How to Select the Most Appropriate Nonsteroidal Intra-Articular Therapy

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1. Introduction
There has been a proliferation of both glycosaminoglycan-type products (hyaluronan [HA] and semi-synthetic preparations of a form of glycosaminoglycan) as well as biological products (platelet-rich plasma, autologous conditioned serum, mesenchymal stem cells) that have become available in the last number of years for intra-articular therapy. Furthermore, there are reports of practitioners using a number of products that are available for systemic treatment of lameness in an off-label manner intra-articularly, for instance, the biphosphonate tiludronate and pentosan polysulphate. For many of these products, particularly the biologics, we have an incomplete understanding of their indications for use, dose, and dosing frequency.

2. Hyaluronan
Of the established pharmaceutical products, HA is the only product the author uses with any regularity for intra-articular administration. HA is a glycosaminoglycan, and it is a normal component of the articular cartilage, synovial membrane, and synovial fluid. It plays an important role in the formation of proteoglycan aggregates, necessary for maintaining the compressive stiffness of cartilage, and is predominantly responsible for the viscoelasticity of synovial fluid. It also provides lubrication within the joint. Within the synovial membrane, HA acts to prevent the entry of certain plasma components into the joint cavity (steric hindrance). The concentration of endogenous HA has been shown to decrease in osteoarthritic joints.1

The specific role of HA in the treatment of joint disease is uncertain. As a result of steric hindrance, HA has an anti-inflammatory effect. A more direct effect of HA exists in preventing inflammatory cell migration and the production of inflammatory mediators, such as prostaglandins. Moreover, HA may protect the cartilage matrix from the effects of inflammatory mediators and degradative enzymes. I principally use HA in cases of acute synovitis with obvious joint effusion and inflammation but only minor or no radiological signs of joint disease. HA is available as formulations for both intravenous and intra-articular administration. Experimental data from an animal model of osteoarthritis (OA) indicated that intravenous HA treatment did not improve the articular cartilage morphology but did improve lameness and reduced levels of the inflammatory mediator PGE₂ for up to 72 days after treatment.2 Experimental animal model studies published using intra-articular HA have produced
uncertain results, and there are a number of clinical studies indicating potential benefit of such treatment. I normally administer a combination therapy of intra-articular corticosteroids (usually triamcinolone) with HA as a one-off treatment for acute synovitis, although there are no published data regarding additional benefit from this combination in comparison to corticosteroid administration alone. Occasionally, postinjection flares are seen within 24 hours of intra-articular injection of HA.

3. Polysulfated Glycosaminoglycans
Polysulfated glycosaminoglycans (PSGAGs) are a semi-synthetic preparation of a form of glycosaminoglycan (GAG). GAGs are the predominant matrix macromolecule of articular cartilage, with their loss from articular cartilage being evident in osteoarthritis. PSGAG therapy is indicated for early stages of OA. As with HA, the exact mechanism of action of PSGAGs in joints is uncertain. PSGAGs decrease levels of inflammatory mediators in diseased joints and inhibit the effects of some degradative enzymes. They have been shown to have both an anti-inflammatory effect and to stimulate the synthesis of both endogenous hyaluronan within the joint and of proteoglycans within articular cartilage. PSGAG is available for both intramuscular and intra-articular administration. Intra-articular administration has been associated with an increased risk of iatrogenic synovial sepsis, and, as a result, many clinicians will administer the drug in combination with an antibiotic such as gentamicin or amikacin. Acute hemarthrosis can also occur after medication due to the heparinoid effect of PSGAG. There are some clinical data showing efficacy in improving levels of lameness. However, in a number of animal studies using models of OA, the data are conflicting, with different studies showing inconsistent effects. I do not personally use PSGAG at all in intra-articular therapy.

4. Autologous Conditioned Serum
Autologous conditioned serum (ACS) is an example of an available treatment that may become more targeted in the future, when clearer indications are developed. It uses the idea of specific inhibition of deleterious cytokines and mediators using anti-inflammatory substances produced by the animal’s own blood cells. Extrapolation from the human data and recently published equine data suggest that there would be upregulation of interleukin (IL)-1 receptor antagonist, IL-4, IL-10, fibroblast growth factor, and transforming growth factor-β in such serum. Blood from the patient is harvested into a syringe containing chromium-coated beads and incubated. The white blood cells in the blood bind to the glass beads and are stimulated to produce a variety of anti-inflammatory proteins. After incubation, the serum is separated and collected for immediate intra-articular injection or frozen for later use. Controlled data on its efficacy in clinical cases are currently lacking, although in animal models of OA, treated horses showed a significant improvement in lameness and improvement in some parameters of articular morphology. I use it in cases of mild synovitis and early OA, particularly in patients in which corticosteroids may be contraindicated. I also often use ACS to treat periarticular soft tissue injuries such as collateral ligament desmitis of the distal interphalangeal joint, by intraligamentous injection. Further work is required to identify the clinical indications for such therapy.

5. Platelet-Rich Plasma
Platelet-rich plasma (PRP) is increasing in popularity as a therapy in equine lameness practice. A number of systems and techniques are available in the horse for production of PRP, using either centrifugation or filtration. While such therapies are more frequently used in treatment of tendon and ligament injuries, PRP is also being increasingly used for treatment of mild to moderate OA. It is most likely to be beneficial in cases with early cartilage pathology. I do not currently use PRP for joint therapy.

6. Mesenchymal Stem Cells
The use of intra-articularly administered mesenchymal stem cells (MSCs) is currently gaining some attention. There is some compelling evidence for efficacy of such therapy from a goat model of meniscal injury. The mechanism of potential benefit of MSCs is unclear, but they are more likely to have a trophic role rather than a direct structural effect. There are a number of different sources of MSCs, with bone marrow and fat being the most commonly used. We use culture-expanded bone marrow-derived cells and inject approximately 10 million cells into joints, suspended in HA. The exact indication for such therapy is still far from certain. An experimental study using the carpal chip model of OA showed no benefit of such therapy when comparing bone marrow-derived and fat-derived MSCs with control treatments. There are anecdotal clinical data supporting the intra-articular use of MSC therapy in cases of stifle injury, with significant improvement in cases treated with cells, even in the face of very chronic lameness. Our experience with such cells has been poor in any joint with obvious OA changes, but we have seen some significant improvements in horses with stifle pain with minimal radiographic changes.

7. Conclusions
We are in the middle of an interesting era for development of intra-articular therapies. This provides a number of exciting therapeutic opportunities for practicing veterinarians; however, this expansion of options leads to undoubted confusion and uncertainty, as there is currently a lack of a good evidence base with regard to making an appropriate choice of...
intra-articular therapy. Although we do have a wide choice of treatments, it is likely that some currently available treatments will not last the test of time and will ultimately be found to lack clinical efficacy.

References