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Mesenchymal Stem Cell Therapy for Nonhealing Cutaneous Wounds

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Summary

Chronic wounds remain a major challenge in modern medicine and represent a significant burden, affecting not only physical and mental health, but also productivity, health care expenditure, and long-term morbidity. Even under optimal conditions, the healing process leads to fibrosis or scar. One promising solution, cell therapy, involves the transplantation of progenitor/stem cells to patients through local or systemic delivery, and offers a novel approach to many chronic diseases, including nonhealing wounds. Mesenchymal stem cells are multipotent, adult progenitor cells of great interest because of their unique immunologic properties and regenerative potential. A variety of preclinical and clinical studies have shown that mesenchymal stem cells may have a useful role in wound-healing and tissue-engineering strategies and both aesthetic and reconstructive surgery. Recent advances in stem cell immunobiology can offer insight into the multiple mechanisms through which mesenchymal stem cells could affect underlying pathophysiologic processes associated with nonhealing mesenchymal stem cells. Critical evaluation of the current literature is necessary for understanding how mesenchymal stem cells could potentially revolutionize our approach to skin and soft-tissue defects and designing clinical trials to address their role in wound repair and regeneration.

WOUND HEALING

The incidence of nonhealing cutaneous wounds in the United States alone is 5 to 7 million per year, with an annual cost of over \$20 billion. As the largest organ of the body, the skin is responsible for thermoregulation, sweat production, and barrier protection against a variety of insults. Loss of skin integrity or its continuity is often secondary to trauma, surgery, or underlying abnormality, such as vascular insufficiency, hypertension, or metabolic derangement. Cause, surface area, and depth of wounding all dictate the means by which the wound should be managed, and contribute to the clinical prognosis.

Chronic or nonhealing wounds are often more challenging to the health care team than the underlying disease itself. Normal wound healing is a complex, coordinated sequence of

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events proceeding from hemostasis through inflammation to organized tissue regeneration.¹ After dermal injury, platelet aggregation initiates the clotting cascade and clot formation. The wound bed is then infiltrated with proinflammatory cytokine-producing leukocytes, including neutrophils, monocytes, and macrophages. In later stages of healing, fibroblasts are recruited to the wound, depositing extracellular matrix and providing the foundation for new tissue regeneration.²

Impaired wound healing results when these processes fail to progress through the sequential stages of healing and instead is characterized by chronic inflammation and increased local injury.³ There is evidence that resident cells in a nonhealing wound bed are phenotypically altered; for example, prolonged exposure to inflammatory cytokines, reactive oxygen intermediates, and bacterial toxins all contribute to fibroblast senescence and further suppression of the normal healing process.⁴ Standard therapeutic modalities in clinical practice include débridement, pressure offloading, dressing regimens, hyperbaric oxygen, antibiotics, and topical growth factors. However, even with most current therapies, greater than 50 percent of chronic wounds remain refractory to treatment.⁵ New treatment strategies in wound healing, such as bioengineered dressings and cellular applications, aim to replace senescent resident cells and reestablish the normal cycle.^{6,7} In recent years, many different cell-based products have emerged on the market with U.S. Food and Drug Administration approval, including those containing living cells. Tissue-engineered dressings such as Dermagraft (Advanced BioHealing, Westport, Conn.) and Apligraf (Organogenesis, Inc., Canton, Mass.) are currently available with U.S. Food and Drug Administration approval for diabetic foot ulcers and venous leg ulcers, respectively, although both have shown only limited clinical success.⁸ During the past decade, adult tissue-derived mesenchymal stem cells have rapidly moved from in vitro and animal studies into human trials as a therapeutic modality for a diverse group of clinical applications.⁹ Limited case reports or series illustrate the potential clinical use of mesenchymal stem cells in reconstruction/augmentation,¹⁰ tissue engineering and composite transfer,¹¹ and wound healing.¹²

MESENCHYMAL STEM CELLS IN THE CLINICAL SETTING

Bone marrow–derived mesenchymal stromal/stem cells are fibroblast-like cells in bone marrow that provide the microenvironmental support for hematopoietic cells. These cells are characterized by combinations of cell surface markers and functional characteristics such as the potential to differentiate into bone, fat, and cartilage.^{13,14} It is now evident that mesenchymal stem cells reside within most adult connective tissues and organs.¹⁵ Of particular interest is the isolation of cells with characteristics similar to bone marrow–derived mesenchymal stem cells from the stromal vascular fraction of adipose tissue.¹⁶ Enthusiasm about mesenchymal stem cells has been fueled by studies suggesting they possess the ability to not only differentiate along multiple tissue lineages but suppress activation and proliferation of immune cells and participate in the tissue repair and regeneration process through a variety of other paracrine mechanisms as well.¹⁷ Studies suggest that mesenchymal stem cells isolated from these diverse tissues possess similar biological characteristics, differentiation potential, and immunologic properties.^{18–20}

