Recent Advances in Equine Osteoarthritis
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Introduction

It is widely recognized that osteoarthritis (OA) is the most common cause of chronic lameness in horses and that it places a significant burden on the equine industry due to the cost of treatment and loss of use of affected animals. Depending on the disease definition and target population, the reported prevalence of OA varies. It was reported at 13.9% in a cross-sectional survey of horses in the UK, but at 97% (defined by loss of range of motion) in a group of horses over 30 years of age. Among Thoroughbred racehorses that died within 60 days of racing, 33% had at least one full-thickness cartilage lesion in the metacarpophalangeal joint, and the severity of cartilage lesions strongly correlated with a musculoskeletal injury leading to death. The majority of the horses in this study were less than 3 years of age, emphasizing the importance of OA in young equine athletes. Unfortunately, a major challenge in managing OA is that by the time clinical signs occur (i.e. lameness), irreversible cartilage damage has already occurred. Although novel treatment modalities are being tested that show promise for modulation of the course of disease, such as viral vector delivery of genes that produce anti-inflammatory products, there are no generally accepted treatments that can be used to reliably reverse its effects once a clinical diagnosis has been made. Thus, there is much research effort being put both into the development of improved diagnostic markers and the development of new treatments for this devastating disease.

Pathophysiology of Osteoarthritis

Osteoarthritis is a heterogenous condition leading to a common endpoint – the degeneration and loss of articular cartilage within a joint. Trauma, either as a single episode or repeated events, is considered to be the initiating factor in disease. “Trauma” in this case may reflect supraphysiologic (“abnormal”) forces on normal tissue or physiologic (“normal”) forces on abnormal tissue, and does not have to directly affect the articular cartilage. The joint is, in fact, an organ comprised of many tissues, and injury to any of these can lead to OA. For example, there is good evidence that inflammation originating in the synovium or joint capsule can initiate a catabolic cascade that eventually results in cartilage destruction, even in the absence of initial structural damage to the cartilage itself.

Normal articular cartilage is comprised of chondrocytes embedded in a dense extracellular matrix (ECM). The ECM is primarily made up of Type II collagen, which provides the tensile strength of this tissue. In the adult, collagen fibrils are arranged in a characteristic arcade pattern, parallel to the joint surface in the superficial layers of cartilage, and perpendicular to the joint surface in the deeper layers. Cross-linking between collagen fibrils adds strength and provides a framework in which other matrix molecules, including hyaluronan and proteoglycans, are embedded. Proteoglycans are comprised of a protein core (often aggrecan) and numerous chondroitin sulfate and keratin sulfate side chains (glycosaminoglycans, or GAGs) that give it a “bristle brush” appearance. These side chains are highly hydrophilic; in fact, 70-80% of the “wet weight” of cartilage is due to water. When the joint is loaded, water is squeezed out of the ECM, aiding in lubrication. When the joint is unloaded, the water is drawn back in by the GAGs; this action provides articular cartilage with much of its shock absorptive abilities. Although some turnover of ECM molecules is normal, in OA, enzymatic damage to these molecules by
inflammatory cytokines outstrips the ability of the body to replace them, ultimately resulting in tissue breakdown.

