Stem Cell Therapy for Musculoskeletal Injuries

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Introduction

Musculoskeletal injuries and disease such as tendonitis, desmitis, and osteoarthritis are overwhelmingly common in equine athletes. Standard treatments include systemic and local anti-inflammatory therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, rest and rehabilitation. During the past decade, significant research and clinical focus has been placed on stem cell therapy in both equine and human patients alike. Unlike standard treatments, the goal of stem cell therapy is to repair or regenerate damaged tissue to its native state such that it will have normal structure and function. Initially, the mechanism of action of stem cells was believed to be differentiation of stem cells into the predominant cell type of the injured tissue. Although complete differentiation and engraftment do not appear to be a predominant feature, stem cells are now known to exert their effect by modulating the host’s inflammatory, healing and repair phases following injury. Stem cell immunomodulation leads to an end product that is more like native tissue than it would be without stem cell intervention.

What is a stem cell?

Stem cells are undifferentiated cells that are capable of self-renewal and are able to differentiate into different cell types (potency). The potency of stem cells varies from totipotent (able to give rise to all cells types e.g. early embryonic cell), pluripotent (able to differentiate into any of the three germ layers e.g. embryonic- and early fetal-derived stem cells), multipotent (able to differentiate into a number of closely related cells e.g. adult-derived stem cell), to unipotent (able to give rise to only one cell type e.g. progenitor cell). Adult-derived mesenchymal stem cells (MSCs) are used most commonly in equine regenerative medicine as they have the ability to differentiate into osteoblasts, chondrocytes, myocytes and adipocytes i.e. they are multipotent.

How do you get equine stem cells?

Adult MSCs can be obtained from a variety of sources including bone marrow, fat, synovium, umbilical cord blood and tissue, tendon, muscle, and periosteum. Bone marrow is the most common source of MSCs used in clinical cases as it can be easily obtained in the sedated, standing horse from the sternum or tuber coxae. Adipose-derived MSCs are also used clinically with fat being collected on either side of the tail head.
Following collection of bone marrow or fat, MSCs can be immediately concentrated for subsequent use or they can be culture-expanded in the laboratory. Bone marrow aspirate concentrate (BMAC) refers to bone marrow that undergoes immediate centrifugation following collection. The centrifugation process concentrates progenitor cells and allows for patient-side application, although the density of MSCs is significantly lower than culture-expanded products. adipose-derived stromal vascular fraction (ADSVF) refers to adipose that is collagenase digested prior to concentration of progenitor cells. This product can also be used patient-side. Large numbers of bone marrow-derived MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs) can be produced through culture expansion over a 2-4 week period, depending on isolation protocol and the individual horse.

**What do you do with stem cells?**

MSCs have been used increasingly to treat a variety of musculoskeletal diseases including tendonitis, desmitis, articular cartilage lesions, osteoarthritis, and laminitis. Experimental and clinical studies support the use of MSCs for SDFT and suspensory ligament injuries, with most studies showing improved tissue architecture, biomechanical function and resistance to re-injury.4–7 Tendon and ligament lesions are best treated in the acute phase when a hypoechoic lesion is present on ultrasound. Chronic lesions with increased echogenicity are difficult to inject and likely too fibrotic to remodel effectively. Tendon and ligament lesions can be accurately injected under ultrasound-guidance. A sterile prep should be applied to the selected sites of injection followed by a local anesthetic skin bleb. The needle (20-23g recommended to avoid shearing cells and damaging tendon/ligament) is inserted parallel to the beam of the ultrasound into the core of the lesion. The lesion can then be filled with the cells. The number of cells injected varies tremendously with most lesions being injected with ~10-50 million cells. The injection can be repeated every 4 weeks, 3-4 times to facilitate healing. Extensive lesions in the SDFT or suspensory are sometimes treated with regional limb perfusion of MSCs, instead of direct injection.

MSCs can also be used to help improve cartilage healing and treat osteoarthritis. Several equine studies have reported the resurfacing of full-thickness cartilage lesions with MSCs.8–10 This can be performed arthroscopically using a self-polymerizing fibrin glue to maintain the MSCs in the grafted defect. Alternatively, MSCs can be injected directly into the joint to improve healing and alleviate clinical signs associated with osteoarthritis.11–13 The number of cells for injection depends on the size of the joint, generally ranging from 10-50 million cells/joint. Injections can be repeated every 4 weeks for 3-4 treatments. The administration of an NSAID is recommended to help prevent joint flares.

Finally, MSCs have been used to treat laminitis via regional limb perfusion. Currently, there is no literature that supports the use of MSCs for laminitis; however, many clinicians claim that horses respond favorably. It is recommended that MSCs be administered as early as possible in the acute phase as the cells may be able to modulate the pro-inflammatory state in the laminae.
Where do we go from here?

Research is actively being done on pluripotent (embryonic-derived) and induced pluripotent stem cells (iPSCs), as these cells have greater differentiation capabilities. Equine iPSCs cells have been described, although these cells have not been used clinically yet.\textsuperscript{14,15} Additionally, much interest lies in using allogeneic cells because these would be a patient-side product with no lag time for culture expansion. At this time, it is uncertain whether allogeneic cells are effective or safe due to recognition by the host immune system.\textsuperscript{16}

Stem cell therapy has developed extensively in the past 10 years, with experimental and controlled clinical studies finally catching up with clinical use. There is good evidence to support the use of stem cells in many different musculoskeletal injuries; it appears that cells aid in producing a healed product that is stronger and more resistant to re-injury.

References


