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# "New approaches in therapeutic joint injections for the arthritic dog"

Osteoarthritis (OA) is a chronic, progressive disease that affects both dogs and cats. It has been noted that up to 20% of adult dogs and 60% of adult cats have radiographic evidence of OA.[1,2] Owners, themselves are becoming increasingly aware that bone and joint problems are and issue with their pet. Much of this increased awareness has come through the use of the Internet and social media. The overall outcome of osteoarthritis is centered on destruction of the articular cartilage and breakdown of the joint. Because of this OA must be thought of as a global disease process rather than an isolated disease entity. There is considerable cross talk among the tissues that make up a joint. For this reason the joint must be thought of as an organ and the final pathway of OA is organ failure of the joint.

OA primarily affects diarthrodial joints. A diarthrodial joint is composed of the joint capsule, synovial lining, articular cartilage, and the surrounding muscles, ligaments, tendons, and bone. The joint capsule is composed of two layers: the outer fibrous layer and the inner subsynovial layer. Both layers have a rich blood and nerve supply. One explanation of pain associated with OA is distention of the joint capsule due to joint effusion. The synovial lining covers ever structure in the joint except for the cartilage/menisci. It provides a low friction lining and is responsible for the production of synovial fluid. Two major cell populations are present in the synovial lining: type A synoviocytes and type B synoviocytes. Type A synoviocytes are macrophage-like cells that are responsible for phagocytosis. The type B synoviocytes have a more fibroblastic-like appearance and are responsible for producing hyaluronan acid (HA) and other enzymes.

The physiology of cartilage is important because damage to chondrocytes will not only lead to death of that particular chondrocyte but also an inflammatory response that creates problems with neighboring chondrocytes. Thus a downward, progressive spiral occurs which leads to destruction of the "work-horse" (chondrocytes) and loss of extracellular matrix production. The loss of ECM production leads to the loss of cartilage's ability to soften and transfer loads to the underlying subchondral bone.

The pathophysiology of OA is described as a non-infectious disorder of diarthrodial joints. It is categorized by deterioration of articular cartilage, bone formation at synovial margins (osteophytes), peri-articular fibrosis, and a localized inflammatory response. For OA to develop there has to be some insult to the articular cartilage such as hip dysplasia, a cranial cruciate ligament tear, elbow dysplasia, or an articular fracture. Once the chondrocyte is damaged the inflammatory cascade begins and is followed by the release of multiple cytokines. The two main cytokines involved with OA are interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). IL-1β is responsible for the breakdown

of the matrix, while TNF-α drives the inflammatory response. Furthermore, prostaglandins are released, particular prostaglandin E2 (PGE2), which increases the release of metalloproteinases (MMPs). MMPs are responsible for the continued breakdown of the ECM.

In summary of OA inflammation: Osteoarthritis is a chronic progressively destructive disease that involves the entire joint. Inflammation is a key component of both joint destruction and pain. Acute pain resolves after the initial injury heals. Chronic pain involves structural changes of the dorsal horn, is more intense than acute pain and more difficult to control. Treatment considerations for osteoarthritis should address inflammation as well as pain.

Radiographs are key to aiding in the diagnosis of OA. However, just as with any diagnostic modality there are limitations. Radiographs only provide bony information, they are taken in a non-weight bearing position, and osteophytes are useful to diagnose OA but they are not pathognomonic for OA. Furthermore, the value of osteophytosis for staging OA is controversial and does not correlate with OA progression. Probably the biggest issue with radiographs is that they do not correlate with clinical signs. The radiographic key features of OA are: osteophytosis, enthesophytosis, effusion, soft tissue swelling, subchondral sclerosis, intra-articular mineralization (especially in cats), and subchondral cyst (rarely seen).

Other additional diagnostic modalities include CT, MRI, and arthroscopy. Arthroscopy is probably the most valuable means to objectively evaluate the cartilage. However, it is a surgical procedure and can be costly to perform. It does allow the evaluation of the cartilage, which can then be classified by the Modified Outerbridge score. One looming question is if you don't perform arthroscopy and radiographs are helpful to diagnose but don't help stage for monitoring for progression of OA is there some type of subjective based assessment? The answer is yes, the Canine Brief Pain Index (CBPI) was developed and validated in 2013 to provide reliable assessment of dogs with OA in terms of staging as well as response to treatment.

A multimodal approach to OA management is needed. Non-Steroidal Anti Inflammatory Drugs (NSAIDS) represent the cornerstone of therapy, but other modalities include intraarticular therapy.

Potential intra-articular therapies include regenerative medicine (platelet rich plasma with or without stem cell treatment), hyaluronic acid, or steroids.

Corticosteroids can have deleterious effects to cartilage, but these are often used in palliative care, or if other options are not financially available. Methylprednisolone acetate has historically been used in these cases for both dogs and horses. A 20mg dose is used for most medium to large breed dogs. I prefer to use triamcinolone which has been shown to have less damage to equine cartilage than methylprednisolone.

Triamcinolone is dosed at about 6-8mg per joint. Both triamcinolone and methylprednisone can be individually repeated up to 4 times per year.

HA is a viscosupplementation that restores the physiochemical properties to the joint. From a molecular standpoint it stimulates production of ECM as well as continued production of HA from resident synoviocytes. It will also inhibit inflammatory mediators. It is important to use a product that closely mimics a dog's HA such as Evervisc from Everost (sold through Patterson). Evervisc is about 2 million Daltons in size and is made from a fermentation process rather than rooster combs. What has been shown is that approximately 80% of dogs respond well to HA, 10% respond fair, and 10% don't respond. The duration of response is about 4-6 months of relief. When compared to regenerative medicine a response of about 9 months is expected following a platelet rich plasma injection and about 12 months or longer following a platelet rich plasma and stem cell injection.

Regenerative medicine is an emerging field for both animals and humans. There are many variables with products and product preparation. In clinic and outside laboratory preparations are available. Each has their own pros/cons to be considered by the clinician. Currently either requires patient donation or baseline cells. An over-the-counter synthetic product is not yet available.

Platelet rich plasma (PRP) has positive effects on angiogenesis and extracellular matrix remodeling, provides fibrin for matrix, a potent source of growth factors, cell proliferation and differentiation and stem cell recruitment and chemotaxis. Results will be patient depending, and may need a series of injections over a few months to maximize effect.

Stem cells can be of bone marrow or adipose tissue origin. Research is not clear as to which is superior at this time. Stem cells are reported to contribute to generating new tissue, chemotactic for progenitor cells, supply growth factors, make extracellular matrix, angiogenesis, anti-apoptosis, anti-inflammatory and are anti-fibrotic. These are usually combined with platelet rich plasma and can last for 9-12 months.

Radioosynoviorthesis (Synovetin OA) is a novel therapy approved for elbow OA management in canines. This is an injection of radioactive Tin-117m that decreases macrophages and subsequently decreases synovitis which is associated with pain and inflammation. Initial research showed about an 92% response rate in mild to moderate cases and 71% response rate in severe cases, with effects lasting 12 months in most cases.

In summary, OA is a chronic progressive disease and the goal of management needs to be to slow and minimize the progression. Any injection is predominantly designed to decrease inflammation and pain. A proper controlled exercise program is still needed for improvement and return to function.

Owners need to be well educated to know that it will progress and there will be flare-ups. Treatment needs to be multimodal and patient centered.

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