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Regenerative Medicine

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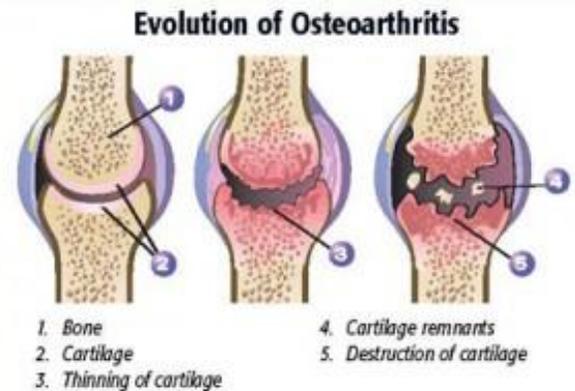
Introduction to Regenerative Medicine

Regenerative medicine is a new therapeutic approach or philosophy to help manage osteoarthritis/degenerative joint disease and soft tissue injuries. These therapies are utilized in both veterinary and human medicine with some promising results. The basic concept is to use materials that come directly from the horse's own body as therapeutic tools. Once the material (blood or stem cells) is collected and modified in some fashion, it is then injected directly back into the horse at the site of a damaged tendon/ligament or joint to help facilitate healing. These techniques have the ability to help soft tissue injuries heal, mostly tendons and ligaments, or help decrease inflammation within joints thus improving the health of cartilage within the joint. This article covers some of the more common therapies currently in use in equine medicine, to include **IRAP, PRP, and STEM CELLS.**

Osteoarthritis/Degenerative Joint Disease Overview

Osteoarthritis/Degenerative joint disease is one of the biggest causes of poor performance and a decreased competitive lifespan in the horse. This is true for all types of equine athletes, from racehorses through to dressage and show horses. Both young and old horses are affected resulting in a loss of athletic ability and possible early retirement.

Osteoarthritis/Degenerative joint disease is characterized by inflammation within the joint space and the synovium (lining of the joint) which sparks an inflammatory cascade resulting in the production of a large amount of inflammatory enzymes. These inflammatory enzymes eventually degrade articular cartilage, which results in the loss of cartilage leading to pain and lameness. In the early stages of this process the symptoms are subtle and insidious. They often go unnoticed, until it has progressed into more advanced destruction. These newer regenerative therapies, and to a certain degree older therapies, are intended to help decrease this inflammatory cascade within the joint. By decreasing this inflammatory cascade the overall health of articular cartilage is greatly improved.



IRAP

IRAP is an effective intra-articular treatment for joint disease. The IRAP system is designed to stimulate the horses' own white blood cells to produce anti-inflammatory mediators and enzymes that can reduce the inflammatory process seen in degenerative joint disease. Blood is collected from the jugular vein and incubated for 24 hours in special syringes that contain glass beads. These beads induce the white blood cells present in the blood to produce and secrete therapeutic anti-inflammatory proteins. After 24 hours, the

blood is centrifuged and the serum is separated from the red blood cell portion. The protein rich serum is then split into individual 3ml to 4ml doses which are frozen for use later. Typically, each collection produces enough serum for 4 to 6 injections. It is important to note that the injections are only suitable to treat the horse from which the original blood was collected. The injections can be stored for up to 12 months from the date of collection.



When injected into a joint, the protein rich serum stimulates a regenerative response from cartilage cells, through a process of cell division and increased cell recruitment. This is actually what sets IRAP apart from other intra-articular treatments for joint disease. The fact that IRAP stimulates cartilage cells means that it has a disease modifying component as well as an anti-inflammatory component from the cytokines and anti-inflammatory proteins produced during the incubation period now present in the serum.

What does IRAP treatment involve?

The therapy involves three joint injections at 7-day intervals. Most positive effects are seen after the second and the third treatment. Many of these horses return to soundness following the third injection. Once the horse is sound, the horse can resume normal work. If lameness returns after a certain time period, any remaining frozen samples can be defrosted and the injections repeated. Follow up therapy can range from a single injection to multiple injections depending on clinical response.

Why use IRAP?

IRAP is different from other products because it treats the cause of joint disease and its action is aimed at restoring joint lining and cartilage function. Studies performed at Colorado State University show that treated horses demonstrate reduced lameness, improved joint histology (cellular make up) and a tendency towards cartilage preservation. **Our clinic has seen resolution of lameness, a general improvement in the range of motion of the joint and a decrease in joint effusion in IRAP treated horses.**

Traditionally the most common intra-articular medication for the management of joint disease has been corticosteroids and hyaluronic acid. Clinically, with steroid/HA injections we often see a sudden response and improvement in the degree of lameness that then gradually wears off over a period of time. These injections are then often repeated, but it is not uncommon for the therapeutic response to subsequent injections to last for a shorter duration of time than the response from the original injection. The use of IRAP often allows us to delay the use of cortisone injections and prolong the athletic life of the horse.

Platelet Rich Plasma – PRP

Platelet rich plasma (PRP) is a therapy for the treatment of injured or damaged soft tissue. It is often used to help tendon and ligament injuries heal but has also demonstrated healing and anti-inflammatory ability within osteoarthritis/degenerative joint disease. It is a welcome addition to the range of therapies available to treat these injuries because it is reasonably affordable, practical and scientifically based.

