Emerging Applications of Stem Cell and Regenerative Medicine to Sports Injuries

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Background: The treatment of sports-related musculoskeletal injuries with stem cells has become more publicized because of recent reports of high-profile athletes undergoing stem cell procedures. There has been increased interest in defining the parameters of safety and efficacy and the indications for potential use of stem cells in clinical practice.

Purpose: To review the role of regenerative medicine in the treatment of sports-related injuries.

Study Design: Review.

Method: Relevant studies were identified through a PubMed search combining the terms *stem cells* and *cartilage*, *ligament*, *tendon*, *muscle*, and *bone* from January 2000 to August 2013. Studies and works cited in these studies were also reviewed.

Results: Treatment of sports-related injuries with stem cells shows potential for clinical efficacy from the data available from basic science and animal studies.

Conclusion: Cell-based therapies and regenerative medicine offer safe and potentially efficacious treatment for sports-related musculoskeletal injuries. Basic science and preclinical studies that support the possibility of enhanced recovery from sports injuries using cell-based therapies are accumulating; however, more clinical evidence is necessary to define the indications and parameters for their use. Accordingly, exposing patients to cell-based therapies could confer an unacceptable risk profile with minimal or no benefit. Continued clinical testing with animal models and clinical trials is necessary to determine the relative risks and benefits as well as the indications and methodology of treatment.

Keywords: stem cells; sports medicine; tissue engineering; regenerative medicine

The application of stem cells, cell-based therapies, and other related biological products to sports injuries has gained increasing attention recently, not only as a focus of basic science and clinical research but also in the lay press with reports of high-profile athletes undergoing procedures involving stem cells in Asia, Europe, and Latin America.[2] The unique properties that stem cells possess make them particularly attractive for multiple applications in medicine.

Musculoskeletal injuries represent a significant opportunity cost to society as a whole. Just over 1 in 10 people in the United States reported a musculoskeletal injury that caused missed work in 2005; this amounted to 72.1 million work days lost.[50] All athletes, whether professional or recreational, are potentially affected by injuries. Sports injuries contribute to lost time from work, lost wages, and changes in emotional and social health due to impairments in function and mobility. Clinically, the quality of tissue healing is important for an athlete's performance; healing may potentially be enhanced and expedited by the addition of stem cells to local environments to promote healing.

DEFINITIONS

Stem cells are progenitor cells that provide the replacement units for normal cell turnover and apoptosis.[1,6] They are defined by (1) a capacity to remain in a quiescent, undifferentiated state until stimulated; (2) the ability to differentiate into multiple tissue lineages (multilineage differentiation); and (3) the ability to undergo more replicative cycles (self-renewal). There are many different types of stem cells, as discussed below, but a unifying definition of specific cell-surface markers identifying various cells remains incompletely characterized.

Stem cells cannot be defined in isolation; they must be considered in context of part of the broader field of tissue engineering, comprising 4 components: (1) production—cells and cellular precursors, (2) conduction—scaffolds, (3) induction—growth factors and cellular signaling molecules/receptors, and (4) mechanical stimulation—physiologic/pathologic stress.[17,25,38]

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There is a spectrum of differentiation potential for various stem cells. Totipotent stem cells, of which embryonic stem cells are prototypic, are capable of regenerating an organism in its entirety and differentiation into all cells found within the body. Pluripotent stem cells possess the capacity to generate all 3 germ layers: endoderm, ectoderm, and mesoderm, but lack the ability to form the trophoblast necessary for complete recapitulation. Multipotent stem cells are capable of generating 1 of the germ cell lines. Unipotent cells are differentiated to the extent of only being capable of generating 1 cell type and are also therefore referred to as precursor cells. All of the tissue types of interest in sports medicine, such as cartilage, bone, muscle, adipose, and fibroblasts, are derived from mesenchymal stem cells (MSCs) from the mesodermal germ cell layer. As such, MSCs are of particular interest for their therapeutic capacity.

