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Can IV Infusions Of Bone Marrow Derived Mesenchymal Stem Cell Extracellular Vesicles Be The Fountain Of Youth?

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Abstract

There is increasing published literature to support the safety and efficacy of IV infusions of bone marrow-derived expanded allogeneic mesenchymal stem cells (MSCs) for the treatment of various auto-immune diseases. Frailty Syndrome was created to provide a way of objectively measuring aging with physical activity scales and bio-inflammatory markers. IV infusions of allogeneic MSCs have been reported to statistically significantly increase physical function and decrease inflammatory biomarkers in Frailty Syndrome. Replacing cellular allogeneic IV infusions with acellular bone marrow-derived MSC extracellular vesicle isolate products (EVIP) containing active growth factors (GFs) and exosomes has numerous advantages. Regenerative medicine researchers and clinicians now realize that living MSCs are not required to achieve clinical efficacy.The clinical efficacy of MSCs is due to their paracrine release of GFs and exosomes. Living MSCs are not required to accomplish the paracrinesignaling of GFs and exosomes. Acellular MSC EVIP containing active GFs and exosomes are the future of regenerative medicine. Acellular exosomesderived from bone marrow MSCs provide a consistent product that has extensive characterization, which includes advanced particle analysis, proteomic evaluation and USP<71> sterility assurance. The future "Fountain of Youth" will be the frequent (3 to 4 times per year) IV infusion of bio pharmacologic quality bone marrow-derived MSC EVIP. These active GF and exosome infusions will result in a continual down regulation of systemic inflammation and based on published research reverse many of the inflammatory effects of aging.

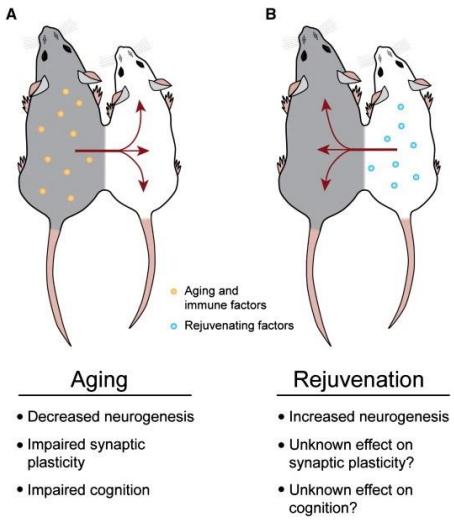
Keywords

Mesenchymal Stem Cells; Frailty Syndrome; Exosomes; Progenitor Cells

Introduction

Humans have always searched for the elusive "Fountain of Youth." In March of 1513, the famous Spanish explorer and conquistador Juan Ponce de Leónlanded in what he later named Florida. There was rumored to be a spring located in this "Garden of Eden" that contained miraculous waters supposedly capable of reversing the aging process and curing sickness, "the Fountain of Youth" [1]. This water was, of course, never located. Historically the most overarching technique for achieving the "fountain of youth" has been variations on the technique of parabiosis (exchanging old blood with young blood). Two papers published by a research group at the Stanford University School of Medicine in 2005 and 2010 respectively purported that young blood infused into older animals is capable o f revitalizing organs [2,3]. Numerous researchers have observed that tissue regenerative capacity declines with age. In tissues such as muscle, blood, liver, and brain, this decline has been attributed to diminished responsiveness of tissue-specific stem and progenitor cells [4-7] (Figure 1).

Figure 1: Figure one illustrates the concept of Parabiosis.



Evidence indicates that chronic systemic inflammation is an important etiology for aging. Recently the term Frailty Syndrome (FS) has been introduced [9,10]. Think of FS as encompassing all of what we consider to be the downside of aging. The FS has been clinically defined as "a state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple organ systems such that the ability to cope with acute or chronic stressors is compromised". [8]

There are numerous etiologies for the symptoms of FS that includes decreases in muscle strength, endurance, activity, energy levels, and physiologic function [9,10]. There is a close correlation between severity of FS and physical and cognitive impairments, co-morbidities and mortality rates [11-15].

