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Allogeneic Mesenchymal Stem Cells as a Treatment for Aging Frailty

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Additional information is available at the end of the chapter

Abstract

As life expectancy is projected to increase in the ensuing decades, individuals of older age continue to exceed the previous generation's lifespan. Advancing age is associated with a reduction in physical and mental functional capacity, and chronic inflammation is a major factor contributing to this decline. A heightened inflammatory state can lead to exhaustion, weakness, weight loss, slow gate speed, and an overall decrease in activity level. These phenotypes define the onset of the disease process known as frailty. Frailty is a growing epidemic, which severely undermines a person's ability to deal with outside stressors, and increases their rate of hospitalization, institutionalization, and mortality. Current interventions focus on preventative care by improving exercise capacity, strength, nutritional supplementation, diet, and mobility. However, a biological cure has heretofore remained elusive. Here, we introduce the novel therapeutic principle that mesenchymal stem cell (MSC) therapy may represent a safe, practical, and efficacious both the treatment and prevention of frailty in individuals of advancing age. To date, a phase I safety trial reveals an excellent safety profile and suggests that mesenchymal stem cells can ameliorate signs and symptoms of frailty. These early studies lay the groundwork for future large-scale clinical trials of this exciting and novel therapeutic concept that has the potential to expand health span in the aging population.

Keywords: mesenchymal stem cells, immunomodulation, frailty, tumor necrosis factor-alpha, regenerative medicine

1. Introduction

Projected life expectancy continues to grow worldwide owing to the advancement of new treatments and technologies for leading causes of death such as cardiovascular disease and cancer [1]. Meanwhile, frailty is gaining relevance as a significant clinical syndrome that is associated with increased risk of falls, depression, and disability, leading to higher mortality [2]. Frailty is defined by an age-related decline in reserve and function leading to a reduced ability to cope with acute or external stressors [3] and is characterized by easy tiring, decreased libido, mood disturbance, accelerated osteoporosis, diminished muscle strength, and susceptibility to disease. However, the pathophysiology underlying this syndrome is complex and not clearly understood [4].

Inflammation is a pathophysiologic change that is closely linked with frailty [5]. Aging is associated with immunosenescence or the dysregulation of the innate immune system, resulting in an increase of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β, further leading to a chronic low-grade inflammatory state [6]. Chronic inflammatory response inhibits the repair, turnover, and adaptation of many tissues, including skeletal muscle [6]. Regeneration of skeletal muscle involves the cross-talk of muscle cells with immune cells, where the pro-inflammatory phenotype of immune cells promotes migration of satellite cells to the injured area, activates satellite cells, and matures newly formed muscle fibers [7]. Muscular degeneration caused by the altered pro-inflammatory state in frail patients is referred to as sarcopenia, another critical physiologic component of frailty.

Aging also produces physiologic changes in the brain, contributing to the development of frailty. Neurons with high metabolic demands, such as the hippocampal pyramidal neurons, are an important mediator in the pathophysiology of cognitive decline and are a key component of the stress response [3]. Concomitant with changes in the immune system, microglial cells, which are the resident immune cells of the central nervous system, are also structurally and functionally altered with aging and undergo senescence, likely causing damage and neuronal death [8]. Accumulating evidence supports an association between frailty, cognitive impairment, and dementia [9, 10].

The brain and endocrine system are intrinsically linked through the hypothalamo-pituitary axis, controlling metabolism via a series of homeostatic hormones. Four major circulating hormones are affected by aging: first, the decrease of insulin-like growth factor 1 (IGF-1) is associated with lower strength and decreased mobility [11]. Second, decreased sex hormone (estradiol and testosterone) increases the release of luteinizing hormone and follicle-stimulating hormone [12]. Third, decreased activity of the adrenocortical cells produces the major sex steroid precursor dehydroepiandrosterone sulfate (DHEA-S), which is associated with a gradual rise in cortisol. DHEA-S directly maintains muscle mass and indirectly prevents the inflammatory pathways that contribute to muscle decline [13, 14]. Finally, the reduced level of 25(OH) vitamin D is associated with the development of osteoporosis [15].

