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Continued Use of Unproven Stem Cell Therapies in the Clinic: The Need for Controlled Studies that Demonstrate Efficacy and Preclinical Studies to Optimize Treatment

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Stem cell therapy is increasingly common in veterinary practice, with thousands of animals treated with stem cells for a variety of conditions, including injuries to tendons and ligaments in horses, arthritis in dogs, cats, and horses, fractures, and cartilage damage. These therapies have not been approved by the FDA, and vary markedly from approved stem cell therapy for use in the clinic for human patients. Hematopoietic stem cells are the only stem cells approved for use in human medicine for a small number of related conditions including the treatment of blood disorders and loss of bone marrow function. In contrast, mesenchymal stem cells (MSC) isolated from bone-marrow, or a mixture of cells from bone marrow referred to as bone marrow mononucleate cells, or a mixture of cells known as the stromal vascular fraction derived from adipose tissue are commonly used in the clinic for veterinary applications.

Unapproved stem cell therapies are employed in human and veterinary medicine and both instances are marketed to the public as commonly used treatments that are the standard of care for a wide variety of conditions [1]. They are portrayed as mainstream, low-risk and curative, concepts supported by patient testimonials or testimonials from pet owners rather than by pre-clinical data or clinical trial results published in peer-reviewed journals. In fact, there are minimal or no data from controlled studies supporting the efficacy of the majority of these expensive and unapproved treatments or indicating that they have a benefit greater than other treatment options or than even no treatment at all. In addition, there are growing numbers of reports of negative side effects from these unproven treatments in human medicine, as independent scientists and clinicians have taken the initiative to assess patients before and after some of these treatments. Side effects observed in these independent studies include development of infections such as meningitis, as well as tumor formation, fevers, headache, and neuropathic pain [2,3]. No reports of detrimental effects related to unproven stem cell therapies for veterinary patients have been published by the clinicians performing the procedures or by the companies promoting them and no independent assessments of the function and condition of these recipients have been reported. Despite this, the lack of controlled studies demonstrating efficacy continues to be a concern in veterinary medicine, as it also is in human medicine, because the treatments are expensive and offer hope to patients or the owners of veterinary patients for a result that may not be possible with the treatment.

Only one controlled, double-blinded study for stem cell therapy in veterinary medicine has demonstrated efficacy. Black et al [4] published a well-conducted controlled study for stem cell therapy of dogs with osteoarthritis. Adipose-derived stromal vascular fraction was injected and benefit was observed in lameness at trot, range of motion, and pain on manipulation, that exceeded the effects reported for the control group [4]. This study followed dogs for 90 days after the procedure and reported statistically significant improvements over dogs receiving placebo in all 3 parameters at 30 days. The statistically significant benefit over controls in 'lameness at trot' and 'range of motion' was also present at 60 and 90 days as well, although the improvement in 'pain on manipulation' was lost by 60 days after treatment and scores for that parameter were even lower at 90 days after treatment. Similar results have not been reported by other independent groups, and no further studies focusing on extending the relief from pain on manipulation beyond the 30 days after stem cell injection have been reported.

In contrast to the benefit observed in the previously cited study, controlled studies for stem cell therapy for other conditions in veterinary medicine have not demonstrated efficacy. One common condition where stem cell therapy has been used frequently is for treatment of tendon injuries in horses, with company websites advertising hundreds and even thousands of horses treated for these injuries with stem cells. Very few controlled studies have been reported to test this treatment, but of those conducted, either no benefit, or minimal, transient differences in stem cell-treated and control horses were reported. Injection of either bone-marrow derived, cultured MSC or adipose-derived stromal vascular fraction containing a mixture of cells including MSC resulted in no statistically significant differences in comparison to control groups in the majority of parameters tested at 6 or 8 weeks, or 8 months after injection [5-7]. These parameters included ultrasound analysis of tendons, gene expression and collagen content, tensile modulus, and proteoglycan content [5,6]. No functional assessment was reported. A significant increase in tendon fiber architecture in MSC-injected tendons in comparison to saline-injected tendons was reported at 6 and 8 weeks in two studies [5,6], and a reduction in inflammatory cell infiltrate and increase in COMP were observed at 6 weeks post-injection in one of the studies [5]. However, a separate study conducted over a period of 8 months reported that beneficial effects of MSC were short-lived and that there was no difference between MSC- and vehicle-injected tendons at 8 months post-injection [7]. Another study reported no difference in the histologic appearance of tendon lesions at any time during a 90 day study, regardless of injection of serum, or equine MSC or equine embryonic stem cells (ESC) [8]. The short duration of benefit from cells in some of these reports is similar to the brief improvement in pain on manipulation observed in dogs treated with adipose tissue-derived cells [4], and to the transient benefit observed with MSC in many human clinical trials as well.