MESENCHYMAL STEM CELL CHARACTERISTICS

A more specific set of criteria based on cell properties has been reported by the International Society for Cell Therapy Mesenchymal Stem Cells[11] for more uniform isolation of human MSCs: (1) adherence to plastic in standard culture conditions; (2) expression of cell-surface molecules; and (3) capacity for differentiation to osteoblasts, adipocytes, and chondroblasts in vivo. This definition is, however, specific to human mesenchymal stem cells, particularly in reference to expression of cell-surface molecules. This differential expressivity of receptors not only enables the isolation of these cell populations from committed cells but may also govern their behavioral characteristics in vitro and in vivo. The pool of stem cells is maintained by asymmetric division, which allows for self-perpetuation and differentiation simultaneously by generating a multipotent daughter cell that retains stem cell properties and a committed cell.[11]

SOURCES

Stem cells can be isolated from various sources, both pre- and postnatal. Embryonic stem cells have the ability to proliferate indefinitely in vitro without loss of differentiation but have some disadvantages and limitations to widespread use. The potential for oncologic transformation from implantation of embryonic stem cells has been a potential concern that has been reported in the literature. Previously, studies involving murine-derived bone marrow MSCs resulted in tumor formation in various organs. Reports have been refuted, however, as the transformed cell lines were ultimately identified as cell lines cross-contaminated with oncogenic cell lines.[22] In addition, Wang et al[53] reported that fusion of human umbilical cord MSCs with esophageal carcinoma cells inhibited their tumorigenicity. The artificial fusion hybrids exhibited declined cell growth, increased apoptosis, and benign transdifferentiation. Numerous large animal preclinical studies have shown no evidence of tumor formation with use of MSCs.[54] A 2010 study by Centeno et al[7] showed no evidence of ectopic tumor formation on magnetic resonance imaging in 227 patients for up to 3 years after implantation of MSCs in either peripheral joints or intervertebral disks.

There are also considerable ethical considerations and limitations based on availability of prenatal stem cells. Federal funding was previously only permitted for embryonic stem cell lines available before August 9, 2001. This was revised by President Obama in 2009 and allows for the use of embryonic stem cells but not their derivatives.[41]

Adult stem cells are isolated after birth and are considerably less complicated by availability issues and political and ethical ramifications. Multiple sites are available for isolation of adult stem cells, including adipose, peripheral blood, periosteum, synovium, pericytes, blood, bone marrow, skeletal muscle, umbilical cord, and dental pulp. Stem cells can also be grouped by differentiation potential: Hematopoietic stem cells are progenitors for endothelial and peripheral blood cells; MSCs to chondrocytes, adipocytes, and osteoblasts. Stem cell density corresponds with degree of angiogenesis in the donor tissue.

Muscle-derived stem cells (MDSCs) have a few notable qualities favoring their use in research. Muscle comprises the largest proportion of total body mass, can be isolated with a minimally invasive biopsy, and has a higher capacity for regeneration. Peripheral blood and adipose tissue have a more limited capacity for differentiation. MDSCs are capable of differentiation into multiple cell types from endodermal, ectodermal, and mesodermal. Isolation is performed in 3 general steps: (1) harvest, (2) enzymatic digestion, and (3) serial plating onto collagen-coated plates. Committed cells (fibroblasts) adhere early, whereas progenitor cells adhere late. They exhibit differential cell-surface molecule expressivity. Another described progenitor cell, found in skeletal muscle beneath the basal lamina in a quiescent state, is the satellite cell; they are distinguished from stem cells by expression of different surface molecules. There are some sex-based differences as well. Male MDSCs display more chondrogenic differentiation and may have better cartilage regeneration potential.[32]

Adipose-derived stem cells are appealing because of their ease of harvest, their abundance in the adipose tissue, and the low morbidity associated with their harvest. Their use is of particular interest in the plastic surgery community; however, their use in the sports medicine community remains largely unexplored. They are typically harvested from subcutaneous abdominal fat using a liposuction cannula without vacuum.[27] Baptista et al[4] described a successful method of cryopreservation of MSCs isolated from lipoaspirate, which conserved cell viability after thawing. Successful cryopreservation could potentially allow the use of prestored cells.