Due to the complexity of multiple inter-related physiological systems that contribute to frailty, there is no gold standard for diagnosing the syndrome. There are currently two models for evaluating frailty: the phenotype model and the cumulative deficit model that forms the basis

Frailty phenotypes	MSC response	Postulated mechanism of action
Weight loss	Maintains total caloric expenditure	↓ Inflammation which suppresses the onset of sarcopenia
Exhaustion	↑ Pulmonary function, ↓ chronic inflammation	↑ Endothelial function, ↓ markers of inflammation
Weakness	↑ Physical performance	↑ Mitochondrial transfer, ↑endogenous stem cell function
Slow gate speed	↑ 6-minute walk distance	↑ Endothelial function, ↑ cardiac performance, ↑skeletal muscle performance
Decreased activity level	↓ Chronic inflammation, ↑ quality of life	↓ TNF-α, ↓ IL-1β, ↑ IL-10

Notes: MSCs home to sites of injury and to enhance repair of damaged tissue (heart, joints, muscle, and blood vessels) and exert their regenerative effects via paracrine signaling, mitochondrial transfer, direct cellular contact, and exosome excretion.

Table 1. The effect of MSCs on the phenotypes of frailty.

of the Canadian Study of Health and Aging (CSHA) frailty index [16]. The phenotype model defines frailty as meeting three or more of five criteria: weight loss (>5% of body weight in the previous year), exhaustion (positive response to questions regarding effort required for activity), weakness (decreased grip strength), slow gait speed (>6–7 seconds for walking 15 feet), decreased physical activity, or low energy expenditure (kcal spent per week: males expending <383 kcal, females expending <270 kcal) (**Table 1**) [17]. This model is simple and easy to use; however, it fails to include factors such as cognitive impairment and highly prevalent conditions associated with functional decline and disability [3].

The cumulative deficit model is based on the accumulation of illnesses, functional and cognitive declines, and social situations that are added together to calculate frailty [16]. This model utilizes 20 or more medically and functionally related questions and 92 baseline variables. The deficit model fashioned the origin of the CSHA frailty index [3]. The frailty index measures a number of age-associated health deficits (signs, symptoms, and laboratory values) [18], which is calculated by dividing each 'deficit' by the total number tested [3]. The higher the number of deficits, the higher the score, with '1' being the maximum index, which indicates a poorer prognosis. Specifically, Rockwood and Mitnitski noted that an index >0.7 indicates a high risk of mortality [19]. In an effort to simplify this index, the same authors proposed the CSHA clinical frailty score, a 7-point rapid screening tool that was highly correlated with the frailty index; with 7 being the maximum score, indicating "severe frailty" [20]. The clinical frailty score is currently widely used in clinical practice [21].

2. Epidemiology

Universal characteristics that are associated with an increased prevalence of frailty include: chronological age, female sex, racial, and ethnic minority, those in supportive residential settings, and lower income [22]. The prevalence among community-dwelling people over 65 years of age

ranges from 4 to 17% in studies with varying geographic features [23, 24]. There are similar trends in Japan, the country with the highest life expectancy in the world. The reason for longevity in Japan is multifactorial. The universal health insurance system, the high population density with close access to hospitals, fish-based diets, awareness of healthy aging in the general public, and lower prevalence of lung cancer despite a higher population of smokers are some contributors [25]. Interestingly, a meta-analyses of frail Japanese patients using the phenotype model demonstrated that the age-stratified-weighted prevalence of frailty was lower in younger age groups (1.9% in 65–69 years, 3.8% in 70–74 years), the same in the 75–79-year age groups (10.0%), but higher in older age groups (20.4% in 80–84 years, 35.1% in ≥85 years) when compared to Western countries [25]. One explanation is that non-Japanese frail older individuals die younger, while Japanese frail older individuals survive longer, leading to a higher prevalence of frailty in their 80s.

3. Intervention and preventive care

While there is no cure for frailty, exercise is considered the most effective intervention to improve quality of life and functionality in frail adults. Improvements in muscle strength and mobility [26, 27] are among the most successful changes reported. Several studies have demonstrated an improvement in muscle strength in older persons with resistance exercise [28–30]. A longitudinal study of aging showed that physical activity is associated with a slower progression in functional limitations in older adults over a follow-up period of 6 months [31]. A randomized, placebo-controlled trial compared resistance exercise training, multinutrient supplementation, both interventions, and neither intervention (control group) in frail adults over a period of 10 weeks. The study suggested that high-intensity resistance exercise training improved muscle strength, gait velocity, and stair-climbing power. However, nutritional supplementation did not reduce muscle weakness or physical frailty [28]. Similarly, the LIFE-P (lifestyle interventions and independence for Elders pilot) exploratory study demonstrated that regular physical activity reduces frailty prevalence at a 12-month follow-up time point [32].