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One of the primary etiologies of FS is chronic systemic inflammation. There are specific biomarkers associated with the various symptoms of FS. Serum levels of circulating IL-6 correlate with the development of physical impairments [16]. Serum levels of both IL-6 and TNF-α are connected with reduced muscle mass and strength [17,18].Serum levels of C-reactive protein (CRP) are wholly dependent on decrease in physical performance and strength in the elderly [19-21]. There is a strong correlation between mortality and elevated CRP, tumor necrosis factor-alpha (TNF-a), and IL-6 [22-26]. It was also observed that Chronic inflammation diminishes immune responses and contributes to increased mortality in subjects over 60 years of age with FS [27-30].There is currently no cure for aging or FS. Extensive research is being conducted to develop medications or therapeutic regimens that may slow down or even reverse the effects of FS. These are designed to exploit the link between FS and chronic systemic inflammation. Examples include the drug Rapamycin to rejuvenate the immune system. Even more promising are the published results of the use of allogeneic bone marrow-derived Mesenchymal Stem Cell (MSC) IV infusions to reverse FS.

The principal purpose of this study is to review the published peer review literature on the safety and efficacy of the use of allogeneic bone marrow-derived cellular MSC IV infusions to treat FS and then correlating those results to the potential advantages of using acellular bone marrow-derived MSC exosomes.

Materials and Methods

Mesenchymal Stem Cells have many characteristics that make them the potentially ideal cell type for decreasing chronic system inflammation and thus helping decrease or reverse the symptoms of FS. There are currently over 1,000 clinical trials registered worldwide at ClinicalTrials.gov studying MSC IV infusions for decreasing chronic systemic inflammation to treat autoimmune diseases [55]. These studies have produced increasing published literature to support the safety and efficacy of IV infusions of bone marrow-derived expanded allogeneic MSCs for the treatment of various auto-immune diseases including Parkinson's, Multiple Sclerosis, Ulcerative Colitis, Fibromyalgia, Rheumatoid Arthritis, Crohn's Disease, ALS, etc [56].

MSCs have a significant influence on the immune system in many different ways. B and T-lymphocyte proliferation get lessen in a paracrine manner and by direct cell-cell contact by these [31,32]. These also reduce the expression of proinflammatory cytokines, including TNF-α, interleukin (IL)-1β, IL-6, and CRP [33-35]. Besides these, the paracrine effects of MSCs are practiced either by secretion of a wide array of growth factors (GFs) or by means of exosomes, small extracellular vesicles that contain proteins, peptides, messenger and microRNAs. Figures two and three illustrate how exosomes are formed, released, and the recipient cell uptake process (Figure 2,3).

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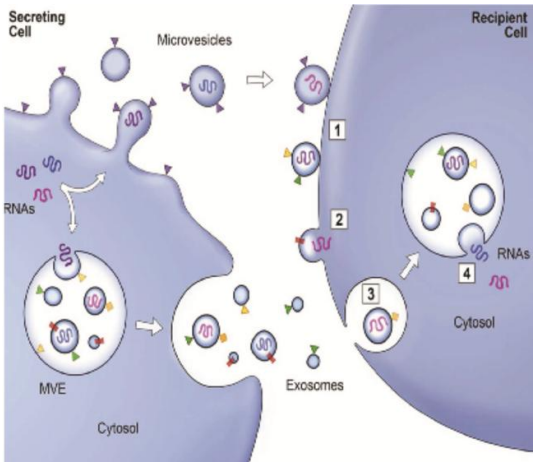
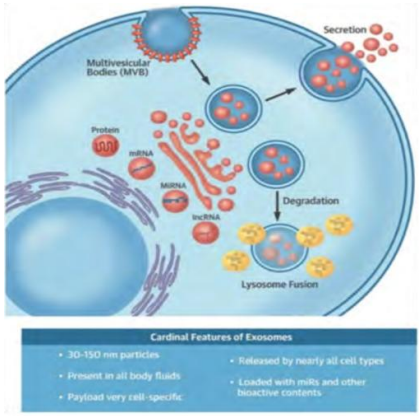
Figure 2: Exosome secretion and uptake.