Bone marrow–derived stem cells are the most abundant and are purported to be perivascular in origin. These stem cells are the most studied in the literature and the first isolated for study and use. Harvesting bone marrow is more invasive when compared with adipose and muscle but just as readily available. Consequently, there has been an increase in interest in other cell sources, namely muscle and fat.[27]

Synovium-derived stem cells have also been evaluated for use in regenerative medicine. They have been shown to exhibit a higher potential for chondrogenic differentiation and expansion compared with other tissues.[27]

IMMUNOGENICITY

Human allogeneic MSCs express antigen-presenting molecules (major histocompatibility complex, class 1) on the cell surface and exhibit an immunosuppressive phenotype via cell-mediated immunity. Allogeneic MSCs also induce production of specific T helper cells to an anti-inflammatory state, as evidenced by decreased interferon gamma, an inflammatory cytokine, and increased interleukin 4, an anti-inflammatory cytokine. Allogeneic MSCs have similar effectiveness as autologous MSCs for repair of focal cartilage defects in a rat model. Both treatments resulted in superior tissue regeneration compared with untreated defects.[49] The lack of a need for lifelong suppression, increase and readiness in availability, and equivalence in efficacy make allogeneic stem cells particularly attractive for use in clinical practice.

STUDY MODELS

In vivo models include various animal models, including nude mice, Sprague-Dawley rats, Lewis rats, and rabbits. In vitro models involve the use of collagenous matrix scaffolds. Scaffolds are 1 of the 3 components required for tissue engineering: (1) biologically viable cells, (2) bioactive media/growth factors, and (3) a compatible scaffold or matrix. Synthetic scaffolds are polymers and include polyglycolic acid (PLGA) and poly-L-lactic acid (PLLA). Natural scaffolds include collagen, hyaluronic acid, chitosan, and alginate. Biosynthetic scaffolds can be manipulated and tailored. In situ host tissue or allograft tissue can also serve as scaffolds for stem cell implantation. Scaffolds influence cell behavior as well as growth factor and nutrient availability.[38] A fibrin/PLGA hybrid scaffold has recently been shown to promote cartilaginous tissue formation both in vitro and in vivo in a nude mouse model and may serve as a potential cell delivery vehicle and a structural basis for articular cartilage tissue engineering.[37] Aligned nanofiber scaffolds have shown superior mechanical properties when compared with nonaligned scaffolds.[36] This suggests that the mechanical orientation and environment play a role in the effectiveness of scaffolds. Mechanical loading has also been implicated to influence the effects of stem cells. Juncosa-Melvin et al[26] showed that mechanical loading could improve the biomechanical properties of healed defects in the patellar tendons of rabbits to which MSCs had been applied. They also demonstrated a statistically significant increase in collagen I and III expression; there was a 200% increase.[26] Kuo and Tuan[28] showed that cyclic loading maintained stem cell expression of scleraxis, a transcription factor associated with tendon and ligament development, with an initial decrease followed by an increase.

CURRENT SPORTS MEDICINE STUDIES AND CLINICAL APPLICATIONS

There are more than 772 adult stem cell clinical trials approved by the US Food and Drug Administration that are currently being conducted with ongoing recruitment,[51] and many of these involve investigations of relevance to injuries of bone, cartilage, tendons, or skeletal muscle, therefore having implications for sports-related injuries.

Articular Cartilage

The use of stem cells in articular cartilage defects is of particular importance given the limited ability for self-repair or regeneration of cartilage following injury. Current methods, including bone marrow stimulation, osteochondral autograft transfer, and osteochondral allograft and autologous chondrocyte implantation, have an unclear impact on the natural history of these lesions. The cartilage formed after healing is predominantly fibrous and differs biomechanically and histologically from articular hyaline cartilage.[14] Focal injuries to cartilage have been shown to increase the overall incidence of osteoarthritis.[34] Arthritis has a significant financial and functional impact on the economy, costing the United States approximately $128 billion or 1.2% of the gross domestic product when other rheumatologic conditions were included.[55]

Platelet-rich plasma (PRP) has also been advocated as an alternative strategy to facilitate tissue repair and regeneration following musculoskeletal injury. PRP is prepared from autologous blood that has been centrifuged to isolate red blood cells and serum from platelets and white blood cells contained in the "buffy coat." These platelets contain a milieu of growth factors that are released to purportedly augment the healing process.[21] Mishra et al[35] proposed that some of the regenerative effects of PRP could enhance stem cell proliferation and promote chondrogenic differentiation of MSCs in vitro. Inactivated PRP in vivo may be activated over time with sustained release of growth factors. Combining PRP and MSCs in vitro demonstrated a 10-fold increase in several chondrogenic markers when compared with controls.[35] This suggests that PRP may in fact exert some of its effects through a stem cell–mediated process at the transcriptional level.

