and perinatal tissues [26][27][28][29]. MSCs can differentiate into adipocytes, osteoblasts, and chondrocytes. Although MSCs do not differentiate into immune cells, MSCs provide a supporting microenvironmental niche for hematopoietic stem cells (HSCs) to differentiate into myeloid and lymphoid cells, which are essentially the immune cells. This specialized environment plays an important role to maintain the longevity of HSCs by controlling their proliferation and apoptotic activities [30].

One of the speculated theories of declining immunity as the host ages is the MSC senescence. Subsequently, the functions and structures of MSCs, which are significant in maintaining the immune system, diminishes [31]. Although they are multipotent, mesenchymal progenitors exist in a small population, only consisting of 0.001% to 0.01% bone marrow mononuclear cells. Therefore, ex vivo expansion of MSCs and subsequent administration of optimized dosage is necessary to maintain and boost the effects of MSCs in vivo [32]. Furthermore, numerous in vivo and in vitro studies have proven that MSCs have low immunogenicity, excellent immunomodulatory function, and homing capability to regenerate damaged tissues through multipotent differentiation and paracrine secretion [11][33][34][35][36]. Despite that, the current studies are not primarily focused on aging or the restoration of the immune system. There have been extensive studies done on pathological conditions than actual aging itself. Aging and MSC were studied separately, but the similarities of the immune markers involved may come into convergence. The proliferative capacity and immunomodulatory function of MSCs could aid in the restoration of the immune cells and reduce the pro-inflammatory markers since these parameters are observed in aging as well. It is imperative to discuss the papers based on the aspects related to immunosenescence and inflammaging.

2. Mesenchymal Stem Cell Therapy to Reverse Aging Effects on the Immune System

According to The International Society for Cellular Therapy (ISCT) 2006, there are three minimal criteria for defining MSCs: "(i) MSC must be plastic-adherent when maintained in standard culture conditions. (ii) $\geq 95\%$ of the MSC population must express CD105, CD73 and CD90, and $\leq 2\%$ of the MSC population express of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA Class II surface molecules. (iii) MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro." [37].

MSCs lack MHC class II, which translates to low immunogenicity and allows both allogeneic and autologous MSC transplantation. Standardization and commercialization of allogeneic MSCs would be readily available at a reduced cost due to the lack of need to create a personalized cell therapy from the autologous source and the potential of expanding the cells in large-scale [38]. To date, MSCs have been used in clinical trials for osteoarthritis, spinal cord injury, diabetes mellitus, autoimmune disease (Crohn's disease, multiple sclerosis, systemic lupus erythematosus, and systemic sclerosis), and systemic diseases such as graft-versus-host diseases and sepsis [30][39][40][41]. Additionally, MSCs also have been used to treat neonatal diseases, i.e., intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis [42].

2.1. Mechanism of MSCs Action on Immune System

Some evidences showed that the ameliorating effects of MSCs on the immune system are not due to direct engraftment and cell replacement, but rather paracrine manner and direct cell-to-cell contact [26][43]. MSCs secrete soluble paracrine factors including TGF- β , prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor (HGF), nitric oxide (NO), interferon-gamma (IFN- γ), IL-2, and IL-10, which produce an immunomodulatory effect. They also express FasL and PD-L1 for contact-dependent inhibition to induce T cell apoptosis [20][26]. MSCs express IL-10, which is an anti-inflammatory and immunoregulatory cytokine. Furthermore, they produce IL-6 and IL-8, which are known to be

associated with MSC tissue repair potential [44]. Subsequently, MSCs control the inflammatory state as evidence of the reduced expression of proinflammatory cytokines such as TNF- α , IL-1 β , IL-6, and CRP [45]. Then, the STAT6 pathway is activated by IL-4, which then stimulates the MSCs to secrete TGF- β . This promotes the development of CD8+ T cells and Treg cells while suppressing the Th1 [46][47][48][49][50][51]. Moreover, MSC-secreted TGF- β has a role in macrophage polarization towards the M2 phenotype. These M2 macrophages stimulate the expression of IL-10, which alleviates inflammation. The macrophage phagocytic ability is also enhanced by TGF- β through Akt-FoxO1 pathway [36][52]. **Table 1** shows the list of potential markers involved in inflammaging, which may be useful to determine the efficacy of MSC therapy.

