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Review

Therapeutic use of stem cells in horses: Which type, how, and when?

Lauren V. Schnabel [a,*], Lisa A. Fortier [a], C. Wayne McIlwraith [b], Karl M. Nobert [c]

[a] Department of Clinical Sciences, Cornell University College of Veterinary Medicine, Ithaca, NY 14853, USA
[b] Orthopedic Research Center, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523, USA
[c] Squire Sanders (US) LLP, 1200 19th Street N.W., Suite 300, Washington, DC 20036, USA

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ABSTRACT

Stem cells are commonly used in equine practice to treat musculoskeletal disorders including tendonitis, osteoarthritis, and more recently laminitis. As the field of regenerative medicine continues to advance, equine practitioners need contemporary information regarding the choice of stem cell type and recommendations regarding clinical implementation of stem cell therapies. Clinicians must also be aware of the limitation in current knowledge regarding stem cells, and the impending regulatory laws that may limit the use of equine stem cells in clinical patients.

Introduction

The use of stem cells in equine veterinary medicine continues to increase at a pace that is more rapid than available scientific and clinical evidence (Frisbie and Smith, 2010; Clegg and Pinchbeck, 2011; Fortier and Travis, 2011; Stewart, 2011). Despite the widespread use of stem cells for the treatment of equine musculoskeletal disorders, there are very few reports providing long-term clinical data. Many experimental and clinical studies have lacked proper control groups and are complicated by multimodal therapeutic approaches. In addition, there are impending changes in regulatory laws by the US Food and Drug Administration (FDA), which eventually may limit the use of some or all types of equine stem cells, at least in the USA (Yingling and Nobert, 2008; Nobert, 2011).

The purpose of this review is to provide contemporary information as to which type of stem cells should be used, how they should be applied, and when they should be applied for the treatment of clinical conditions.

What are the different types of stem cells?

The two most commonly used stem cells in equine veterinary medicine are adult bone marrow-derived and adipose tissue-derived mesenchymal stem cells (MSCs) (Frisbie and Smith, 2010; Fortier and Travis, 2011; Gutierrez-Nibeyro, 2011). Cells from either of these sources can be used after a culture period or after a brief centrifugation step for point-of-care treatment (Fig. 1). Bone marrow aspirate is typically harvested from the sternum (marrow spaces 3–5) or ilium using a Jamshidi needle (Taylor and Clegg, 2011; Adams et al., 2012).

The bone marrow aspirate can be cultured for approximately 2–3 weeks to obtain bone marrow-derived mesenchymal stem cells (BM-MSCs) or immediately centrifuged patient-side to produce bone marrow concentrate (BMC). BMC concentrates both stem cells and platelets compared to raw bone marrow aspirate, but yields a much lower number of stem cells compared to culture-expanded BM-MSCs (Fortier et al., 2010). Both BM-MSC isolation/culture services and BMC centrifugation systems are available commercially and are frequently used by equine practitioners (Fortier et al., 2010; Gutierrez-Nibeyro, 2011; Owens et al., 2011).

Adipose tissue is generally harvested from the tail head region and then collagenase digested and either cultured for several weeks to obtain adipose tissue-derived MSCs (AT-MSCs) or processed commercially to isolate adipose-derived stromal vascular fraction (AD-SVF) cells within 4–24 h (Gutierrez-Nibeyro, 2011). Although equine AT-MSCs have been well described in the literature (Vidal et al., 2007, 2012; de Mattos Carvalho et al., 2009; Pascucci et al., 2011; Raabe et al., 2011), AD-SVF cells have been favored over AT-MSCs in clinical use most likely due to their highly publicized commercial availability and short turnaround time from adipose tissue harvest to clinical application (Gutierrez-Nibeyro, 2011). It is important to note, however, that because of the lack of a culture step, only a fraction (20–40%) of the AD-SVF cells are stem cells (Vidal et al., 2007). As detailed below, there is evidence to support the use of both cultured and processed adult MSCs for the treatment of equine musculoskeletal disorders including tendonitis and osteoarthritis.

In addition to the adult-derived MSCs, several sources of equine neonatal stem cells have been described including fetal fibroblasts,

* Corresponding author. Tel.: +1 607 253 3100.
E-mail address: lvs3@cornell.edu (L.V. Schnabel).

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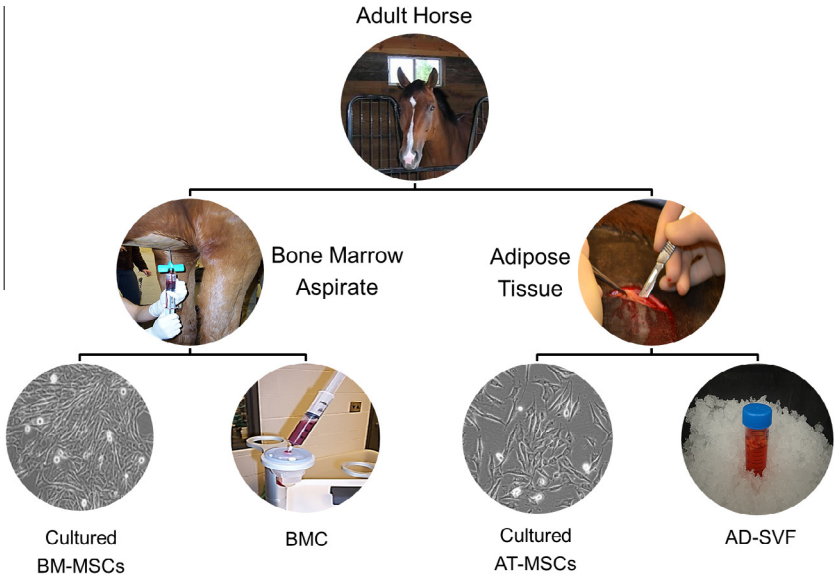