Growth factors secreted by MSCs consist of transforming growth factor (TGF)-β, hepatocyte growth factor (HGF), and numerous types of interleukins [33]. These GFs interact to modulate the immune system [34-36]. In response to their microenvironment MSCs produce specific GFs. Among all the GF secreted by MSCs, the most well-studied GF is TGF-ß. MSCs provide TGF-ß in response to IL-4 receptor-mediated activation of the STAT6 pathway [37].Another GF secreted by MSCs is the potent anti-inflammatory IL-10, and its MSC expression requires direct contact with T-cells [38]. IL-10 reduces the ability of macrophages to form pro-inflammatory cytokines.

Figure 3: (Top) Schematic of exosome biogenesis. Exosomes arise from the fusion of surface membrane invaginations (multi-vesicular bodies) and the products of the Golgi apparatus. The resulting vesicles are either degraded by lysosomes or secreted as exosomes. (Bottom) Cardinal features of exosomes.



The immune system is modulated by MSCs through their release of exosomes. Exosomes are 30–150 nm extracellular vesicles that can be isolated from MSC-conditioned media. It has been studied that the exosomes which are derived by MSC reduce the secretion of pro-inflammatory GFs (IL-1ß, TNF-α) and on the contrary, increase the production of anti-

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inflammatory GFs (TGF-ß and IL-10) [39,40]. When MSC-derived exosomes were administrated in two mouse models of autoimmune disease, Type 1 diabetes mellitus, and uveoretinitis, then it was observed toreduce the immune response. These results and many other studies have suggested that MSC-derived exosomes represent an alternative to allogeneic cellular IV stem cell therapy [41-43]. Mesenchymal stem cells are not all equal. Recent studies indicate that the tissue from which an MSC originates influences its immunomodulatory properties. The most studied source of MSCs is from bone marrow [55,56].

Results

Two studies utilizing allogeneic expanded bone marrow-derived MSCs have been conducted, and the results published. The two studies includingphase I and a phase II clinical trial, CRATUS (NCT02065245), investigating the safety (primary outcome) and efficacy (secondary outcome) of an intravenous infusion of allogeneic bone marrow-derived MSCs as a novel therapy for treating patients experiencing mild to moderate frailty [44-46]. Efficacy outcomes included physical performance, quality of life, and measuring biomarkers as indicators for systemic inflammation.The phase I trial was a dose-escalation non-randomized study in which 15 patients were diagnosed with FS were given allogeneic MSCs intravenously with doses of 20, 100, or 200 million MSCs (5 patients per group) [44]. The doses were given as an 80 mL infusion at a speed of 2 mL/min, for a total infusion time of 40 min.Secondary outcomes were also observed, which were physical function measurements and circulating inflammatory biomarkers, measured at 3 and 6-months post-infusion. There were no adverse incidents with any of the doses at 1-month post-infusion, and also no clinically significant donor-specific immune reactions were seen during the first 6 months post-infusion. In all treatment groups, it was observed that at 3and 6 months the six-min walk distance significantly increased ($p<0.001$) and circulating TNF-α levels significantly decreased at 6 months ($p<0.001$). The best results of improvement in all efficacy outcomes were observed with the 100-million dose. This study indicated that for FS patient's allogeneic infusion of MSCs is safe and immunologically tolerated.

On the other hand, the phase II trial was a double-blinded, randomized, dose-finding study of intravenous allogeneic MSCs at doses of 100- or 200-million compared to placebo in 30 FS patients (mean age 75.5 ± 7.3) [45,46].Physical performance improved to a greater extent in the 100-million dose group ($p<0.01$). The 6-min walk test, short physical performance exam, and forced expiratory volume improved significantly only in the 100-million dose group. Moreover, there was improvement noted in the female sexual quality of life questionnaire and decreases in serum TNF-α levels in the 100-million dose group ($p<0.03$). B cell intracellular TNF-α improved significantly in both the 100-million and 200-million dose groups compared to placebo ($p<0.0001$). Early and late activated T-cells were decreased as well by MSC infusion compared to placebo. Although there were no safety concerns with the 200-million dose, there was no added benefit observed with this higher dose compared to the 100-million

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dose. In summary, intravenous allogeneic bone marrow-derived MSCs were found to be safe in individuals with FS and produced significant benefits in measures of physical performance as well inflammatory biomarkers, which are important therapeutic outcomes in frailty syndrome.