Functional characteristics of mesenchymal stem cells that may benefit wound healing include their ability to migrate to the site of injury or inflammation, participate in regeneration of damaged tissues, stimulate proliferation and differentiation of resident progenitor cells, promote recovery of injured cells through growth factor secretion and matrix remodeling, and exert unique immunomodulatory and antiinflammatory effects.^{21–25} Thus, in contrast to most pharmacologic agents targeting single pathophysiologic pathways, mesenchymal stem cells could affect tissue healing and regeneration through many different routes. One of the most intriguing properties of ex vivo expanded mesenchymal stem cells is their ability to affect the immune response through interaction with a broad range of immune cells, including T lymphocytes, B lymphocytes, natural killer cells, and dendritic cells.^{26–28} Based on these characteristics and their potential immunoprivileged status,²⁹ many human studies have received ex vivo expanded bone marrow– and adipose tissue–derived mesenchymal stem cells from third-party donors without any human leukocyte antigen matching.¹⁷ This lack of requirement for tissue typing/human leukocyte antigen matching makes use of mesenchymal stem cells, from bone marrow, adipose tissue, or other sources, very practical and feasible in different settings. These cells have been shown to be safe and potentially efficacious in several phase I, II, and III clinical trials. Indeed, bone marrow–derived mesenchymal stem cells are being tested aggressively in many areas of medicine, including cardiology (myocardial infarction and heart failure),³⁰ pulmonology (chronic obstructive pulmonary disease),³¹ gastroenterology (Crohn disease),³¹ endocrinology (diabetes mellitus type 1),³² and neurology (stroke and amyotrophic lateral sclerosis).^{33,34}

Although the majority of the published literature concerns bone marrow–derived mesenchymal stem cells, plastic surgeons have used autologous fat grafting for more than a century, and since this time the technique for harvest and administration has been modified to address the viability of mesenchymal stem cells within the lipoaspirate.^{35,36} Adipose tissue–derived mesenchymal stem cells are considered a desirable cell population because of their availability, ease of harvest, and ability to be expanded in culture for clinical use like their marrow counterparts.³⁷ One of the earliest indications in which bone marrow–derived mesenchymal stem cells were investigated was graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Interestingly, preclinical models have shown that adipose tissue–derived mesenchymal stem cells have anti-graft-versus-host disease characteristics similar to bone marrow–derived mesenchymal stem cells. These observations led to a few limited studies using adipose tissue–derived mesenchymal stem cells as salvage therapy for steroid-refractory acute graft-versus-host disease.³⁸ Use of adipose tissue–derived mesenchymal stem cells in clinical trials has also been shown to be safe and potentially efficacious in treating Crohn disease–related skin fistulas.^{39,40} However, to date, bone marrow–derived mesenchymal stem cells have remained as the most commonly used preparation of mesenchymal stem cells for clinical applications.

This wealth of clinical data on the safety of bone marrow–derived mesenchymal stem cells warrants considering the use of these cells, and adipose-derived mesenchymal stem cells, in a wider range of applications, including wound repair. Tissue hypoxia, inflammation, repetitive ischemia-reperfusion injury, and aging or cellular senescence are factors leading to dysfunctional wound healing,^{3,5} and are all potential pathways for mesenchymal stem cells to take effect. Although there have been case reports of bone marrow–derived cells

used in wound applications, the role of mesenchymal stem cells in the context of nonhealing wounds has not yet been adequately investigated, specifically by means of prospective, randomized trials. Indeed, most of the current literature regarding the therapeutic use of mesenchymal stem cells in wound repair is merely based on small, nonrandomized clinical trials.

USE OF BONE MARROW–DERIVED CELLS FOR WOUND REPAIR

The few clinical series focused on the application of mesenchymal stem cells in human wounds show promising potential. When evaluating the literature, particular attention should be paid to nomenclature and methodology. Reports on the use of bone marrow–derived mesenchymal stem cells range from bone marrow aspirate without any prior manipulation to culture-expanded mesenchymal stem cells with or without skin graft or other dressing material, and are outlined in Table 1.^{12,39–45} One of the early proof-of-principle reports of cell therapies of this nature in cutaneous wounds included the direct application of autologous bone marrow aspirate to wounds that were recalcitrant to standard therapeutics and present for more than 1 year.⁴¹ Remaining aspirate was cultured with or without hydrocortisone in the media to maximize the progenitor cells in culture. At the time of subsequent administration, cells from the steroid-containing media were mixed with cells from the steroid-free media. Ultimately, the authors reported healing of all of the wounds ($n = 3$) within three consecutive treatments. Two wounds closed with cell treatment alone, whereas one was closed with a bioengineered skin substitute (Apligraf). However, it is not clear whether the cells cultured by these investigators were mesenchymal stem cells or other types of cells present in the bone marrow, as there was no information on the identity of the cells cultured.