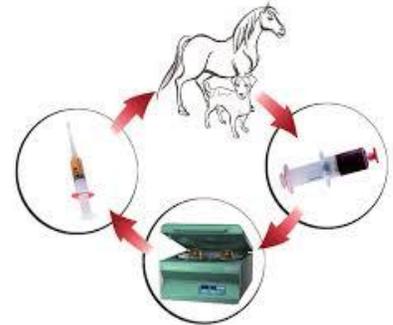
Horses suffering tendon and ligament injuries and osteoarthritis/degenerative joint disease have historically had a poor prognosis for a return to the same level of athletic ability due to the limited ability of tendons and joints to fully repair after injury. With respect to tendons, the repaired tissue is often functionally inferior to normal tendon tissue and this goes hand in hand with an increased risk of re-injury. In the normal, uninjured tendon, there is an abundance of type 1 collagen. After injury, tendons tend to repair with an abundance of type 4 collagen. Type 1 collagen is preferable to type 4 because it is made up of long fibers with few cross links. In contrast, type 4 collagen is made up of short fibers with many cross links. Thus, when a tendon heals it loses a lot of its ability to stretch under load and is much more prone to re-injury. With respect to osteoarthritis/degenerative joint disease the degenerative process within the joint is often a result of injury or

stress to the soft tissue component of joints. In order for the degenerative process within the joint to be reversed the injured soft tissue must heal.

Platelets are found in the blood stream and are mostly known for their role they play in blood clotting. However, platelets are not just involved in blood clotting, but are in fact an integral part of the early repair process at the site of any injury. When platelets organize into a clot, they release a variety of growth factors that are important for the repair of injured tissue. Platelets also send signals to other cells within the body to move to the site of injury. The clot also acts as a scaffold to retain the growth factors at the site of injury. Thus, the use of platelets at the site of an injured tendon or joint is to initiate this healing process from the release of large concentrations of growth factors locally and signal for other healing components begin to migrate toward the damaged tissue to help with the repair process.

Collecting and processing PRP

The collection and preparation of platelet rich plasma (PRP) is simple, non-invasive and takes only about 30 minutes. First, venous blood is aseptically collected from the horses' jugular vein and placed into a centrifuge. The centrifuge and PRP device allow us to separate the platelet rich part of the plasma from the red and white blood cell component. Once separated it is then ready to be injected into the injured area. With tendon/ligament injuries the injection may be done with ultrasound guidance.



Why use PRP?

At this time, PRP is a newer therapy and there are many things to be learned on how to enhance its ability to induce healing. In the veterinary community there are many different opinions on which PRP system is the best and how to use PRP to get the best results. The end product from the different PRP systems varies dramatically on number of platelets harvested, number of white and red blood cells, activated or not activated prior to injection and use of anticoagulant drugs. Currently there is mixed science suggesting one system is better than the other, preference is mostly based on clinical responses to treatment between different veterinarians.

Stem Cell

Stem cell therapy is another new area of treatment for equine injuries. Although there is much we still need to learn, some early research is encouraging. Stem cells are undifferentiated cells that have the ability to replicate and differentiate into a diverse range of cell types. These cell types include tendon, ligament, cartilage, muscle and bone. There are two basic types of stem cells, hematopoietic and mesenchymal. We are primarily concerned with mesenchymal stem cells because they appear to have the best potential to help injured tissue heal. These mesenchymal stem cells are found in bone marrow, fat, umbilical cord blood and tissue, and many other organs throughout the body. The younger or more immature the stem cell, the more potential they may have. The younger stem cells have an increased ability to heal and regenerate tissue compared to the adult stem cells.

Why use stem cells?

In the laboratory, equine stem cells were able to differentiate into multiple cell lines, including cells that produce cartilage and tendon fibers. In joints, injection of stem cells following experimental injury demonstrated the ability to help early cartilage repair, which ultimately improved athletic outcome in a multi-center clinical trial. Studies have reported that stem cells have the ability to improve tissue healing following tendon (superficial digital flexor) and ligament (suspensory) injuries. They markedly decreased re-injury rate in a large series of clinical tendon injuries. Other studies have demonstrated improved tendon architecture, fiber organization, and biomechanical characteristics following treatment with stem cells. While the majority of studies demonstrate the promising results of stem cells, it is worth noting that other studies have failed to

demonstrate such significant effects. Therefore, the veterinary community is learning more about stem cell therapy with inconsistent findings currently.

Process of collecting stem cells

Stem cells are harvested from bone marrow typically obtained from the sternum or the tuber coxae. Once the bone marrow has been collected it is sent to a lab where it is cultured and expanded into millions of stem cells. This process can take up to three to four weeks. Following culture and expansion of the stem cells, the stem cells will be shipped back for application in the injured horse. The typical dose ranges from 10 to 25 million stem cells per treatment. The stem cells are then injected into the affected tendon, ligament or joint.



The Cost

Stem cell therapy is costly and the cost is probably the reason it is not used more frequently. The average cost for the stem cell harvest, lab expansion to 10million cells, and implantation will be around \$2500 to \$4000. If the injury requires a larger cell expansion, or if cells are frozen and stored for additional treatments, the price will increase accordingly.

Conclusion

IRAP, PRP and stem cell therapies offer the possibility of successful treatment of previously life-threatening or career-ending injuries. These therapies have all shown some promising results but they are also all newer therapies with much more to learn. Consult your veterinarian to determine if one of these treatments may be appropriate for your horse.