Despite the lack of efficacy reported in controlled trials, many

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horses receive injections of stem cells or mixtures of cells containing MSC in the clinic. Some peer-reviewed manuscripts have reported a beneficial outcome of stem cell injection in injured tendons in some of these client-owned horses. Herthel et al. [9] reported an increase in the percentage of horses returning to work after receiving bone marrow-derived MSC for tendon injuries, and Pacini et al [10] also reported a benefit in the percentage of horses returning to work and remaining free of re-injury up to 1 year after transplantation of bone marrow-derived MSC, in contrast to a control group of horses that all experienced re-injury within that same time frame. Although these results indicate that bone-marrow-derived MSC may be beneficial for tendon injury, they do not address whether the injuries in the control and MSC-treated populations were similar, whether MSC-transplanted and control horses were similar in age and maintained in similar conditions. There was no objective, quantitative assessment of function before and after transplantation or long-term follow-up. Long term analysis of treated animals may be particularly important, given the transient improvement in tissue architecture in controlled studies in horses with tendon damage. It is therefore difficult to assess reports of functional benefit from MSC outcome in client-owned horses or why the improved outcome in that population may be different than the reports from controlled studies.

One potential difference in the assessment of outcome in client-owned horses with tendon injuries and controlled studies of experimental horses with tendon injuries is the inclusion of assessments of treated animals by owners. When reporting benefit in client-owned horses receiving stem cells, some publications and websites report the percentage of animals that have returned to work, made a full recovery, or the degree of recovery achieved in treated animals based on owner responses to surveys rather than pre-determined criteria established by veterinarians and/or objective, quantitative assessments of function by blinded observers. In addition, glowing testimonials from owners of horses and dogs treated with stem cells, which cite dramatic improvement after stem cell injection, are featured on websites of multiple companies offering stem cell therapy for veterinary patients as evidence of the efficacy of the treatments. Similar testimonials are found on websites for companies or practices offering unproven stem cell therapies for human patients, also in lieu of controlled studies demonstrating efficacy. One obvious problem in using assessments of patients or owners of veterinary patients receiving stem cells lies in the potential influence of the placebo effect on reporting. Dobkin et al. [3] assessed the lesions and condition of human patients with spinal cord injuries before and after injection of stem cells from aborted fetuses in China, using criteria accepted by the American Spinal Injury Association to assess the impact of the injury and whether changes in strength or function occurred following stem cell injection. Despite belief by all of the patients and/or their families that improvements had occurred after stem cell transplantation, EMG recordings and clinical muscle testing revealed no change in any of the patients. Similarly, in the controlled study by Black et al. [4], owners of dogs receiving either stem cells or a placebo for osteoarthritis were asked to rate the improvement they observed in their pet after injection. Owners of dogs receiving stem cells reported a 30 and 40% improvement in a number of parameters after treatment. However, owners of dogs receiving placebo reported a 20-30% improvement in these same parameters. These results are not surprising, given the claimsof dramatic improvement with stem cell treatments which likely influence the expectation of human patients and owners of veterinary patients receiving the stem cell injections.

The lack of proven efficacy and potential negative effects that may result from unproven stem cell therapies prompted the International Society for Stem Cell Research (ISSCR) to form a Task Force of members from 13 countries to establish policies and guidelines for regulating translation of stem cell therapies from basic and translational studies to the clinic. The Task Force drafted the "Guidelines for the Clinical Translation of Stem Cells" (http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf), which provides a framework for basic and preclinical studies to provide necessary information for their translation into the clinic and to facilitate compliance with regulation of cell therapy by the FDA. The Guidelines also address the issue of the potential physical and financial harm that may be done by offering unproven therapies to patients for large sums of money. The field of veterinary medicine has not developed independent guidelines for translation of stem cell therapies to the clinic, but the North American Veterinary Regenerative Medicine Association (http://www.navrma.org/about-navrma) was formed in 2010 to facilitate research and information relating to regenerative medicine applications in veterinary medicine. One of the goals of this organization is to consider policy and regulation of regenerative medicine applications in veterinary medicine, although it is presently unclear how or whether regulation of translation of stem cell therapy in veterinary medicine will differ from the ISSCR Guidelines.