Another approach to delay frailty is the use of nutritional supplements, which increase protein and caloric daily intake. Administration of leucine-enriched essential amino acids can increase muscle synthesis through stimulation of the mechanistic target of rapamycin (mTOR) signaling pathway [33]. The PROT-AGE study [34] reviewed the dietary protein intake in older healthy people (>65 years). They found that the optimal protein intake in older persons with sarcopenia is 1.0–1.2 g/kg body weight per day, and higher protein intake >1.2 g/kg body weight per day for those who are exercising. The PROVIDE trial [35] assessed protein supplements enriched in leucine and vitamin D in sarcopenic older adults at high risk for disability. The study demonstrated that the group receiving high quantity protein supplements gained significantly more muscle mass and improved their chair stand ability relative to the control group.

The randomized Controlled Trial of Community-based Nutritional, Physical and Cognitive Training Intervention Programmes for At Risk Frail Elderly (FIT) compared the effects of 6-month interventions with either nutritional supplementation, cognitive training, physical activity, the combination treatments, or no intervention (control) in prefrail and frail

adults [36]. Frailty score and status were measured at 3, 6 and 12 months. While these parameters were reduced in all groups, including the controls, the other four groups were significantly improved compared to the controls, at all three time points. However, none of the interventions improved the secondary endpoints, which included: hospitalizations, falls, and performance of activities of daily living [36]. Recent studies suggest that vitamin D plays a role in the pathogenesis and management of frailty [37, 38]. One such study demonstrated that daily doses of ≥800 IU of vitamin D has beneficial effects on balance and muscle strength [39]; while another reported an improvement in balance with a single large dose of vitamin D [40]. While an analysis of 53 trials showed that vitamin D supplementation alone does not prevent fractures in older adults [41], supplementation of vitamin D in combination with calcium can prevent disabling hip fractures among others [41].

While diet and exercise have been thoroughly evaluated, hormone therapy has also been tested. Testosterone undecanoate plus a high-calorie supplement (2108–2416 kJ/day) was compared with a control group (placebo plus a low-calorie supplement (142–191 kJ/day)) in a randomized controlled trial. The results showed that there were no significant differences in frailty scores at either 6- or 12-month follow-up between the groups [42]. While testosterone treatment improves muscle strength, it also increases incidence of adverse cardiovascular events [43]. Estrogen in combination with progestin therapy in postmenopausal women increases the risk of incident breast cancer after 5.6- or 7.1-years of follow-up [44, 45]. Likewise, the benefits of dehydroepiandrosterone sulfate (DHEA-S) supplementation in frail patients have not been demonstrated. Older subjects who received DHEA for 2 years exhibited no beneficial effects on body composition, physical performance, or quality of life [46]. Similarly, 1 year of treatment with insulin-like growth factor 1 (IGF-1) did not alter bone mineral density, fat mass, muscle strength, blood lipid parameters, and measures of postprandial glucose disposal in postmenopausal women [47].

Frailty is increasingly recognized as a clinical state of vulnerability with increased risk of adverse health outcomes. The pathogenesis that underlies this syndrome is multifactorial and elusive, and there is not yet a gold standard for diagnosis or treatment. Exercise and nutritional supplementations are currently the key interventions for frailty. Although helpful, none of them have been proven to treat the disease process. Therefore, an alternative approach to treating frail adults needs to be investigated. Here, we focus on a novel intervention, allogeneic mesenchymal stem cells (allo-MSCs) as a potential therapy for the treatment of frailty. While the mechanism is as yet unclear, we propose that the beneficial effects of MSCs for frailty are due, in large part, to a combination of their immunomodulatory, antifibrotic, and pro-regenerative effects.

