Bone Marrow Derived Mesenchymal Progenitor Cell Therapy for Tendon Regeneration in a Large Animal Natural Disease Model

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INTRODUCTION: Exercise-induced tendinopathy is common in human and equine athletes. Healing results in a stiffer disorganised scar tissue, reducing performance and leading to re-injury. Mesenchymal progenitor cells (MPC's) offer the potential for tendon regeneration and improved functional outcome associated with a regenerated matrix and is used clinically in injured equine superficial digital flexor tendons[1] (SDFT). An evaluation of efficacy in clinical disease cases at the tissue level has not yet been reported. Hypothesis: Autologous MPC implantation reduces re-injury rates compared to conventionally managed horses and induces greater normalization of the tendon matrix.

METHODS: *Experimental:* 8 horses with naturally occurring SDFT injury were used. Autologous bone marrow derived MPCs were expanded *in vitro,* suspended in citrated bone marrow supernatant and $1x10^7$ implanted in the damaged SDFT of 4 horses under ultrasound guidance. Saline was injected into 4 controls. Horses received controlled exercise and were euthanased after 6 months. Non-destructive mechanical testing assessed structural stiffness of the SDFT. Morphological and compositional analysis was performed. *Clinical:* MPCs were implanted into 25 National Hunt racehorses with naturally occurring SDFT injury. Re-injury rate at 2-year follow-up was compared with 17 conventionally treated National Hunt racehorses[2].

RESULTS: *Experimental:* MPC-treated SDFT had greater elasticity than saline-treated SDFT ($p<0.05$). Cross-sectional area of MCP-treated tendons was lower than saline-treated tendons ($p<.0.05$). Histologically, MPC-treated tendons had improved cellularity and organisation scores at the injured site and were comparable to uninjured sites of the treated tendon (Fig 1). In the MPC-treated SDFT collagen-linked fluorescence was higher and DNA content lower than the saline-treated SDFT ($p<0.05$). Collagen and GAG content was lower in MPC-treated SDFT but not significantly. *Clinical:* Re-injury rates for MPC-treated horses was lower (24%) than in conventionally managed horses (56%; $p<0.05$).

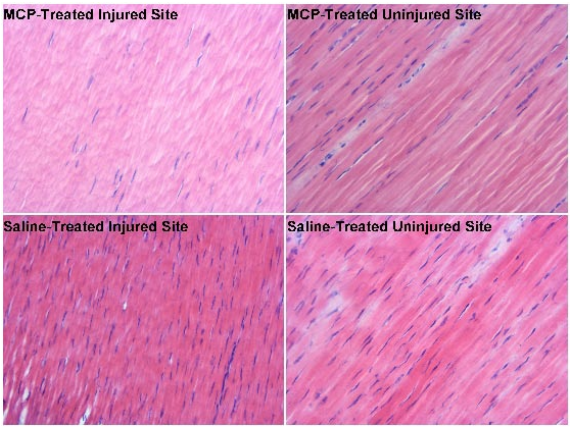

Fig 1: Representative H&E images of MCP-treated and saline-treated SDFT.

DISCUSSION & CONCLUSIONS: Markers of regeneration have not been identified in tendon but a normalisation of biomechanical (reduced stiffness), histological (lower scores) and compositional parameters (lower GAG content) towards those levels in normal (or less injured) tendon could be considerable surrogate markers of regeneration. The evidence of optimised healing seen experimentally is supported clinically where a reduction in re-injury rate was found. MPC implantation results in a tissue more like normal matrix rather than fibrous scar tissue formed after natural repair. These findings support the potential use of MPC's in human tendon and ligament injuries which share many similarities with equine tendinopathy.

REFERENCES: [1]Smith RK et al., Equine Vet J 2003, 35:99-102. [2]Dyson SJ, Equine Vet J 2004, 36:415-419.

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