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Recent Advances in Orthopaedics

Chaired by Alistair Barr

11.30–12.10

Update on medical treatment of joint disease

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In recent years the armamentarium of medication available to equine practitioners for osteoarthritis (OA) therapy has rapidly expanded but the evidence available for efficacy of some of the more novel products is sparse. The goal of this presentation is to review and appraise emerging and new knowledge in the field for the equine practitioner. Selected recent therapeutic approaches are briefly described here and a more comprehensive overview of new knowledge related to the more traditional therapeutics will be made in the main presentation.

AUTOLOGOUS CONDITIONED SERUM (ACS OR 'IRAP')

The pro-inflammatory cytokine interleukin-1 (IL-1) induces cartilage matrix destruction in OA. In healthy joints there is a balance between IL-1 and its antagonist, interleukin-1 receptor antagonist (IL-Ra). In OA it is believed that there may not be enough IL-Ra to block the destructive effects of IL-1. Hence, increasing the levels of IL-1Ra in an OA joint is a rational therapeutic strategy. Researchers recently discovered that human blood mononuclear cells, stimulated with glass beads, produced many anti-inflammatory cytokines including IL-1Ra (up regulated 140-fold). However, the increase in IL-1Ra measured in equine serum, employing similar methods to condition the sample, was only approximately 2-fold. Despite this low increase, a significant improvement in lameness (at 70 days) and synovial membrane histopathological score was observed with IRAP treatment (4 weekly injections of 5 ml), but no protective effects on articular cartilage were detected when compared to a placebo using an equine experimental model of OA (Frisbie *et al.* 2007b). IRAP therapy may be classified as a symptom-modifying therapy but does not appear to arrests or reverse the degenerative OA processes in cartilage (disease-modification). A series of questions need to be answered concerning this therapy. Perhaps most important, considering the cost, is it better than other SMOADS (symptom-modifying OA drugs) that we currently possess (NSAIDS, corticosteroids, HA)?

STEM CELLS

A recent blinded, experimentally controlled study, evaluated the use of adult stem cells delivered by IA injection (bone marrow and adipose derived) for the treatment of OA in a well characterised equine model (Frisbie *et al.* 2006). No improvement was observed in lameness, inflammation parameters or cartilage degeneration on histological assessment when compared to a placebo. Consequently there is currently no current strong published evidence to support the use of stem cell therapy for equine OA.

GLUCOSAMINE

The levels of glucosamine attained in equine serum (oral bioavailablity of 2–5%) and synovial fluid are very low following oral administration (Laverty *et al.* 2005) now shedding doubt on many of the previously reported beneficial effects identified *in vitro* (observed at doses far higher than those achieved clinically). Our laboratory has shown that the levels of glucosamine attained in the joint are higher in the presence of inflammation (Meulyzer and Laverty, unpublished data). At the levels we have measured, glucosamine could improve proteoglycan synthesis and have anti-inflammatory effects (reduce COX2, and cartilage degrading enzymes) based on emerging *in vitro* study results (Chane *et al.* 2007). To date there have been no clinical studies on the efficacy of oral glucosamine alone for OA therapy in horses. Information from other animal models of

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OA investigated in our laboratory suggest very modest, positive effects of long-term treatment on articular cartilage and subchondral bone degeneration in experimental OA (Tiraloche *et al.* 2005; Wang *et al.* 2007). There is also a debate raging in the human field concerning the efficacy of glucosamine sulphate vs. glucosamine hydrochloride and it has been suggested that the absorption of these 2 compounds may be different and account for the beneficial effects observed with the former. We have now shown that the human glucosamine sulphate preparation used in Europe attains higher levels than glucosamine hydrochloride in the joints (Meulyzer *et al.* 2008) after oral administration, but we believe that it was due to palatability compounds added to the formulation.

COMBINATION OF GLUCOSAMINE SULPHATE AND CHONDROITIN SULPHATE

Chondroitin sulphate is also a component of the cartilage matrix and manufactured from shark and bovine cartilage. There has only been one clinical experimental study in horses assessing the effects of a chondroitin sulphate preparation and no beneficial effects were noted .

However, 3 equine clinical trials evaluating combinations of glucosamine hydrochloride and chondroitin sulphate for OA therapy have been reported and all reported beneficial effects on symptoms of joint disease. The most recent study (Forsyth *et al.* 2006), reported significant improvements in lameness and joint motion in older horses suggesting that the combination is a SMOAD.

AVOCADO-SOYBEAN UNSAPONIFIABLES (ASUs)

ASUs are neutraceutical compounds composed of unsaponifiable fractions of avocado and soybean oil (1:2 ratio). Recent *in vitro* studies on equine tissues indicate that ASU, when combined with glucosamine and chondroitin sulphate, may have an anti-inflammatory effects on stimulated equine chondrocytes and osteoblasts (Au *et al.* 2007). However it is difficult to extrapolate these findings to the clinical setting as there is no information available on the pharmacokinetics of ASUs and the levels attained *in vivo* are unknown. To date there has been one blinded controlled study assessing the efficacy of ASU for the treatment of experimental equine OA (Kawcak *et al.* 2007). A statistically significant anabolic effect was detected in articular cartilage from OA joints in treated animals (increased proteoglycan synthesis when compared to placebo-treated animals). It was also reported to have a beneficial effect on the combined gross cartilage and synovial membrane score in OA joints at necropsy but when the cartilage scores were analysed alone no significant effect of treatment was observed. The synovial membrane haemorrhage score was not reported alone. No significant effects of treatment with ASU on clinical signs of lameness were observed or on the histological assessment of cartilage and synovial membrane parameters. Taken together, these findings suggest that ASU administration may provide a partial chondroprotection i.e. a change detected at the molecular level (increased cartilage matrix proteoglycan synthesis), but not detected on histology or gross assessment of the cartilage in the OA joints of treated animals when compared to placebo treated. No symptom modifying effects were observed with this compound.

REFERENCES

Full reference list will be supplied on request (sheila.laverty@umontreal.ca).

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