4. Regenerative medicine

Frailty is a multifactorial condition triggered by genetic and environmental factors. As previously described, there is a direct association between frailty and the loss of proliferative homeostasis, neurodegeneration, DNA/mitochondrial mutations, free radical accumulation, a rise in pro-inflammatory markers, and increased immunosenescence. Stem cell depletion is

a key mechanism postulated to contribute to frailty and its epigenetic dysregulation [48–50]. Thus, the repletion of stem cells is an appealing approach to treat this multifactorial dysregulation and MSCs are a particularly attractive candidate. MSCs are a multipotent, self-renewing somatic progenitor cell type that exhibits immunoprivileged properties [51–53] and are relatively easy to collect (bone marrow harvest), isolate, and expand [54, 55].

MSCs home to sites of injury, upregulate endogenous stem cells, and reduce inflammation and organ dysfunction [56–61]. With respect to age-related diseases, MSCs have demonstrated improvements in ischemic and nonischemic cardiomyopathies [62–64], stroke [65], systemic inflammation [66], and Parkinson's, among others [67]. Although not completely understood, the beneficial effects of stem cells are likely due primarily to paracrine signaling [68, 69] including microvesicle/exosome release [70, 71] and secondarily to direct cellular contact including gap junction formation [72] and mitochondrial exchange via tunneling nanotubes [73, 60].

MSC effects at the molecular level are secondary to the secretion of growth factors, chemokines, and metalloproteinases, including vascular endothelial growth factor (VEGF), angiopoetin-1, fibroblast growth factor, placental growth factor, stem cell-derived factor (SDF), plasminogen activator [74], hepatocyte growth factor/scatter factor (HGF/SF) [75], secreted frizzled-related protein 2 (Sfrp2), hypoxic-induced Akt-regulated stem cell factor (HASF) and IGF-1 and -2 [76]. These molecules stimulate the Akt pathway [77], promote vasculogenesis [56], and protect native cells under hypoxic conditions [68]. In the heart, injection of MSCs produces antifibrotic, anti-inflammatory, and proangiogenic [57–59] effects and upregulates the proliferation of endogenous cardiac stem cells [60, 61], while improving the preservation of function of the cells surrounding the sites of injection.

MSCs mediate metabolic changes and stimulate resident cell activation after injury. *In vitro* studies have shown that MSC-conditioned culture media stimulates resident cardiac stem cells to proliferate, differentiate, and migrate [53, 78] via IGF-1. HASF and Sfrp2 prevent cardiomyocyte apoptosis, promote cardiac stem cell differentiation, and reduce fibrosis after myocardial infarction (MI) [79–81].

The absence of major histocompatibility complex (MHC) class II antigens underlies the lack of allo-MSCs to stimulate a major immune response [82] and has generated an interest in their systemic and local application without the need for immunosuppression [62]. In the clinical setting, multiple trials have evaluated and proven the safety and efficacy of MSC therapy [63, 64, 83–85]. Several disease processes have been studied in humans: autoimmune diseases, organ transplantation, and as a therapeutic agent after solid organ injury.

5. Immune biomarkers in aging and frailty

Aging and frailty are associated with a dramatic impairment of the ability of the immune system to provide protection from new pathogens. Older frail individual has serious complications that cause adverse health outcomes including acute illness, heightened inflammatory state, and immune dysregulation, which cause a severe impairment in both innate and adaptive immunity and greater susceptibility to infectious diseases, comorbidities, and

increased mortality [86, 87]. The accumulation of reactive oxygen species (ROS) in the aging process leads, in part, to chronic activation of Toll-like receptors (TLRs), which in turn leads to an increase in the inflammatory process [88–90]. In frailty, the immune phenotype is dysregulated due to incrementing chronic inflammation known as inflammaging and includes increased IL-6, C-reactive peptide (CRP), and TNF-α [87]. Inflammaging plays an important role in the suppression of the immune system and the remodeling of the immune phenotype (**Figure 1**). The remodeling of the immune phenotype in aging is known as immunosenescence and is marked by several immune biomarkers described below.