Although the majority of wounds treated clinically with cell-based therapies have been chronic in nature, there is also report of a severe radiation burn injury treated successfully with a combination of serial débridements, split-thickness skin graft, and mesenchymal stem cell injection.⁴² The cells were cultured from autologous bone marrow aspirate and injected directly into the wound following a two-step expansion process. The cells administered were positive for surface markers characteristic of mesenchymal stem cells and pluripotency confirmed with differentiation assays. Complete healing was observed within 6 months, with no functional impairments noted. Although encouraging, the single-case-report nature of this study and combined use of other modalities to treat this case should be considered.

A unique delivery system using fibrin glue was investigated in both acute ($n = 4$) and chronic ($n = 6$) wounds by Falanga and colleagues.⁴³ Autologous bone marrow–derived mesenchymal stem cells were expanded in culture to passages 2 to 10 and characterized as mesenchymal stem cells by flow cytometry. These cells were then combined with fibrin spray for topical application. The acute wounds studied were surgical defects following excision of nonmelanoma skin cancers. The authors assessed that these wounds were likely to heal secondarily but were not ideal for primary closure. In this group, all wounds were healed within 8 weeks, suggesting that mesenchymal stem cells contributed to accelerated resurfacing. To study mesenchymal stem cells in the setting of chronic wounds, the authors chose lower extremity wounds present for longer than 1 year and refractory to standard

treatments, including topical growth factors and bioengineered skin substitutes. Wounds were significantly decreased or healed completely by 16 to 20 weeks. Autologous culture-expanded mesenchymal stem cells were used with a fibrin glue system for up to three applications. Given the variation in the baseline size of the wound bed, the study found a strong correlation between the number of mesenchymal stem cells applied per square centimeter surface area and the reduction in ulcer size. Biopsies of both the acute and chronic wounds treated with topical mesenchymal stem cells and fibrin glue showed higher concentrations of CD29⁺ cells, one of the surface markers found on mesenchymal stem cells. These results indicate that fibrin glue potentially provides a delivery system to maintain mesenchymal stem cells in the acute wound bed but allows for migration out of the fibrin matrix as healing progresses. Again, mesenchymal stem cells were used in a nonrandomized, multimodality treatment regimen.

The largest series, so far, has been published by Yoshikawa and colleagues.¹² Twenty patients with various nonhealing wounds (i.e., burns, lower extremity ulcers, and decubitus ulcers) were treated with autologous bone marrow–derived mesenchymal stem cells expanded in culture and a dermal replacement (Pelnac; Gunze Limited Co., Tokyo, Japan) with or without autologous skin graft. The authors report that 18 of the 20 wounds appeared healed completely with the cell-composite graft transfer, and the addition of mesenchymal stem cells facilitated regeneration of the native tissue by histologic examination. Moreover, the process of cell harvest, culture expansion, and application with a dermal replacement or skin graft can be repeated and performed under local anesthesia if indicated. However, these authors only used a low concentration of cells that were available at the end of passage 0 and did not report on the characterization of cultured cells. This is especially important because passage 0, when the culture flasks are confluent after initial plating, potentially contains many other types of cells, including macrophages, which would affect wound healing as well.

Considered together, this literature shows that the addition of bone marrow–derived mesenchymal stem cells to nonhealing wounds is associated with dermal rebuilding in addition to remodeling, an increase in wound vascularity, and reduced fibrosis or scarring. Although these reports demonstrate the heterogeneity of the type of wounds treated with mesenchymal stem cells, they illustrate the variations in culture and application techniques that limit the current body of evidence in support of mesenchymal stem cell therapy. At this time, there are no randomized, controlled clinical trials using mesenchymal stem cells in the setting of acute or chronic wounds.

USE OF ADIPOSE TISSUE–DERIVED MESENCHYMAL STEM CELLS FOR WOUND REPAIR

There are, however, studies of autologous adipose tissue–derived mesenchymal stem cells used to treat complex perianal fistulas. The phase I clinical trial by Garcia-Olmo et al. was the first to show safety and feasibility of culture-expanded mesenchymal stem cells derived from lipoaspirate.³⁹ In a follow-up multicenter phase II trial by the same investigators, a group of patients with similar fistulas (related to Crohn disease and other underlying disease) were treated with fibrin glue, with or without adipose tissue–derived mesenchymal

stem cells, in a prospective, randomized, controlled fashion.⁴⁰ The treatment group achieved healing in 71 percent of patients, with a recurrence rate of 17.6 percent. Although the underlying pathologic mechanism associated with fistula-in-ano is different from that of chronic cutaneous wounds, these studies establish the foundation for similar safety and feasibility studies using mesenchymal stem cells derived from bone marrow, or adipose tissue, for nonhealing wounds.