Table 1. The potential ‘inflammaging markers’ related to inflammatory diseases and aging. These markers may be used to validate the efficacy of MSC treatment. (‘↓’ = decrease; ‘↑’ = increase; ‘-’ = no change).

Potential ‘Inflammaging Markers’	Status in Inflammaging	References
IGF-1	↓	[17][53][54]
CD4+ T cells	↓	[19][55][56][57]
CD28+ T cells	↓	[11][58][59]
CD19+ B cells	↓	[60][61]
IL-10	↓/-	[2][35][62][63]
TGF- β	↓	[33][54][64][65]
IL-2	-	[66]
IFN- γ	↑	[66][67]
TNF- α	↑	[66][68][69]
IL-6	↑	[15][36][54][70][71]
WBC	↑	[17]
CD8+ T cells	↑	[19][55][56][57][72][58][73]
CD56+ NK cells	↑	[74][75][76][72][77][78]
IL-1 β	↑/-	[36][69]
IL-15	↑	[69]
IL-18	↑	[69]
CD68	↑	[68]
MCP-1	↑	[68]
IL-17	↑	[34]
IL-8 (CXCL8)	↑	[11][74]
CXCL10	↑	[79][80]
CCL2	↑	[80][81]

The study of MSC effects on the immune system is largely focused on T cells rather than B cells, as its effects are more prominent in the former. Rosado et al. suggested that the prerequisite of MSCs to exert effects on B cells is a functional T cell population. Cell-to-cell contact between MSCs and T cells inhibit the proliferation and antibody production of B cells, which in turn, may aid in the management of autoimmune conditions and graft rejections [82]. Moreover, Lee et al. noted that the xenogeneic transplantation of human MSCs (hMSCs) in SLE mice models only inhibited the T cells but not the B cells. However, hMSCs that are primed with IFN- γ have increased CXCL10 and IDO expression, which effectively attracts B cells for contact inhibition [45].

In a study by Shin et al., they found that adipose tissue-derived MSCs (AT-MSCs) treatment successfully prevented the ill-effects of sepsis by mitigating the systemic inflammation and multi-organ damage. They observed the drop in pro-inflammatory markers namely IL-6 and TNF- α and reduced damage in kidney, lungs, and liver [35]. During the treatment with MSCs, there is an increased expression in inflammatory cytokines including IL-1 α , IL-1 β , and IL-6. It is important to

note that this increase is not associated with the severity of inflammation, but it is to prime the MSCs for a sustained immunosuppression [44].

The mechanism of action of MSCs on the immune system is not constitutively inhibitory, but is acquired after exposure to the inflammatory environment with IFN- γ . IFN- γ is one of the cytokines released by T cytotoxic cells during inflammation. Therefore, in Th17 centered inflammatory response, MSC treatment would require the addition of Treg to successfully regulate the inflammation [45][83]. Lim et al. found that combination of MSCs and Treg has shown promising results in IFN- γ knockout mice with reduced inflammation and IL-7 production [83]. Additionally, Fan et al. divulged that the IFN- γ stimulation could also induce a higher expression of galectin-9 (Gal-9) in the umbilical cord-derived MSCs (UC-MSCs) through the signal transducer and activator of transcription (STAT) and c-Jun N-terminal kinase (JNK) signaling pathways. Gal-9 is one of the constitutively expressed immunomodulatory components of MSCs, which acts by suppressing CD4+ T helper cells (Th1 and Th17) and CD8+ T cytotoxic cells and regulates the suppressive activity of Treg. Even so, when Gal-9 production is inhibited, MSCs could still exert its immunosuppressive function through paracrine manner [83]. Roux et al. also observed a significant reduction in the population of both CD4+ and CD8+ T lymphocytes post-treatment with human iPSC-derived MSCs. The immunosuppression on T cells by MSCs was further substantiated with the increased expression of LAG3 and CTLA4, and cytokines including IL-10, TGF- β , and LIF [44]. Li et al. observed a significant increase in CXCR3+ Tregs in the lungs and lymphoid tissues post-MSC infusion. MSCs also increased the production of CXCL9 and CXCL10 produced by lung phagocytes which mediate the recruitment of Tregs [34].