The immune risk phenotype (IRP), which is the ratio of CD4+ to CD8+ T cells, decreases to <1 in aging and frailty, has been linked to increased risk of mortality [91, 92]. The decreased IRP associated with aging and frailty is due to an expansion of the CD8+ compartment in comparison to the CD4+ compartment. In spite of the expansion of the CD8+ T-cell compartment, the effector T cells in frail individuals have diminished function mostly due to antigen experienced CD8+ T cells re-expressing the naïve marker CD45RA, also known as TEMRA T cells [87]. This expansion of the TEMRA T cell population is exacerbated by factors such as chronic activation due to Cytomegalovirus (CMV) exposure known to be present in >60% of the US population [93]. Finally, the ability to produce protective antibodies upon new antigenic exposure is also severely impaired in aging and frailty due to a remodeling of the B cell compartment. In addition, there is an intrinsic defect in B cells in aging, which causes a decrease in the enzyme, activation-induced cytidine deaminase (AID) leading to diminished ability to switch antibody isotype, which has been correlated to increased TNF-α [94]. The inflammaging process depletes the B cell compartment of switched memory B cells, which are a predictive biomarker for protective vaccine response. In addition, the refractory/exhausted B cell compartment is expanded filling up the B cell niche with unresponsive cells [86, 94, 95].
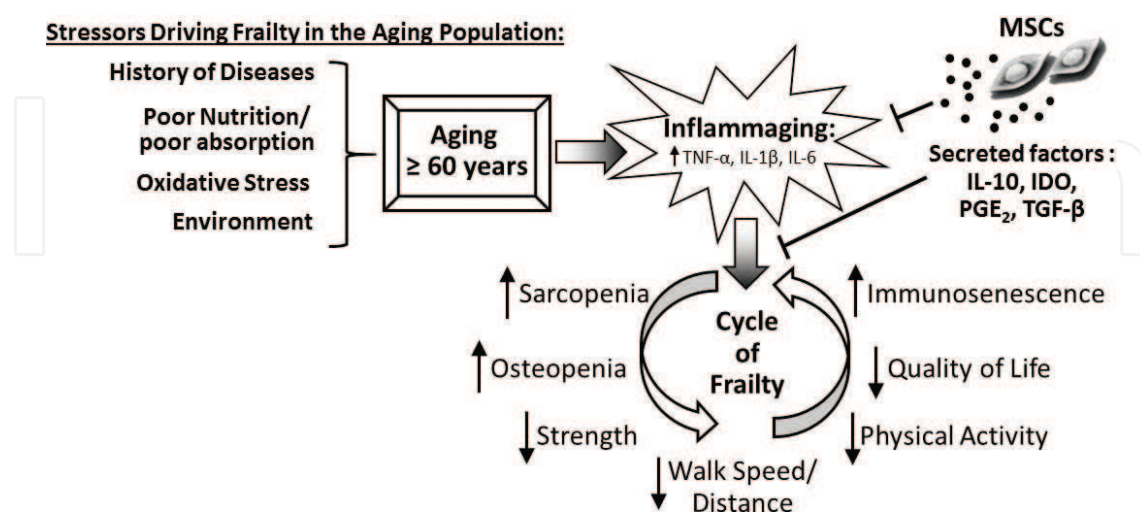

Figure 1. The role of stressors, aging, and inflammation in frailty and the effects of mesenchymal stem cells. As individuals grow older, several stressors (poor nutrition, diseases, oxidative stress, and environmental factors) increase the inflammaging process leading to frailty. Mesenchymal stem cells (MSCs) secrete several factors that block or reverse the inflammaging process and ultimately reverses the effects of frailty.

6. The role of MSCs in inflammaging and immune modulation

Human bone marrow-derived MSCs downregulate the expression of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (**Figure 2**) [96, 32]. Other immuno-modulatory properties include the inhibition of dendritic cells, natural killer cells [97–99], and T/B cell proliferation via the downregulation of the molecules programmed death-1 (PD-1) trans-forming growth factor-β, HGF, nitric oxide, indoleamine 2,3-dioxygenase, and prostaglandin-E2 release [52, 68]. Interestingly, MSCs are able to transform pro-inflammatory macrophages (M1) into anti-inflammatory macrophages (M2) by upregulating IGF-1 and IL-10 [100], thereby pro-moting angiogenesis and cardiomyocyte recovery [101, 102]. Most importantly, MSCs suppress T cell activation, which is crucial due to the high incidence of CMV virus among the US popula-tion, causing chronic activation of T cells leading to an exhausted immune phenotype [103].