Discussion

Eggenhofer published the definitive study to determine the fate of living cellular IV infusions of MSCs [47]. Within the first few hours after intravenous infusion the MSCs were observed in the lungs. This observation had been previously reported [48-50]. Some of the exogenous MSCs remained viable in the lungs up to 24 hours after the infusion. These MSCs maintained their proliferation capacity. After 24 h, living MSC disappeared from the lungs but did not ever reappear in the blood, liver, spleen, kidney, or bone marrow. This was shown during autopsy examination and extensive culturing of these tissues. He showed that all of the IV infused allogeneic MSCs were trapped in the lungs and died in the lungs within 24 hours. Based on his definitive finding, several questions arise about the potential adverse clinical effects of allogeneic cellular MSC infusions. What is the systemic effect in disposing of the cellular debris of 100 to 200 million allogeneic MSCs? What is the long-term effect of having all that foreign DNA? In the long term, is this foreign DNA possibly carcinogenic?

The clinical efficacy of MSCs for regenerative medicine is not dependent on the living cells but on the paracrine signaling of GFs and exosomes produced by those cells. If enough signaling proteins and exosomes can be collected and protected, live MSCs are not required. These cellular products are the future of regenerative medicine. Acellular exosomes, derived from bone marrow MSCs, can provide a consistent product with extensive characterization which includes advanced particle analysis, genomic evaluation, and USP<71> sterility assurance. Growth Factor proteomic identification and quantification can also be performed. Think of acellular bone marrow derived MSC exosomes as a bio-pharmacologic product that is consistent standardized, and quality tested regarding dose and activity.

The MSC produces numerous GF proteins and exosomes capable of modulating inflammatory pathology. The exosome created by the endosome is a 30 to 150 nanometer (1 billionth of a meter) bi-phospholipid membrane-enclosed structure and an MSC (12 to 18 microns) is 1,000 times larger than an exosome. For comparison, the diameter of a hair is 80,000 nanometers. Exosomes do not contain any DNA rather they contain growth factors, signaling lipids, and micro and messenger RNA. The RNA contents present in exosomes mediate most of their anti-inflammatory effects. The exact type and quantity of anti-inflammatory GFs, signaling lipids, and RNA placed into an exosome are dependent on the surrounding inflammatory microenvironment of the MSC. The exosomes which are released into the extracellular matrix and taken up by a receptor cell then the exosome RNA is taken into the receptor cell ribosome where the RNA is translated to create a number of anti-inflammatory GFs, chemokines, cytokines, and secretomes. Allogeneic exosomes do not contain DNA and hence elicit acute immune rejection, and there is no risk for tumor

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formation. The effects of exosome RNA may last months or longer as the receptor cell ribosomes continue to translate the donor RNA.

Conclusion

There is an increasing amount of published literature to support the safety and efficacy of IV infusions of bone marrow-derived expanded allogeneic MSCs for the treatment of various auto-immune diseases [55,56].The term Frailty Syndrome was created to provide a way of objectively measuring aging with physical activity scales and bio-inflammatory markers [9,10]. IV infusions of allogeneic MSCs have been shown to statistically significantly increase physical function and decrease inflammatory biomarkers in FS [44-46]. Replacing cellular allogeneic IV infusions with acellular bone marrow-derived MSC exosomes has numerous advantages. The future "Fountain of Youth" will be the frequent (3 to 4 times per year) IV infusion of bio-pharmacologic quality bone marrow-derived MSC exosomes. These exosome infusions will result in a continual down regulation of systemic inflammation and based on published research reverse many of the inflammatory effects of aging [57]. Perhaps science has finally discovered the "Fountain of Youth".

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