Fig. 1. The two most common sources of adult-derived equine mesenchymal stem cells and the products that can be obtained from each source. Bone marrow aspirate can be obtained from the sternum (depicted) or the tuber coxae (not shown). Bone marrow aspirate can be cultured to obtain mesenchymal stem cells (BM-MSCs) or immediately processed to obtain bone marrow concentrate (BMC) which can then be applied to the patient without a delay for culturing. Adipose tissue is obtained from either side of the tail head (depicted). Adipose tissue can be cultured to obtain mesenchymal stem cells (AT-MSCs) or digested to obtain a heterogenous cell population termed adipose-derived stromal vascular fracture (AD-SVF).

umbilical cord blood, umbilical cord tissue/matrix (Wharton's Jelly), placental tissue, and amniotic fluid (Koch et al., 2007, 2009; Watts et al., 2011; Carrade et al., 2011a,b; Iacono et al., 2012; Violini et al., 2012). Of these sources, only cells derived from fetal fibroblasts, a commercial cell line referred to as OK 100, have been evaluated for efficacy in an equine model of tendonitis (Watts et al., 2011). While OK 100 fetal cells have been used clinically to treat tendon and ligament injuries, they are not presently available to practitioners while the company seeks FDA approval, and therefore will not be discussed further (Gutierrez-Nibeyro, 2011).

Umbilical cord tissue-derived and placentally-derived MSCs have been assessed for safety in the literature primarily because of the fact that they are generally used in an allogeneic fashion (i.e. not isolated from the patient; Carrade et al., 2011a,b), but have not yet been evaluated for efficacy in the treatment of any equine disorder. Nevertheless, umbilical cord-derived MSCs are being used clinically and so are mentioned here. Only those stem cells for which peer-reviewed publications containing pre-clinical and/or clinical data exist, however, will be discussed further.

Tendonitis

The use of cultured BM-MSCs for the treatment of equine tendonitis is supported in the literature both by experimental and clinical studies (Pacini et al., 2007; Smith, 2008; Schnabel et al., 2009; Crovace et al., 2010; Godwin et al., 2012). Peer-reviewed publications with clinical data only currently exist for BM-MSCs and not for other types of stem cells. Smith et al. (2003) first described the culture process and use of BM-MSCs for the treatment of naturally occurring superficial digital flexor tendonitis in a single case report of a polo pony (Smith et al., 2003).

In the first case controlled study on the use of BM-MSCs for the treatment of naturally occurring superficial digital flexor tendonitis, reported by Pacini et al. (2007), 11 BM-MSC treated horses were compared to 15 control horses treated by traditional methods with both groups using the same rehabilitation protocol. In this study, 9/11 (82%) of the BM-MSC treated horses returned to racing in 9–12 months and were still racing without re-injury at 2 years post-treatment compared to the control group in which all of the 15 horses had experienced a re-injury event within 1 year (median re-injury time of 7 months) (Pacini et al., 2007).

In a later large clinical case series by Godwin et al. (2012) in which BM-MSC treated horses were compared to historical controls from the literature (Dyson, 2004; O'Meara et al., 2010), a significant reduction in re-injury rate was found for National Hunt horses treated with BM-MSCs compared to National Hunt horses treated with other therapies as previously reported by Dyson (2004) (25.7% compared to 56%, respectively) and O'Meara et al. (2010) (25.7% compared to 53%, respectively). Interestingly, no differences in the percentage of National Hunt horses treated with BM-MSCs compared to historical controls as reported by O'Meara et al. (2010) were found in terms of return to racing and completing three and five races. Only eight Thoroughbred flat racehorses treated with BM-MSCs were compared to three Thoroughbred flat racehorses treated with medical therapies by Dyson (2004). The small sample sizes in each study make translation of these findings to Thoroughbred flat racehorses difficult.

Suspensory ligament desmitis

Neither experimental nor clinical studies on the use of stem cells for the treatment of suspensory ligament desmitis have been published in the peer-reviewed literature.

Joint disease

The efficacy of stem cells for the treatment of equine osteoarthritis (OA) and cartilage injuries has been evaluated in the form of experimental and clinical studies and with more favorable results for bone marrow-derived cells than adipose-derived cells (Wilke et al., 2007; Frisbie et al., 2009; Fortier et al., 2010; Ferris et al., 2013).

In the only study published on the use of intra-articularly (IA) administered stem cells for the treatment of OA in the horse, Frisbie et al. (2009) created early OA using a carpal osteochondral fragment model (Frisbie et al., 2008, 2009). Injured joints were treated