The effect of MSCs on cartilage injuries has been studied in an attempt to define and access their ability to contribute to cartilage repair. Tay et al[49] showed that both allogeneic MSCs and autologous MSCs have enhanced ability to regenerate tissue in focal cartilage defects in rabbits versus untreated defects. Importantly, they also demonstrated that allogeneic MSCs are comparable with autologous MSCs in regeneration of focal cartilage defects.[49] Marquass et al[31] showed that collagen gel embedded with chondrogenically predifferentiated MSCs showed superior bonding to native cartilage at the periphery of the lesion after 12 months in vivo. Bekkers et al[5] demonstrated that the treatment of swine cartilage defects with chondrin and MSCs in a fibrin glue resulted in better cartilage regeneration than microfracture alone. Dashtdar et al,[10] in a preliminary study, demonstrated superior healing of cartilage defects

with the application of either allogeneic chondrogenically predetermined stem cells or undifferentiated mesenchymal stem cells when compared with untreated defects. In addition, Nejadnik et al[40] showed no difference in clinical outcomes in patients treated with autologous bone marrow–derived stem cells versus autologous chondrocyte implantation. Recently, Saw et al[46] found that the addition of peripheral blood stem cells to intra-articular injections of hyaluronic acid following arthroscopic subchondral bone drilling for articular lesions improved cartilage repair both histologically and by magnetic resonance imaging evaluation.

A clear advantage of utilizing MSCs would be the obviation of the need to harvest cartilage and delay in re-implantation during a second procedure. Together, these studies suggest that more effective and consistent treatment of injuries to cartilage may not only improve the time and quality of healing but also potentially limit the sequelae of these injuries. Human clinical trials are needed to address the concerns of safety and efficacy that are alluded to during animal trials.

Ligaments

Ligaments are composed of mainly fibroblasts and extracellular matrix. MSCs from multiple sources are able to differentiate into the fibroblasts that maintain and repair ligamentous tissue. The other consideration is the site-dependent nature of ligament healing; the extracapsular medial collateral ligament heals reliably without operative intervention compared with the intrasynovial anterior cruciate ligament, which has limited capacity for primary healing.[24]

Several attempts to create protocols for ligament regenerations from MSCs have been reported. Flynn and Woodhouse[15] proposed that adipose-derived stem cells represent an alternative choice to the MSC and, as such, may be a suitable stem cell for ligament engineering. However, adipose-derived stem cells treated for up to 4 weeks with transforming growth factor–beta 1 (TGF-β1) or insulin-like growth factor 1 (IGF-1) did not show any significant and consistent upregulation in the expression of collagen types 1 and 3, tenascin C, and scleraxis.[15] Tenascin C and scleraxis are important transcription factors with roles in tendon formation during embryogenesis and chondrocyte-specific gene expression.[43] Therefore, simple in vitro treatment of human adipose-derived stem cell populations with growth factors may not stimulate their ligament differentiative potential.[12] Accordingly, attempts to utilize human adipose-derived stem cells may not preferentially stimulate their conversion to ligament end tissue. Perhaps the effect of these stems in ligament reconstruction is less on their differentiation into ligament tissue and more on the surrounding environment they create through stimulation and response of other cells that enhance ligament repair. Further research is needed to investigate this.

By applying MSCs to the allograft tendon–bone interface during anterior cruciate ligament reconstruction of 36 rabbits using Achilles tendon allografts, Soon et al[48] demonstrated that the use of MSCs increased osteointegration at the bone-ligament interface and increased biomechanical strength. This suggests clinical potential use of stem cells in humans to promote healing in reconstructive procedures that rely on bone to ligament healing, particularly in cases where allograft bone is used and slower incorporation is expected.

With regard to human trials, there was 1 study noted on the clinical trials database. There is an ongoing double-blinded trial (NCT01076673) accessing the safety and efficacy of adult stem cells combined with hyaluronic acid versus hyaluronic acid as a control in patients who have undergone autograft reconstruction of the anterior cruciate ligament within 6 months. They will be monitored clinically for side effects and with interval imaging.