**Systemic Medications and “Joint Health” Supplements**

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone for medical management of OA. Horses may be maintained on a daily dose, or treated on an “as needed” basis, depending on the level of work they are being asked to do and the severity of their disease. However, the potential for side effects, particularly related to the gastrointestinal tract and kidneys, makes chronic dosing a less than ideal treatment option. The mechanism of action for NSAIDs is blockage of the cyclooxygenase (COX) pathway, which results in reduced prostaglandin formation. There are two known major COX isoenzymes; COX-1 is constitutively expressed and is important for normal tissue homeostasis, while COX-2 is inducible and has been largely associated with inflammation. Phenylbutazone and flunixin meglumine are non-specific COX-inhibitors, and it is their inhibition of COX-1 that has been linked to the formation of gastrointestinal ulcers. Within the past decade, NSAIDs that are more selective for COX-2 have been introduced, and these have been demonstrated to have fewer side effects than the nonspecific COX inhibitors. Firocoxib is a COX-2 inhibitor licensed for horses under the trade name Equioxx®. In a study in horses with naturally-occurring OA, firocoxib was found to be effective at reducing lameness over the 14 day study period; in a separate study, it was found to be approximately equal in effectiveness to phenylbutazone. There is a chewable tablet form of firocoxib available for dogs (Previcox®) that some owners prefer to Equioxx® paste because of cost. A recent study showed that both formulations were effective at suppressing the COX pathway under experimental conditions in horses; however, veterinarians need to be aware that use of the dog formulation in horses is not currently considered to be a legal off-label use of this drug in most situations because a licensed equine form is available.

Performing an internet search for “joint supplement horse” returns over 550,000 hits. The majority of these supplements (or “nutraceuticals”) contain glucosamine, chondroitin sulfate, methylsulfonylmethane (MSM), or sodium hyaluronate/hyaluronic acid, either alone or in some combination. However, despite their popularity, there is relatively limited scientific evidence for their effectiveness. Some studies have shown improvements in stride characteristics of treated horses, while others have shown no benefits over moderate exercise alone. A review found that the majority of *in vivo* studies of glucosamine supplements were of poor quality, particularly in regards to low statistical power and lack of blinding. Moreover, the actual content of some commercial products has been called into question by a study that found actual levels of glucosamine to be between 0% and 220% of label claims. Of 23 products tested, 9 (39%) had less glucosamine than they were supposed to have based on the label, and 4 of these had less than 30% of the expected amount.

There is also relatively little scientific literature examining the effects of intravenous hyaluronic acid (Legend®) or intramuscular polysulfated glycosaminoglycans (PSGAGs; Adequan®) in horses with OA, despite widespread anecdotal reports of their effectiveness. All studies examining these treatments have been performed in an experimental model of carpal OA. Intramuscular PSGAG administration had no effect on lameness, the degree of cartilage damage, subchondral bone parameters, or levels of biochemical biomarkers in the synovial fluid. Treatment with intravenous hyaluronic acid reduced lameness scores and resulted in less evidence of inflammation within the joint compared to untreated controls, but the amount of cartilage damage was equivalent between treated horses and untreated controls. Conversely,
treatment with a combination of sodium pentosan polysulfate, N-acetyl glucosamine, and sodium hyaluronan (Pentosan®) resulted in reduced macroscopic pathology in the joint, but did not improve clinical signs of OA. Interestingly, the PSGAG studies used extracorporeal shockwave therapy (ESWT) as a control comparison; this modality improved lameness scores, but did not affect pathology within the joint.

Intravenous tiludronate (Tildren®) has been proposed as a treatment for osteoarthritis, particularly of the distal hock joints. A single double-blind placebo-controlled trial has been published, and reported improved lameness in horses treated with one dose of Tildren at 1mg/kg IV compared to placebo controls. However, although the difference between groups was statistically significant, the clinical significance of this difference is less clear (mean lameness of 2.6 ± 1.7 compared to 3.3 ± 2.0 on a 10-point lameness scale). All horses were also subjected to a controlled exercise program, which could have contributed to the reduction in lameness in both groups compared to baseline (4.5 ± 1.1).