The ISSCR Guidelines emphasize the importance of demonstrating efficacy in preclinical studies in small and large animal models prior to embarking on stem cell therapy in the clinic. Preclinical studies are also important for testing multiple conditions for stem cell treatments to optimize the likelihood of a positive outcome. Parameters important to test in preclinical studies include timing or route of delivery of stem cells, localization and survival of donor cells after injection, and assessment of reproducibility and how it relates to the content of the adipose-derived stromal vascular fraction or bone marrow derived mononuclear cells. Underscoring the important of preclinical studies in veterinary medicine, two published reports by Guest et al. [11] may offer insight into the transient benefit observed with MSC injection in horses with tendon injuries and dogs with osteoarthritis. Guest et al. [11] examined the survival and localization of equine MSC and embryonic stem cells (ESC) following injection into injured tendon in horses. Although equine MSC survive initial injection into the tissue and a small number of cells integrate into the tendon, only 5% or less are present 10 days following injection [8,11]. In contrast, equine ESC survive up to 90 days following injection into injured tendon, and also appear to integrate into the tendon [8]. These data indicate that MSC may not be the optimal choice for treatment of damaged tendon because of their limited survival *in vivo*. Alternatively, repeated injections of MSC may be necessary to extend or enhance benefit from the cells. These data may also be indicative of the why improvement in tendon fiber architecture observed in some horses following injection of MSC was transient [7], and may also be related to the transient relief from pain on manipulation observed following MSC injection into dogs with osteoarthritis [4]. These preclinical and clinical data also correspond to findings in human patients, in which MSC promote indirect, transient benefit by production of trophic factors but do not survive long following transplantation. As a result of observations of short-lived benefit in clinical studies in human medicine, a number of research projects are focusing on enhancing MSC survival and thereby prolonging the beneficial effects of MSC *in vivo*. Given the significant but transient benefit reported with MSC in dogs with osteoarthritis [4] and in histological appearance of damaged equine tendon [5,6], basic and preclinical studies focusing on improving MSC survival after injection would also likely be of benefit to the veterinary field as well.

The current widespread use of stem cells in veterinary medicine has

the potential to yield a wealth of information important in developing cell therapy for humans in addition to improving healing and quality of life for veterinary subjects. However, greater numbers of controlled clinical and pre-clinical studies will be necessary to demonstrate efficacy and determine methods for obtaining optimal results in the clinical setting.

References

1. Lau D, Ogbogu U, Taylor B, Stafinski T, Menon D, et al. (2008) Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. Cell Stem Cell 3: 591-594.
2. Barclay E (2009) Stem-cell experts raise concerns about medical tourism. Lancet 373: 883-884.
3. Dobkin BH, Curt A, Guest J (2006) Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. Neurorehabil Neural Repair 20: 5-13.
4. Black LL, Gaynor J, Gahring D, Adams C, Aron D, et al. (2007) Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. Vet Ther 8: 272-284.
5. Nixon AJ, Dahlgren LA, Haupt JL, Yeager AE, Ward DL (2008) Effect of adipose-derived nucleated cell fractions on tendon repair in horses with collagenase-induced tendinitis. Am J Vet Res 69: 928-937.
6. Schnabel LV, Lynch ME, van der Meulen MC, Yeager AE, Kornatowski MA, et al. (2009) Mesenchymal stem cells and insulin-like growth factor-I gene-enhanced mesenchymal stem cells improve structural aspects of healing in equine flexor digitorum superficialis tendons. J Orthop Res 27: 1392-1398.
7. Wilke MM, Nydam DV, Nixon AJ (2007) Enhanced early chondrogenesis in articular defects following arthroscopic mesenchymal stem cell implantation in an equine model. J Orthop Res 25: 913-925.
8. Guest DJ, Smith MR, Allen WR (2010) Equine embryonic stem-like cells and mesenchymal stromal cells have different survival rates and migration patterns following their injection into damaged superficial digital flexor tendon. Equine Vet J 42: 636-642.
9. Herthel DJ (2001) Enhanced suspensory ligament healing in 100 horses by stem cells and other bone marrow components. AAEP Proceedings 47: 319-321.
10. Pacini S, Spinabella S, Trombi L, Fazzi R, Galimberti S, et al. (2007) Suspension of bone marrow-derived undifferentiated mesenchymal stromal cells for repair of superficial digital flexor tendon in race horses. Tissue Eng 13: 2949-2955.
11. Guest DJ, Smith MR, Allen WR (2008) Monitoring the fate of autologous and allogeneic mesenchymal progenitor cells injected into the superficial digital flexor tendon of horses: preliminary study. Equine Vet J 40: 178-181.