Ground-breaking immune-modulatory results in the Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells for Nonischemic Dilated Cardiomyopathy: POSEIDON-DCM study demonstrated that 6 months post-TESI, allogeneic human mesen-chymal stem cells (hMSCs) were more efficient than auto-hMSCs in reducing serum levels of TNF-α, increased switched memory B cells, decreased exhausted B cells concomitant with a decrease in the percentage of B cells expressing TNF-α, decreased T cell activation and decreased TEMRA T cells [62]. This reversal on the effects of chronic inflammation on these immune biomarkers opens up the feasibility of using allo-hMSC as a treatment to reverse the process of inflammaging and immunosenescence.

Together, these findings are indicative of the safety of MSC therapy in a variety of disease pro-cesses. Furthermore, given that MSCs are known to elicit immunomodulatory, neoangiogenic,
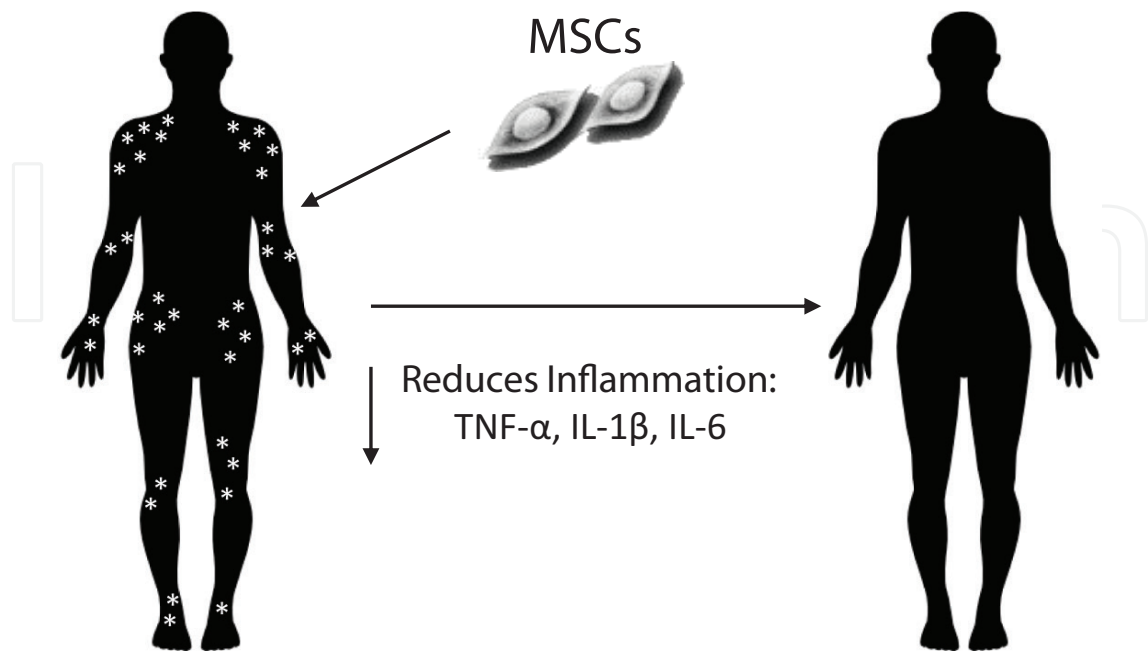

Figure 2. MSCs serve as an anti-inflammatory treatment. (A) Depiction of systemic inflammation (white asterisks'). (B). The anti-inflammatory effects of MSCs. Reproduced from Golpanian et al., with permission from the publisher.

endogenous cellular proliferative, and antifibrotic effects post-MI in both animal models and clinical trials alike, we anticipate that MSC therapy will act in a similar manner and prove beneficial in older individuals with frailty.