Tendons

Tendons have a similar composition to ligaments on a cellular level. They function to allow muscles to act on their attachments to bone, imparting motion to joints. Stem cell therapy within the context of regenerative medicine could potentially offer accelerated or higher quality healing in tissue that has limited vascularity, particularly in patients with comorbidities that could potentially delay healing.[23]

Daher et al[9] worked with Achilles tendons in Sprague-Dawley rats after transection and suture repair that were seeded with allogeneic circulating stem cells in a biodegradable scaffold. They demonstrated a decreasing cross-sectional area with time, complete bridging of the transection site with parallel collagen fiber arrangement, and significant increase in the ultimate tensile strength of the tendons versus suture alone as the control group. This suggests that addition of these cells may actually change the 3-dimensional structural arrangement of the tendon.[9]

Chong et al[8] investigated the effect of bone marrow–derived stem cells on Achilles tendon healing in a rat model. They were able to show improved biomechanical properties and collagen organization at 3 weeks but not at 6 or 12 weeks. The lack of significance after 3 weeks could be related to a smaller effect size. Alternatively, it could mean that these changes are emphasized in the early phases of tendon healing.[8]

Zhang and Wang[57] recently demonstrated rabbit-derived patellar tenocyte stem cell proliferation and increased gene, protein, and collagen production from active tenocytes after the addition of a platelet-rich clot releasate, a combination of growth factors released from PRP clots.[57] This suggests that platelet-rich clot releasate may promote differentiation of tenocyte stem cells into active tenocytes. This suggests that the biologic effect of PRP may be modulated by stem cell upregulation. The number of active tenocytes may be indirectly regulated by stem cell activation during the regenerative process.[57]

Gulotta et al,[20] in a rat model with rotator cuff repair, demonstrated that the group with adenovirus scleraxis (Scx)–transduced bone marrow–derived stem cells in a fibrin glue carrier had more fibrocartilage formation, a higher ultimate load to failure, a higher ultimate stress to failure, and a higher stiffness value when compared with nontransduced MSCs at 4 weeks. Furthermore, Yokoya et al[56] added a polyglycolic acid sheet scaffold with seeded

MSCs to surgically created infraspinatus tendon defects in rabbits and found that at 16 weeks, the MSC group had significantly higher tensile strength than the control group. These studies suggest that their action may result in an improved biomechanical testing profile.

Membrane-type 1 matrix metalloproteinase (MT1-MMP) is upregulated during embryogenesis at tendon-bone interfaces. Gulotta et al[18] further demonstrated in a fibrin glue carrier that the group with adenovirus MT1-MMP–transduced bone marrow–derived stem cells had more fibrocartilage formation, a higher ultimate load to failure, a higher ultimate stress to failure, and a higher stiffness value when compared with nontransduced MSCs at 4 weeks but no differences at 2 weeks in a rat model after rotator cuff repair. Conversely, the addition of MSCs to the healing rotator cuff insertion site in the Lewis rat did not improve the structure, composition, or strength of the healing tendon attachment site despite evidence that they are present and metabolically active.[19]

Mazzocca et al[33] showed that adult stem cells, known as connective tissue progenitor cells, could be isolated and used safely from the proximal humerus during rotator cuff repair. The study did not demonstrate a functional difference when compared with the control group, but the study only included 23 patients. It is possible that the effect size is not large enough to show a statistical difference with this number of patients.[33] In addition, Utsunomiya et al[52] investigated tissue sources of MSCs for rotator cuff injuries. This study compared tissue from several different areas within the shoulder of patients with rotator cuff injuries. Tissue from the subacromial bursa and synovium had the greatest expandability, yield, and osteogenic potential.[52] Of note, this was an in vitro study and therefore the potential of these MSCs in vivo was not described. There were no current clinical trials involving stem cells and tendons noted on the clinical trials database.

Muscle

Muscle injuries are particularly challenging injuries to address surgically with repair, particularly when in the substance of the muscle. They often heal because of relatively abundant vascularity. The role of MSCs may be to facilitate higher quality healing with less fibrosis and potentially more functional tissue with less fatigue and pain.

Ota et al[42] recently examined the effects of muscle-derived stem cells transplanted at 1, 4, and 7 days after muscle contusion in a murine model. Transplantation at day 4 showed high levels of vascular endothelial growth factor (VEGF) and angiogenesis at 1 week, increased muscle strength at week 2, and decreased fibrosis formation at week 4. The group implanted at 7 days also showed a statistically significant decrease in scar tissue formation when compared with all other groups.[42] This shows that stem cells may have the potential to accelerate the healing process in muscle injuries and decrease the formation of scar tissue that can lead to chronic symptoms from these injuries.