DISCUSSION

Despite all of these promising small-scale clinical reports, there are several factors to take into account when discussing novel cellular therapies for chronic wounds. These include wound bed preparation, method of isolation, cell source, allogenicity, delivery method or application technique, timing of treatment, and culture expansion, among others. Addressing associated comorbidities is as important as addressing the defect. Wound bed preparation refers to optimizing the mechanical and physical properties of the wound to facilitate advanced therapeutic modalities. As technology advances, surgical débridement, edema control, revascularization, and pressure offloading remain mainstays of treatment in wound healing. The mechanism of delivery of mesenchymal stem cells to the wound bed is another factor for consideration. Direct application of bone marrow aspirate was one method used in pilot studies reviewed; however, this heterogeneous mixture contains inflammatory cells and cytokines in addition to mesenchymal stem cells. When expanded in culture, the cells were taken at different passages in assorted media and administered by means of injection or a topical delivery system such as collagen matrix or fibrin spray. These systems may serve as a scaffold for mesenchymal stem cell attachment and native cell recruitment, with the potential to further improve tissue regeneration. The widespread use of stem cell therapies will depend on the availability of validated methods for large-scale culture, storage, and distribution. At the present time, mesenchymal stem cells cannot be isolated prospectively for research or clinical use but rather are identified by means of culture expansion by a set of defined phenotypical and functional characteristics, including cell surface antigen expression and multilineage differentiation potential.¹⁴ Overall, the pilot studies and case reports reviewed show promise in the use of novel cell-based therapies for chronic cutaneous wounds; however, protocols must be developed and verified in the setting of randomized clinical trials. Uniform methodologies for isolation and culture expansion of mesenchymal stem cells are also needed, as many factors can affect the outcomes achieved.

CONCLUSIONS

Increased longevity in our society has resulted in a significant increase in the number of patients with chronic diseases. This trend has translated to a much higher incidence of related sequelae of these disorders such as nonhealing wounds. Because of the highly complex nature of wounds that result from destruction or loss of function of specific native cells, traditional medical therapies have been only moderately effective. The novel work reviewed here is highly promising, with the collective goal of identifying new therapeutic approaches to wound healing that are broadly applicable to many chronic diseases, and can safely accelerate the transition of basic research findings into clinical advances in many areas of plastic and reconstructive surgery.

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Table 1
Summary of Human Clinical Studies Investigating Bone Marrow Cells or Mesenchymal Stem Cells for Wound Repair

Study	Wound Type	Cell Source	Application Technique	Summary of Outcomes
<i>Bone Marrow Aspirate</i>				
Badiavas and Falanga, 2003 ⁴¹	Chronic wounds ($n = 3$)	Fresh BM aspirate followed by cultured BM	Injection into wound (cultured cells applied topically)	All healed within 3 treatments, 1 with bioengineered skin
Ichioka et al., 2005 ⁴⁴	Chronic lower extremity ulcer ($n = 1$)	Fresh BM aspirate	BM-treated collagen matrix followed by STSG	Full graft take
Badiavas et al., 2007 ⁴⁵	Chronic wounds ($n = 4$)	Fresh BM aspirate ($n = 2$) Fresh BM aspirate followed by cultured BM ($n = 2$)	Injection into wound	1 of 4 wounds healed completely
<i>Culture-Expanded Bone Marrow Mesenchymal Stem Cells</i>				
Falanga et al., 2007 ⁴³	Acute surgical wound ($n = 4$) Chronic lower extremity ($n = 6$)	BM-MSCs (P2–P10)	Topical fibrin spray	Wounds healed in correlation with number of cells applied
Lataillade et al., 2007 ⁴²	Radiation burn ($n = 1$)	BM-MSCs (P1–P2)	Injection into wound followed by STSG	Full graft take
Yoshikawa et al., 2008 ⁴²	Chronic wound ($n = 20$)	BM-MSCs (P1)	Treated collagen sponge composite graft	18 of 20 wounds healed completely
<i>Culture-Expanded Adipose Tissue Mesenchymal Stem Cells</i>				
Garcia-Olmo et al., 2009 ⁴⁰	Complex perianal fistula ($n = 25$)	AT-MSCs (passage unknown)	Injection with fibrin glue in the fistula tract	Healing rate 71%, recurrence rate 17.6%

n , number of wounds treated; P, culture passage used; BM, bone marrow; BM-MSCs, bone marrow–derived mesenchymal stem cells; AT-MSCs, adipose tissue–derived mesenchymal stem cells; STSG, split-thickness skin grafting.