7. CRATUS phase I and II

The therapeutic interventions available to frail older individuals focus on improving the functionality of a precipitously declining quality of life. With the understanding that deteriorating endogenous stem cell function is a key mechanism behind this disease process, the allogeneic human mesenchymal stem cells (allo-hMSC) in patients with aging FRAilTy via intravenous delivery (CRATUS) trial (**Figure 3**) was established to reverse the untoward effects of frailty. Conducted at the University of Miami Miller School of Medicine, the pilot phase was designed to establish an optimal dose, and tested the hypothesis that allo-hMSCs were safe, well tolerated, and reduced the signs and symptoms of the disease [104]. The study was conducted in a nonrandomized, nonblinded, escalating dosage via peripheral intravenous infusion in 15 frail subjects [104]. Donors were healthy males and females between the ages of 20 and 45 [104]. Three groups of five patients each received either 20 million (M)-, 100M-, or 200M-cells [104]. Patients were followed out to 1-year postinfusion. The pilot phase revealed the two most salient doses (100M- and 200M-cells) [55] and was followed by
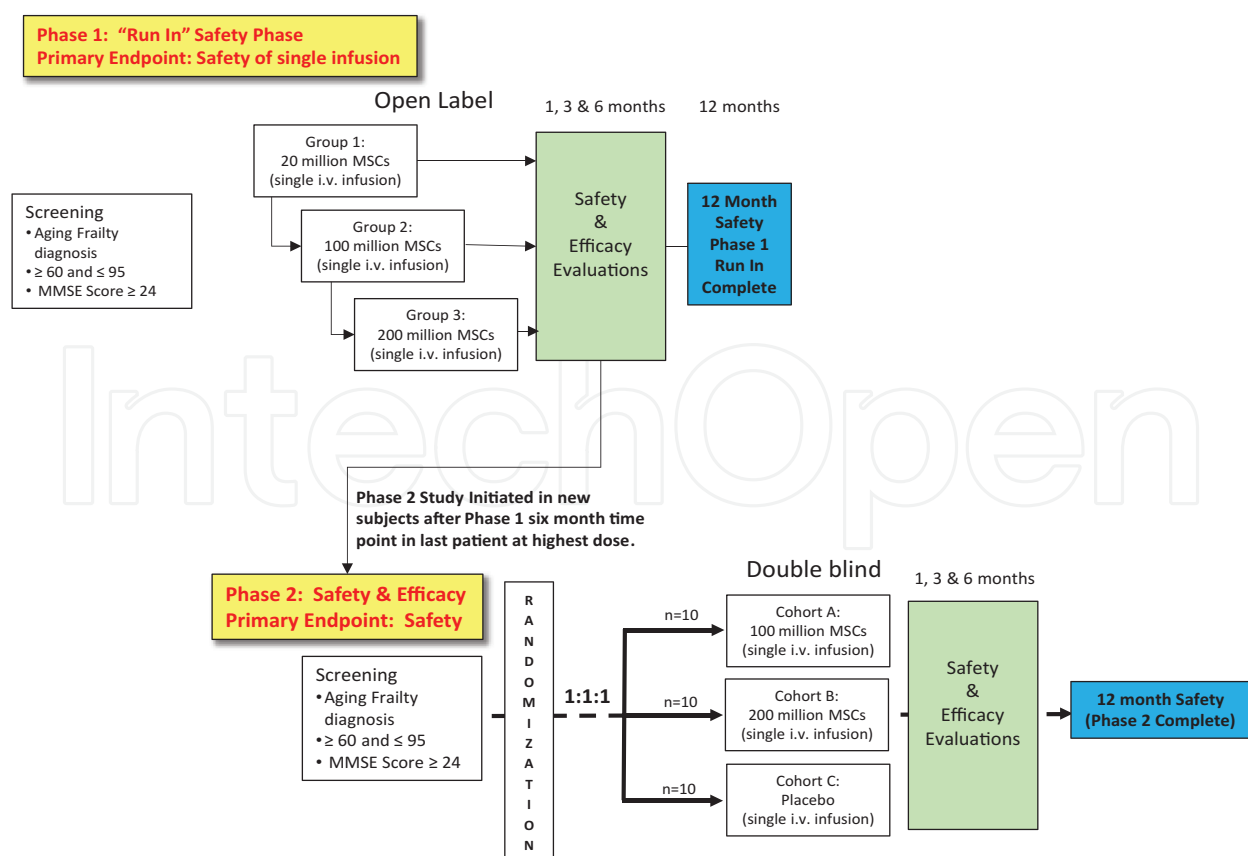

Figure 3. Schematic of the CRATUS pilot and randomized phases.

phase II, a randomized, double-blinded, placebo-controlled trial that further tested the safety and efficacy of allo-hMSCs in frail older individuals.