Anderson et al.'s experiment on mice has also shown that murine AT-MSCs reduced the severity of experimental autoimmune encephalomyelitis (EAE) in mice. It is achievable due to the inhibition of the autoimmune T cell response with no increase in foxp3 Tregs. Moreover, MSCs inhibited the maturation of DCs in vitro via COX-1/2 activity and also lowered the amount of activated DCs in the lymph nodes of EAE mice [84]. DCs from the older adults have increased reactivity to self-antigen, hence their constantly activated state produces proinflammatory cytokines and stimulates the proliferation of T cells [85]. Through the inhibition of DC maturation, the inflammatory state of EAE was managed. Moreover, a study by Liu et al. transplanting human UC-MSCs into mice model showed significant improvements in the EAE pathogenesis in which the transplantation stimulated spinal cord remyelination and induced a shift of Th1 to Th2 [86]. Another study by Donders et al. using Wharton's jelly-derived MSCs (WJ-MSCs) also found reduction in signs and severity of EAE in rats. Nevertheless, they found that the ameliorating effects of MSCs were only temporary, and the transplanted rats will clinically deteriorate again. Although repeated dosages of MSCs were administered, the disease pathogenesis of EAE did not improve [87]. This contradicting data calls for more research data on the extent of MSC regenerative capability in clinical use. [Table 2](#) shows the effect of MSC on the immune system in human clinical studies.

Table 2. A summary of clinical studies of MSC effects on the immune system from 2017–2021.

References	Human Subjects	MSC and Dosage	Results (Related to Immune Cells and Inflammatory Markers)	Additional Notes
Golpanian et al. (2017) [88]	An average age of 78.4 \pm 4.7 years and Clinical Frailty Score of 4–6	Group 1 = 20 \times 10 ⁶ allo-hBM-MSCs, IV injection Group 2 = 100 \times 10 ⁶ allo-hBM-MSCs, IV injection Group 3 = 200 \times 10 ⁶ allo-hBM-MSCs, IV injection	Group 2 and Group 3 showed significant decrease in TNF- α , whereas Group 1 showed moderate reduction. No significant changes were seen in CRP, IL-6, fibrinogen, D-dimer, and white blood cell counts.	100 \times 10 ⁶ cells is the optimal dose level. No additional benefit or loss of effect when 200 \times 10 ⁶ cell dose was used.