Intra-articular Medications

Corticosteroids are the most commonly used intra-articular anti-inflammatory agent. The most commonly used preparations are triamcinolone acetonide (TA) and methylprednisolone acetate (MPA), although betamethasone has also recently returned to the market. Corticosteroids are considered to work “upstream” of NSAIDs, blocking the formation of prostaglandins by inhibiting the production of phospholipase A₂. Corticosteroids may also exert beneficial effects on the joint by reducing the number and activity of neutrophils. In vitro and experimental in vivo models have suggested a potential detrimental effect of MPA on articular cartilage, albeit at doses that exceed those commonly used in practice. In contrast, there is some evidence for a chondroprotective effect for TA. Largely based on this evidence, there is a strong trend for practitioners to reserve MPA use for low-motion joints, or in joints that already have severe pathology, while TA is preferred for high-motion joints, or earlier in the course of disease. However, anecdotally, MPA has a more prolonged effect on lameness, and for that reason is preferred by some veterinarians. There is little evidence from naturally-occurring disease to guide this decision, although one retrospective study showed no difference in outcome between MPA and TA use in horses with distal hock OA. MPA and TA are also used in combination with each other, although TA is more commonly combined with hyaluronic acid. Laminitis is often cited as a potential side effect of intra-articular corticosteroids, particularly TA, but the scientific evidence suggests that the risk is very low in horses that are otherwise normal. Septic arthritis has been reported as a rare complication (7.8 events per 10,000 injections) after intra-articular injection of corticosteroids, and for this reason, many veterinarians chose to add amikacin to their treatment regimen, although adherence to aseptic technique is likely to be the most important defense against this adverse event. Non-septic joint “flares” are also rarely reported; these tend to respond to systemic anti-inflammatory medication.

HA and PSGAG, discussed above as systemic medications, can also be used intra-articularly. Both improved histologic markers of OA in an experimental model, primarily reflecting decreased inflammation, although lameness was not improved. Similar findings were reported in a recent double-blind placebo-controlled study of HA in horses with naturally-occurring OA in the fetlock joint. In contrast, an older report of PSGAG use in naturally-occurring coffin joint OA demonstrated more reduction of lameness after 3 treatments with intra-articular PSGAG than after a single dose of MPA (although a number of factors were identified as playing a role in treatment success/failure). It should be noted that intra-articular PSGAG has a
known increased risk of post-injection sepsis and should always be administered with 125mg amikacin. It is perhaps for this reason that it is currently less popular than HA. There has been much debate about the utility of combining HA with a corticosteroid (generally TA), and about the importance of the molecular weight of the HA product used. HA produced in healthy joints is of high molecular weight, around 3 million Daltons, prompting the recommendation to use high molecular weight HA in intra-articular injections. *In vitro* work supported this recommendation; however, the half-life of both high- and low-molecular weight HA is less than 12 hours, and exogenous HA can no longer be detected in synovial fluid 24 hours after administration. Although numerous anecdotal reports and published case series have supported the use of HA in combination with a corticosteroid, a recent multicenter trial found no benefit of HA + TA over TA alone three months after treatment (success in this study was defined as return to previous level of performance).

**Biological Therapies**

Interleukin-1 (IL-1) is widely accepted to be one of the key players in the pathophysiology of OA, and it exerts its effects through binding with its receptor. Interleukin-1 receptor antagonist (IL-1ra) protein blocks this binding, and thereby has anti-inflammatory effects. Adenovirus-mediated gene therapy with the IL-1ra gene results in increased production of IL-1ra protein within the joint. This treatment was shown in an experimental model to result in improved clinical signs, less severe gross pathology, and fewer radiographic abnormalities when compared to any other intra-articular treatment. However, the robust immune response to the adenovirus vector precludes repeated use of this therapy; more recent work has focused on fine-tuning of an adeno-associated virus vector that will lend itself to more widespread clinical application of this treatment.