Bone

Cell-based therapy may also have utility in the treatment of fractures, particularly stress and fragility fractures that do not heal in the appropriate time frame. Medical management, rest, and immobilization are currently used to manage these fractures. Treatment for these injuries is often challenging because of the complex biologic environment that caused the fractures to begin with.

Peng et al[44] showed that MSCs transduced to express bone morphogenetic protein 4 (BMP-4) with VEGF enhanced angiogenesis and bone formation in immunocompetent mice. Sheyn et al[47] demonstrated increased bone formation rate and end volume in pigs treated with adipose-derived stem cells. Beginning 2 weeks postoperatively, considerable defect repair was observed in the group of pigs treated with adipose stem cell–bone morphogenetic protein 6 (BMP-6) cells. The rate of bone formation in the stem cell–treated group was 2 times faster than that in the control fibrin gel–treated group, and bone volume at the endpoint was 2-fold compared with the control group.[47]

There are human trials utilizing MSCs in the treatment of long bone nonunion and open tibia fractures that are actively recruiting patients (NCT01788059, NCT01626625).

Accordingly, it may be anticipated that MSCs could have substantial value in enhancing fracture healing, particularly in the setting of fragility fractures, areas of watershed, or compromised vascularity, and in nonunions.

CONTROVERSIES

There are numerous reports in the lay press that high-profile professional athletes in the National Football League and Major League Baseball have traveled abroad to receive cell-based therapeutic procedures for a variety of sports-related injuries.[2,16,45] In these reports, patients are reported to have sought therapies that include both autologous adipose-derived stem cells harvested by liposuction without vacuum and isolated by centrifugation.[13,29] This example of medical tourism raises notable concerns within the medical community. First and foremost is the concern regarding exposure to the risk of an unproven therapy. In addition, concerns about performance enhancement have also been raised because these procedures may include adjuvants such as human growth hormone (HGH).

HGH is purported to enhance the regenerative process through the release of insulin-like growth factor 1 (IGF-1), a hormone involved in growth and development, which in turn promotes chondrogenic differentiation of multipotent cells.[12] Currently, scientific evidence is inconclusive on whether HGH actually enhances or improves athletic performance. Although there is evidence that HGH increased lean body mass, it is unclear if its use improves strength. Presently, several professional athletic associations, including the National Football League, Major League Baseball, and the International Olympic Committee, ban the use of HGH.[30] Transforming growth factor–beta 3 (TGF-β3) and dexamethasone also promote chondrogenic

differentiation. Although the process of increased chondrocyte differentiation by dexamethasone is not well understood, some reports suggest that the effect is because of increased expression of specific type II procollagen transcription factors by dexamethasone during chondrocyte differentiation.[3]

PRP and light-emitting diode light have also been included in some advertised protocols for "activation" of stem cells. Application of low-level laser irradiation to human adipose-derived stem cells cultured with epidermal growth factor has been reported to increase the viability and proliferation of these cells.[39] PRP, as previously noted, may play a role in stem cell proliferation and chondrogenic differentiation.

As anticipated, the promise of regenerative medicine strategies to enhance surgical outcomes and tissue recovery following sports-related injuries has increased commercialization of regenerative therapeutics. The role of financial motivation and constraints and motives in stem cell research, particularly in clinical trials, must be considered carefully.

CONCLUSION

In summary, the fields of cell-based therapies and regenerative medicine offer safe and potentially efficacious treatment for sports-related musculoskeletal injuries. This potential benefit provides immense hope for individuals recovering from sports-related injuries.

While there are accumulating basic science and preclinical studies supporting the possibility of enhanced recovery of sports injuries in response to cell-based therapies or related approaches, clinical trials demonstrating the value of these new approaches are scarce. Accordingly, exposing patients to cell-based therapies that have not been appropriately investigated, optimized, or proven effective could confer an unacceptable risk profile with minimal or no benefit. For these reasons, continued animal model testing as well as formal testing in clinical trials aimed at optimizing therapeutic strategies and clearly defining risks and benefits are warranted.

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