7.1. Results of the phase I study

The 15 subjects in the pilot phase had an average age of 78.4 ± 4.7 years [55]. Eight patients were categorized as vulnerable to frailty with a CSHA score of 4 and the others were mild, with a score of 6 (n = 6) and moderate with a score of 7 (n = 1) [55]. Most importantly, the primary endpoint, treatment-emergent serious adverse events (TE-SAE) at 1-month postinfusion, was met with no adverse reactions in any group [55].

Efficacy outcomes were measured out to 6 months postinfusion as a secondary endpoint. The 6-minute walk distance (6-MWD) test is a measure of functional exercise capacity [105], which can reflect a frail subject's ability to perform basic activities of daily living. The test has been specifically used to assess subjects with diseases of the musculoskeletal, pulmonary, and cardiovascular systems [106–108]; and as such, the subjects experienced a significant improvement in all treatment groups at 3 and 6 months postinfusion with the greatest improvement in the 100M cell-dose group in the phase I [55]. Pulmonary function was measured via FEV1, and improved in the 200M cell-dose group [55]. In regard to physical and quality of life improvement, the SF-36 questionnaire, which has a physical and mental component, yielded an improvement in the 100M-group in the pilot phase. Immunomodulation was also reported with a significant reduction in the pro-inflammatory biomarker serum TNF-α in the 100M and 200M cell-dose groups at 6 months postinfusion [55].

7.2. Update on the phase II study

The 30 subjects in phase II had a mean age of 75.5 ± 7.3 and a mean frailty score of 4 based on the CSHA Clinical Frailty Scale, and were equally randomized to receive 100M-, 200M-cells, or placebo [109]. Safety was the primary endpoint of the study and was measured via the occurrence of TE-SAE at 1-month postinfusion. The trial has completed enrollment, however, as reported in phase 1, preliminary findings show that the treatment is safe and produces significant improvements in the treated subjects in both quality of life and functional status [109].

8. Conclusion

Frailty has increasingly been recognized as a constellation of waning physical and mental qualities secondary to outside stressors, which relate to aging, and confer a vulnerability to adverse health outcomes [110]. Biologically, inflammation and stem cell depletion are at the forefront of this disease process. Early intervention is warranted at the onset of recognized symptoms to reduce the burden of disease progression, hospitalizations, and associated healthcare costs [111, 112]. To date, several important multimodal interventions are available to manage frailty; however, a disease-specific treatment has yet to emerge [112, 113]. Given the positive results of numerous studies utilizing MSCs in a variety of disease processes common to frailty as defined by the physical phenotype model, we believe stem cell therapy will be a treatment of choice for this disease process.

Future indications applicable to frailty	Response to MSCs	Proposed mechanisms of action
Osteoporosis	Improved bone mineral content and reduced rate of fractures	Reduction in ROS and increased AMPK
Heart disease	Improved function	Increased endothelial function, decreased inflammation, reduced cardiac fibrosis, and increased cardiomyogenesis
Delayed healing in Injury	Increased wound healing	Decrease inflammation (TNF-α and IL-1β), Increased IL-10
Autoimmunity	Delayed onset/prevention	Suppress TH17, induce T regs, and promote TH2 response

Table 2. MSCs and future indications.

Future implications of stem cell administration in frail or prefrail older individuals may be useful in settings where undo stress may cause rapid physical deterioration. There are a number of medical procedures (breast/colorectal cancer treatment, cardiac surgery, non-cardiac elective surgery, etc.) that are taxing to a young healthy individual let alone older individuals [114–116]. A preemptive or perioperative administration of MSCs may dampen the immune response, aid in the healing process, and keep at-risk older individuals from declining in functional status (**Table 2**) [56, 117–120]. Given the results from the CRATUS, pilot dose finding [55] and randomized placebo controlled study [109] and the number of medical procedures older individuals undergo, large, randomized, double-blinded clinical trials are warranted to elucidate the efficacy of stem cell therapy in regard to the disease process in itself and its ability to suppress the progression of frailty after strenuous medical interventions.

In summary, allogeneic MSCs are immunotolerant in frail older individuals providing clinically meaningful improvements in functional capacity, inflammatory biomarkers, and quality of life patient-reported outcomes. Frailty, the multimodal biologically mediated decline in physiologic reserve, may now have an optimistic therapeutic option.

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