Direct intra-articular administration of the IL-1ra protein has been available for approximately 10 years. Known as autologous conditioned serum (ACS), or by the trade name of the first commercial product, IRAP®, this therapy actually administers a milieu of growth factors normally found in serum, but at enriched levels. Despite strong anecdotal support for the use of ACS, there is little published literature examining its effects. In an experimental model of OA, treatment with ACS both improved lameness and reduced cartilage fibrillation. Treatment with ACS is typically spread over 3 or 4 doses, spaced 7-10 days apart, although some recently available products claim equivalent clinical outcome after a single intra-articular injection. The process by which ACS is prepared does affect the cytokine profile of the product, and this could result in differences in clinical outcome. The “ideal” profile has not been determined, making it difficult to make evidence-based recommendations for one product over another. There is also debate over the appropriate timing of ACS use, with some practitioners preferring to use it as a first line treatment, and others waiting to use it until intra-articular corticosteroids are no longer effective. From a biological perspective, it would seem that the former approach would be best given the potential chondroprotective effects of ACS; however, this supposition needs to be substantiated by experimental and/or clinical evidence.

Platelet rich plasma (PRP) is defined as a plasma product containing significantly more platelets than whole blood; however, no specific concentration is set, and it varies widely between processing techniques. PRP is most commonly used for the intra-lesional treatment of tendon injuries, but its use in arthritic joints has been reported anecdotally. When injected into healthy joints, PRP induces a mild, transient inflammatory response; this appears to be most pronounced for thrombin-activated PRP. Minimal increases in growth factors and anti-
inflammatory compounds have been measured after a single injection. To date, there are no scientific reports looking at the effects of PRP in naturally-occurring OA, although human data suggests that there could be a benefit (mechanism unknown).

Bone marrow concentrate (BMC) is created by centrifugation of a bone marrow aspirate and contains low numbers of mesenchymal stem cells in addition to a milieu of growth factors. A major advantage of BMC over stem cell preparations is that it can be prepared patient-side and injected on the day of collection. In an experimental model of cartilage defects, BMC-treated horses had significantly improved cartilage repair compared to microfractured controls. However, there are no published reports of BMC in clinical use.

Stem cells are undifferentiated cells that have the ability to self-renew. To date, they have been found in nearly every tissue investigated, even those with poor regenerative capacity, including cartilage. These adult stem cells (or mesenchymal stem cells, MSC) are “multipotent” – that is, they have the ability to differentiate down several pathways depending on their local environment. However, MSCs have been shown to exhibit a predilection for certain lineages depending on their origin. Stem cell expansion from both fat and bone marrow aspirates are commercially available, and anecdotal reports suggest that they reduce lameness in horses with OA. In an experimental study, horses treated intra-articularly with bone marrow MSCs had lower prostaglandin E\(_2\) levels in synovial fluid than those treated with adipose-derived MSCs. However, no other parameters were improved with MSC treatment when compared to the placebo, leading the authors to question the utility of MSCs as a therapy for OA in the horse. In contrast, a more recent report of outcome in clinical cases treated with bone-marrow derived MSCs suggested that treatment was beneficial, although the study was skewed towards horses with meniscal tears rather than those with chronic OA. The mechanism whereby stem cell therapy might benefit joints affected by OA is largely unknown, although both direct reparative effects and indirect effects via recruitment of growth factors, etc. have been proposed. There is evidence from a donkey model that MSCs have the ability to home in on damaged tissue and become incorporated into repair tissue. However, other studies have shown that the majority of MSCs are rapidly cleared from the injection site. Treatment of experimental cartilage lesions with MSCs has yielded promising results at early time points in a number of studies, but outcomes at long-term follow-up have been disappointing.

Conclusions

The wide range of available treatment options for OA suggests that there is no one best course of therapy – and given the heterogeneity of disease, perhaps this is only to be expected. A comparison of the scientific literature and the “lay” press, however, reveals a dearth of rigorous evidence for many popular therapies. There is a need for large clinical studies – by preference, randomized double-blinded placebo-controlled clinical trials – to lay the foundation for evidence-based recommendations for practitioners. Achieving this goal will likely require the formation of multi-institutional (likely international) consortia, similar to what has been seen in the past decade in human medicine. In the meantime, standardization of case definitions and outcomes will allow more appropriate comparison of results between studies.

Selected references and recommendations for further reading


