State of the Art

Chaired by Roger Smith

14.00–14.30

Regenerative therapy for equine joint disease - where are we at?

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Regenerative therapies are based in biologics which capture the body's natural ability to heal. There are several types of regenerative therapies being used including platelet rich plasma (PRP), stem cells of several varieties (only bone marrow concentrate is discussed herein), and autologous conditioned serum (ACS)/interleukin-1 receptor antagonist protein (IRAP). Each of these therapies is relatively new so there is very limited clinical data accumulated to date, and none published on naturally occurring joint disease in equine patients.

Autologous conditioned serum (ACS)

ACS was probably the first biologic to be tested in horses. ACS is generated through the same process as IRAP, but for primarily legal reasons, it is called ACS. It is thought to act by blocking the receptor to the inflammatory cytokine interleukin-1 (IL-1). When injected intra-articularly into horses with surgically created synovitis/early arthritis, ACS resulted in decreased synovial hyperplasia and lameness compared to placebo treated groups (Frisbie *et al.* 2007). There is a newer generation of ACS termed IRAP II which boasts increased IRAP levels and is presently being tested by the equine group at Colorado State University.

Platelet rich plasma (PRP)

PRP is defined as plasma with a 2 or more fold increase in platelet concentration above baseline levels or >1.1 x 10^6 platelets/µl (Miller *et al.* 2007). PRP is generated primarily by centrifugation or gravity filtration. There are differences in the volume of autologous blood required, time and speed of centrifugation, addition of an activating agent, leucocyte concentration, method of delivery and qualitative/quantitative differences with respect to final PRP volume and final platelet and growth factor concentrations between the available systems. Overall, the final PRP platelet concentration is 2–8 times over baseline. It is important to recognise and understand that there are obvious differences between types of platelet concentrates being used and the general term/abbreviation PRP will be used herein.

The concept that PRP would improve joint disease is based on the physiological role of platelets in wound healing. Through a modulation of the inflammatory response, promotion of local angiogenesis, attraction of fibroblasts and local stem cells to the site of injury and an induction of autocrine growth factor production by uninjured adjacent cells, platelets and their products are instrumental in normal tissue repair and regeneration.

Once isolated, the PRP can be injected into a joint with or without an activating (clotting) agent. The addition of bovine thrombin to the PRP sample just prior to or during injection is used in some systems to activate platelets resulting in initiation of the clotting cascade. Clotted PRP serves as a fibrin matrix which serves as a scaffold for tissue repair and a reservoir for retention and slow release of growth factors.

The application of PRP in joints is relatively new and therefore there are limited publications investigating its use. Chondrocytes and MSCs exposed to PRP both have significantly increased cell proliferation and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared to controls (Akeda *et al.* 2006; Mishra *et al.* 2009). Synoviocytes from OA patients cultured in PRP demonstrated significantly increased hyaluronic acid production and secretion, suggesting that PRP could potentially serve as an endogenous source of chondroprotection and joint lubrication following intra-articular application (Anitua *et al.* 2007). There are several human clinical studies supporting the use of PRP for arthritis, but no horse data is presently available in peer reviewed form. There are several promising abstracts and conference proceedings reporting its use, but again, nothing yet in peer reviewed form.

Bone marrow concentrate (BMC)

Bone marrow concentrate is generated through centrifugation of bone marrow aspirate. The advantage of BMC over PRP is that it contains MSCs which have demonstrated utility for regeneration of cartilage and other tissues of the musculoskeletal system. Like PRP, BMC is a fully autogenous biologic that can be generated patient-side and when clotted, form a scaffold. Also, like PRP, BMC contains platelets and therefore is a rich source of growth factors including PDGF and TGF-B.

In an equine model of 15 mm diameter, full thickness cartilage defects, BMC resulted in significantly improved cartilage repair compared to microfracture using short-term arthroscopic inspection and longer-term macroscopic, histological and quantitative magnetic resonance imaging analyses (Fortier *et al.* 2010). Differences between BMC and microfracture observed arthroscopically at 12 weeks persisted at 8 month evaluation. In particular, repair tissue in BMC-treated defects was much better integrated into surrounding normal cartilage, the tissue was thicker, and had a smoother surface. Like PRP, BMC is being used as a primary intra-articular joint injection, but no clinical data has been reported on its use.

In summary, regenerative therapies are showing tremendous promise for the treatment of equine joint disease, but the therapies are too new to draw any firm conclusions regarding specific indications, contra-indications, or prognosis following their use.

References and further reading

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