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Indication and results for intra-articular use of stem cells

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A mesenchymal stem cell (MSC) was a term first coined as a synonym for a mitotically quiescent primordial germ cell. MSCs have been described as the natural units of embryonic generation or adult regeneration of a variety of tissues. Recognition of the potential of MSCs in musculoskeletal disease is typified by the landmark paper of Pittenger, et al (1999) who described MSCs as multipotent cells that are present in adult bone marrow and can replicate as undifferentiated cells and have the potential to differentiate into lineages of mesenchymal tissue including bone, cartilage, fat, tendon, and muscle (Pittenger et al 1999). Early work using labeled mesenchymal stem cells (MSCs) has shown that they have an affinity for damaged joint tissue and in vivo studies have confirmed their ability to localize and participate in repair in damaged joint structures, including cruciate ligaments, menisci and cartilage lesions. (Frisbie et al 2009). Isolation of MSCs from the marrow or digested tissue extracts is most commonly achieved by simple adhesion and proliferation of MSCs to tissue culture surfaces. This achieves a significant, if not homogenous, MSC population but near-homogenous MSCs populations have been reported from adhesion sorting (Ferris et al 2010). Research continues on more rigorous methods of identifying stem cells through use of cell surface antigens such as cluster differentiation (CD factors 34 and 44). Consensus on an exact antigen profile of an MSC has not yet been reached.

Most of the in vivo clinical studies in utilizing MSCs have focused on meniscal repair in either carriers or scaffolds or direct intra-articular injection. One study involving total medial meniscectomy and anterior cruciate ligament transaction in goats followed by intra-articular injection of bone marrow-derived cultured standard MSCs showed regeneration of medial meniscal tissue, as well as a decrease in OA that was substantial in 7 of 9 cases. The scope of this study did not allow evaluation of a direct effect on the articular cartilage or progression of OA. However the demonstration that meniscal tissue could regenerate and OA secondary to cruciate sectioning and medial meniscectomy could be reduced prompted us initiating a clinical study for soft tissue injuries in the stifle of horses (see below).

Work by Frisbie et al (2009) at CSU in the osteochondral fragment model showed a significant improvement in synovial fluid prostaglandin E2 (PGE2) levels in response to treatment with bone-derived MSCs, but not with adipose-derived MSCs. There was also a significant negative response via an increase of synovial fluid TNF concentrations in response to adipose-derived cells. As a result of the equine study it was suggested that MSCs by themselves do little to counteract the progression of OA mediated by enzymatic degradation and joint debris and that modification of MSCs is probably needed for them to be useful in OA. There may also be a timing problem in that MSCs appear to have trophism for damaged cells including fibrillated articular cartilage, but in the CSU study the degree of fibrillation was potentially not sufficient for MSCs injected at day 14 to have an effect. We have concluded however that based on the goat meniscal regeneration study; the use of MSCs might be indicated when there is soft tissue damage in the joint. We therefore initiated a prospective, multicenter trial. The goal of the study was long-term follow-up in horses with severe intra-synovial lesions (mainly meniscal, cartilage or ligamentous) treated with autologous bone marrow-derived MSCs. Follow-up information in 40 cases revealed that 15 horses returned to or exceeded their previous level work, 14 horses returned to some level of work and 11 horses were unable to return to work. Ten horses were still re-conditioning at the time of follow-up. There were not controls in this study but we have a fair amount of clinical experience knowing the prognosis after arthroscopic surgery in which there is tearing of the meniscus, meniscal ligaments or cruciate ligaments and intra-articular MSCs definitely improves the results on clinical follow-up. Results of this study support future controlled trials to be undertaken for further definition of the optimal use of intra-articular MSCs in horses.

There has been considerable interest in the possibilities of aiding articular cartilage repair with MSCs. Initial work in our laboratory comparing the ability of adult equine bone marrow derived and adipose derived progenitor cells on chondrogenesis have been conducted. Cells were evaluated after expansion in monolayer culture and then transplantation into agarose or peptide gels. They were cultured under chondrogenic conditions (TGF-β) (Kisiday et al 2008). Histologic analysis of peptide hydrogels seeded with cultured expanded cells with TGF-β and cultured in TGF-β for 21 days revealed significantly increased staining with toluidine blue (as a marker of aggrecan content) and significantly increased staining on immunohistochemical examination for Type II collagen (there was virtually no staining for Type II collagen with adipose-derived cells). Glycosaminoglycan (GAG) accumulation in hydrogel seeded with cultured expanded cells and
TGF-\(\beta\) after 21 days of culture showed significant enhancement of GAGs and with no significant enhancement in agarose and significant enhancement on peptide gels with minor enhancement with adipose cells. An in vivo study with MSCs in fibrin implanted into chondral defects in the lateral trochlear ridge of the horse there was early benefit demonstrated at 30 days but no significant differences were noted when MSCs plus fibrin was compared to fibrin alone at 8 months (Wilke et al 2007). We have recently explored the value of intra-articular bone marrow-derived MSCs injected 4 weeks after creation of microfracture defects on the medial femoral condyle. There was enhancement of the repair tissue firmness at 12 months as well as a significant increase in aggrecan staining with immunohistochemistry (Frisbie, et al 2010).

REFERENCES