References	Human Subjects	MSC and Dosage	Results (Related to Immune Cells and Inflammatory Markers)	Additional Notes
Tompkins et al. (2017) ^[89]	Age ≥60 and ≤95 years with Clinical Frailty Score of 4–7	Group 1 = 100 × 10 ⁶ allo-hBM-MSCs, IV injection	Decreased serum TNF-α levels in Group 1.	No therapy-related side effects occurred.
			Decreased B cell intracellular TNF-α in both Group 1 and Group 2.	
			Decreased early CD 69 and late activated CD25 T cells in both Group 1 and Group 2.	
			Decreased CD8 in Group 2.	
Chin et al. (2020) ^[90]	Healthy, non-frail subjects with mean age of 55 ± 13 years	Group 2 = 200 × 10 ⁶ allo-hBM-MSCs, IV injection	No changes in CD4 in both Group 1 and Group 2.	No therapy-related side effects occurred.
			CD4/CD8 ratio increased in Group 2.	
			No significant changes noted in IL-6, CRP, D-dimer, CBC, and fibrinogen in both Group 1 and Group 2.	
			In Group 1, no significant changes were noted in the serum levels of IL-10, IL-1RA, IL-6, PGE2, and TNF-α.	
Hashemian et al. (2021) ^[91]	11 patients diagnosed with COVID-19-induced ARDS who were admitted to the intensive care unit, age range was 42–66 years old	Group 1: 65 × 10 ⁶ allo-hUC-MSCs, IV injection	In Group 2, the serum IL-1RA level was significantly increased for at least 6 months post-infusion.	The immunoglobulin E (IgE) level remained low within the normal range which indicated that there were no hypersensitivity reaction post-infusion.
			The serum IL-6 level throughout the 6 months monitoring period was higher in Group 2 than in Group 1.	
			The serum TNF-α level was significantly lower at day 2 in Group 2 than Group 1.	
			Both Group 1 and Group 2 observed a significant increase in C-reactive protein at day 2 post-infusion, which then dropped continuously over 6 months.	
Hashemian et al. (2021) ^[91]	11 patients diagnosed with COVID-19-induced ARDS who were admitted to the intensive care unit, age range was 42–66 years old	Group 2: 130 × 10 ⁶ allo-hUC-MSCs, IV injection	The albumin/globulin ratio was higher in Group 2 than in Group 1 at 6 months.	No significant changes in total white cell count or its subfractions post-infusion.
			No significant changes in the lung function tests (FEV1 and FEV1/FVC levels) post-infusion.	
			No significant changes in the growth factors (VEGF, TGF-β, and HGF) level post-infusion.	
			All six survivors were well with no complaints of dyspnea on day 60 post-infusion.	
Hashemian et al. (2021) ^[91]	11 patients diagnosed with COVID-19-induced ARDS who were admitted to the intensive care unit, age range was 42–66 years old	3 × IV injections (200 × 10 ⁶ cells) every other day for a total of 600 × 10 ⁶ hUC-MSCs (6 cases) or PL-MSCs (5 cases).	Significant reductions in serum levels of TNF-α, IL-8 and CRP were seen in all six survivors.	Radiological parameters of the lung CT scans showed great signs of recovery.
			IL-6 levels decreased in five patients.	
			IFN-γ levels decreased in four patients.	
			IL-4 and IL-10 levels increased in four cases, but the differences were not statistically significant.	
Hashemian et al. (2021) ^[91]	11 patients diagnosed with COVID-19-induced ARDS who were admitted to the intensive care unit, age range was 42–66 years old	3 × IV injections (200 × 10 ⁶ cells) every other day for a total of 600 × 10 ⁶ hUC-MSCs (6 cases) or PL-MSCs (5 cases).	IL-6 levels decreased in five patients.	Four patients who had signs of multi-organ failure or sepsis died in average 10 days after the first MSC infusion.
			IFN-γ levels decreased in four patients.	
			IL-4 and IL-10 levels increased in four cases, but the differences were not statistically significant.	
			IL-6 levels decreased in five patients.	

FEV1—forced expiratory volume in one second, FVC—forced vital capacity, COVID-19—Coronavirus disease 2019, ARDS—Acute Respiratory Distress Syndrome, PL-MSCs—placental MSCs, CT—computed tomography.

All the above findings also fortify the concept that MSCs might not be a permanent solution to restore a healthy cell population. MSCs may have been seen as effective in past studies due to their paracrine effects but not cell replacement. This may explain the relatively fast drop in the inflammatory state when MSC therapy commences. Fan et al. noted that transplanted MSCs do not retain its population over time. Yet, the expression of Gal-9 continues to increase post-therapy, suggesting that a certain degree of immunosuppression can persist [83]. Li et al. postulated that the therapeutic protection of MSCs lasts more than 14 days whereas Donders et al. only observed the therapeutic effects for a week [34][87]. Additionally, Chin et al. continued to observe an increased level of anti-inflammatory cytokine IL-1RA in subjects from baseline up until 6 months post-MSC transfusion. However, note that the subjects were healthy and middle-aged which may contribute to the relatively long effectiveness of the treatment [90]. A possible solution to the limitation of MSC therapy is to find ways to sustain the survival of transplanted MSCs and increase the cell homing to the target sites to prolong the therapeutic effects.

2.2. Translational Application of MSCs

Bone marrow-derived MSCs (BM-MSCs) were the default source of MSCs. Nonetheless, the highly invasive procurement procedure, low cell yield (0.001–0.01% of bone marrow mononuclear cells) and multipotency that diminishes with donor age encouraged studies to be conducted on other sources of MSCs. Peripheral blood-derived MSCs (PB-MSCs) mobilized by the G-CSF are identical to BM-MSCs, but are more easily procured. However, both BM-MSCs and PB-MSCs have longer doubling time compared to MSCs from other sources [92]. PB-MSCs have been reported to possess the highest immunosuppressive capability among PB-MSCs, UC-MSCs, AT-MSCs and BM-MSCs [26]. However, contradictory results have been reported in others studies [40]. AT-MSCs can be obtained easily as surgical waste and lipo-aspirates at a high concentration up to 3% whereas UC-MSCs has the highest degree of multipotency than BM-MSCs and AT-MSCs [26].

To date, there is no definite evidence that suggests the best source of MSCs for clinical use. The sources are classified into adult and neonatal tissue derived, which have their advantages and disadvantages depending on its use. The heterogeneity among MSCs from different sources and the differences in cell treatment protocol make it impossible for direct comparison. Naturally, MSCs derived from perinatal tissues have stronger immunomodulatory properties compared to the aged source. UC-MSCs and WJ-MSCs are non-senescent, highly proliferative and with potent differentiation potential [26][93]. In application regarding immunosenescence, declining cellular functions and chronic sub-clinical inflammation are of concern in an aging person. Hence, allogenic UC-MSCs and WJ-MSCs seem more suited to be used in this subject matter. Nevertheless, the plasticity of UC-MSCs relies on the metabolic condition of the mother during pregnancy. UC-MSCs collected from gestational diabetes mellitus mothers displayed earlier cellular senescence and decreased cell growth [94]. Therefore, UC-MSCs should be sourced from healthy mothers to ensure a high biological quality of stem cells is obtained for clinical use. Abolhasani et al. also reported that the gestational age and in vitro expansion can influence the immunomodulatory properties of UC-MSCs [95].

Next, the optimal method of administering MSCs has yet to be determined. The MSCs can be introduced into the body locally or systematically. Local administration of MSCs targeted to the injury site and produced rapid results. However, there is a risk of cell death and bleeding at the site of application [96]. The systemic administration including intraperitoneal (IP), intravascular (IV), subcutaneous (SC), and intramuscular (IM) delivery have varying cell fate and therapeutic efficacy. Castelo-Branco et al. found that the IP method produced better homing and inflammation suppression than IV [33]. On the contrary, Gonçalves et al. contended that the IV administration of MSCs was more effective than IP method in the treatment of colitis as IV administration managed to stimulate a higher level of immunosuppression [97]. However, MSCs administered through the IV route tend to become entrapped in the lungs, with only 10% of the transplanted cells accumulate at the site of damage [34][96][98]. Roux et al. stated the preference of IP over IV as to avoid the risk of pulmonary embolization which may lead to the surge of an anti-inflammatory protein known as TSG6 [44]. IM injection is another possible route of MSC delivery which is advocated by Braid et al. for producing the longest cell retention time in the host body when compared to IV, IP, and SC, which was more than 100 days. Both IM and SC implantation sites also retained most of the MSCs, which shows a potential for controlled MSC dosage [98]. Furthermore, IM is less invasive than IV. Nonetheless, the research data on effects of IM administration of MSCs on the immune system is inadequate compared to the more established IV method.

Ueda et al. injected MSCs contained in collagen scaffold to the dorsum part of mice which considerably prolonged the retention of MSCs at the transplantation site for at least 2 weeks. The collagen scaffold acted as a reservoir for the exogenous MSCs and preserved the self-renewal, multipotency, and homing functions of MSCs. Furthermore, the formation of aggregates, which commonly occurs with IV administration can be avoided [96].

Ebrahim et al. compared the efficacy of standard treatment using antileukotriene drug (Montelukast) versus MSCs in the treatment of allergic rhinitis. MSCs exert immunomodulatory effects on the adaptive immunity by shifting the TH1/TH2 balance through T cell suppression and production of Treg. Rats treated with MSCs showed significant improvement in the allergic and inflammatory response and less damage to the nasal epithelium, which is superior compared the rats treated with antileukotriene drug [99]. El-Gendy et al. compared AT-MSCs with etanercept in terms of preventive and therapeutic efficacy in rheumatoid arthritis. Etanercept is an anti-inflammatory drug commonly prescribed for rheumatoid arthritis and other inflammatory conditions. The results of rats treated with both groups are comparable in terms of suppression of clinical signs, less severity of joint deformity, and modulation of immune responses. The etanercept group showed the lowest TNF- α level but the AT-MSCs group had significantly higher levels of Treg cells and IL-10 [100]. These results showed the promising prospect of MSCs to substitute the current prescription in improving inflammatory conditions.

Golpanian et al. and Tompkins et al. conducted the phase I and phase II clinical trials in aged patients by administering different doses of allogeneic MSCs through the IV route. The studies monitor the adverse effects as well as the patients' physical performances and TNF- α level for six months. Both studies demonstrated that 100 million allogeneic MSCs is the most optimum dosage in frail patients which produced significant improvements in both physical and inflammaging condition, noting reduced circulating TNF- α level. Safety of IV administration of allogeneic MSCs is also demonstrated when treatment emergent-serious adverse events are absent in the treated patients [89][88].

Zheng et al. plotted an extensive immune cell landscape in aging and COVID-19. In general, COVID-19 patients who are elderly have shown immune cell polarization and upregulation of inflammatory genes. There is a decrease in TCR and BCR diversity and an increase in clonality of effector, cytotoxic, and exhausted T cells. The NK cells and B cells have decreased antigen-presenting ability due to the upregulated inflammaging. Besides, the phenotype of mononuclear cells involved are inflammatory and persist at a higher ratio than the T cells. To add insult to the injury, aging also increases the expression of the COVID-19 susceptibility genes. Unsurprisingly, the elderly patients have lowered threshold of triggering cytokine storms and lymphopenia, which result in higher mortality from the infection [74]. MSC has been actively studied for COVID-19 treatment. Along with the urgency of the COVID-19 pandemic, numerous clinical trials have been proposed urgently to suggest MSC as an endogenous biological intervention to reduce the severity of the disease. At the time of writing, there are 53 clinical trials registered on the <https://clinicaltrials.gov/> (accessed on 20 May 2021). In February 2020, a critically ill COVID-19 patient with severe pneumonia, ARDS and multi-organ injury was treated with hUCMSCs adoptive transfer therapy. Shortly after the treatment, their haematologic parameters, immune cell count, blood chemistry and clinical presentation of pneumonia vastly improved in a short time. After 8 days, the patient was discharged from the intensive care unit (ICU). Even though this study had only documented the recovery of one patient, it is remarkable that MSC may hold such premises [101]. Haberle et al. had also seen great improvement in their MSC treatment group. At the start of the study, the selected MSC treatment group had more severe COVID-19 ARDS than the control group, as indicated by the higher Murray score for lung injury. Finally, the MSC group showed significantly better pulmonary function and reduced inflammatory cells at discharge when compared to the control group [102]. Hashemian et al. also reported a significant decrease in the major inflammatory biomarkers (CRP, IL-6, IL-8, and TNF- α) and a significant improvement in the opacities of the lung CT scans after the MSC infusions [91].

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