RADIOSYNOVIORTHESIS:

A new therapeutic and diagnostic tool for canine joint inflammation

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Synovial inflammation is strongly implicated in the pathogenesis of osteoarthritis (OA) and other arthropathies. Synovitis is a common feature of symptomatic but pre-radiographic OA. This indicates that chronic, early-stage joint inflammation occurs well before significant radiographic changes and drives progression toward cartilage loss, osteophyte formation, bone remodeling, and joint space narrowing.[1-3] The pathology of early-onset synovitis and its role in OA has been well characterized. Whereas normal synovium is two or three cell layers thick and devoid of inflammatory cells, synovitis results in a number of profound changes in synovial tissue and the joint micro-environment. These include marked hyperplasia and permeability of the synovial lining, significant over-expression of pro-inflammatory mediators and cytokines, infiltration of inflammatory cells, production of degradative enzymes, synovial neo-vascularization, and increased serum C-reactive protein, a biomarker of inflammation.[1,2,4-6] The inflammatory response sensitizes peripheral neurons in synovial tissue, resulting in a pain response.[7]

OA should not be thought of as a single entity, but as a sequence of events beginning with joint injury followed by synovitis and progressing to OA as the clinical endpoint.[2] The demonstration that significant synovitis precedes structural changes in the progression of OA indicates that early intervention targeting pre-radiographic joint inflammation can delay or prevent chronic arthritic changes.[3] Surgical and non-surgical synovectomy (synoviorthesis) have been used for relieving synovitis in human, canine, and equine patients. This report describes radiosynoviorthesis (RSO) using a homogenous colloid radiolabeled with tin-117m, a novel radionuclide that offers significant advantages over conventional radionuclides.

DEFINITIONS

The following definitions are presented in the order that they appear in this report.

synovectomy: Destruction or surgical removal of the membrane (synovium) that lines an articular joint. Open surgical, chemical, radiation, and arthroscopic synovectomies are all options for removing potentially damaging synovium from articular joints.

synoviorthesis: A medical therapy using intra-articular injection of a compound that diminishes the degree of synovial hypertrophy, thereby mitigating pain and the development of inflammation and arthritis. Can be performed by chemical synoviorthesis or radiosynoviorthesis, with the latter being preferred when a suitable radionuclide is available.

radiosynoviorthesis (RSO): Injection into the synovial space of a radioisotope to treat joint inflammation and mitigate chondromalacia when systemic or other traditional therapies have failed to produce a satisfactory response. The goal of RSO is reduction of both pain and synovial hypertrophy.

radiosynovectomy (RSV): Refers to removal of the synovium and its replacement with fibrotic tissue, for example when joints are injected with beta-emitting radionuclides with a wide tissue-penetration range. Historically, RSV has been used interchangeably though less accurately as a synonym for RSO.

radionuclide: An unstable isotope of an atom that emits radiation released from the atomic nucleus. Some radionuclides exist naturally but those with research and therapeutic applications are usually produced artificially: a radioisotope.

colloid: A mixture of insoluble microparticles (particles 1 – 1,000 µm) that remain distributed in solution without precipitating or settling to the bottom; non-toxic colloids are used for binding radionuclides to prevent them from escaping the intra-articular space into systemic distribution.

homogenous tin-117m colloid (HTC): A novel preparation of the radionuclide tin-117m suspended in a colloid; HTC is well suited for intra-articular administration to treat synovial inflammation caused by traumatic injury, OA, and other arthritides.

radiocolloid: A radionuclide-labeled colloid suitable for intra-articular injection.

beta particle: A high-energy electron emitted from the nucleus of a radioactive atom; beta particles typically have a wide tissue penetration range of 50-5,000 µm that diminishes over distance, making uniform dosing difficult and possibly necessitating shielding during transport and handling.

tin-117m (Sn-117m): An artificially produced radionuclide of tin with medical applications for localized treatment and imaging. Tin-117m has a half-life of 14 days. Two principal forms of the energy that it emits are (1) conversion electrons that have a short penetration range in tissue (~300 µm), and (2) imageable gamma radiation, which enables monitoring of local distribution in tissue. Tin-117m is metastable, indicated by the "m" suffix, meaning that it is a radioisotope with an energetic nucleus and a relatively long half-life and therefore distinct from highly unstable radionuclides with shorter half-lives.

conversion electrons: A low-energy electron released from an atomic shell as a result of radioactive decay, resulting when gamma radiation energy emitted by the nucleus is transferred to the electron; conversion electrons are monoenergetic in contrast to beta particles.

RADIOSYNOVIORTHESIS FOR INTRA-ARTICULAR THERAPY

RSO has been successfully used in human medicine for more than 60 years in many countries, particularly in Europe where it was first described and where its use conforms to guidelines published by the European Association of Nuclear Medicine.[8-11] RSO has been an accepted outpatient therapy for treatment of early stage chronic synovitis in rheumatoid arthritis, psoriatric arthritis, and OA patients for decades.[10,12] RSO has important advantages versus surgical resection, the oldest ablative method. For example, as a minimally invasive procedure, RSO lowers bleeding risk in cases of hemophilic synovitis, where it is routinely used.[13,14] As a localized treatment, RSO avoids problems associated with systemic therapies such as toxicity resulting from chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) or immunosuppressive drugs. RSO also avoids tissue degradation that can occur from overuse of intra-articular corticosteroids. In human medicine, RSO has a favorable cost-benefit ratio, particularly when compared to surgery, a low rate of side effects and application to virtually all articular joints, especially small, peripheral joints such as the finger joints.[10] Current standards in human clinical practice generally take a conservative approach by recommending initial treatment with front-line therapies including systemic NSAIDs, glucocorticoids, and local joint therapies such as corticosteroid and hyaluronic acid injections prior to RSO.[9] However, in patients that either respond poorly or have adverse side effects following these traditional therapies, RSO is a useful option that is now being considered in veterinary medicine.

RADIOSYNOVIORTHESIS IN CLINICAL PRACTICE

The term radiosynoviorthesis was introduced in Europe in the 1960s by Florian Delbarre to describe therapeutically active irradiation of the synovial lining.[8] Rheumatologists administered a colloid embedded with a radionuclide (i.e., a radiocolloid) of yttrium-90 (^{90}Y) into the articular space. Using this process, the colloidal particles are phagocytized by macrophages in the synovial lining, after which they emit therapeutically active irradiation of the synovial tissue until the radionuclide decays to its stable state. The number of inflammatory cells causing synovitis is reduced and inflamed tissue is replaced with a fibrotic synovial membrane, with a corresponding alleviation of pain and improvement in function.[9,10] An early study of RSV using beta-emitting samarium-153 in horses had mixed results, producing effective synovectomy but with transient lameness and swelling and exposure of some non-targeted, periarticular tissue.[15]

A key aspect of RSO is the choice of a radionuclide. Three radionuclides are widely used in clinical practice to treat synovitis: ^{90}Y, rhenium-186 (^{186}Re), and erbium-169 (^{169}Er), all of which are artificially produced in a nuclear reactor.[9-11] In the case of RSO treatment, the radionuclide emits radiation that penetrates the outermost layer of the synovial membrane where they produce energy of sufficient duration and intensity to achieve ablation of the inflamed cells. For this to occur, the radionuclide must have an adequate half-life ($t_{½}$), a selective tissue penetration range approximating the synovial thickness, and sufficient energy for therapeutic effect.

As ^{90}Y, ^{186}Re, and ^{169}Er decay, they emit radiation in the form of beta particles with a relatively wide tissue penetration range (Figure 1). While these radionuclides are therapeutically useful and have been evaluated in large clinical trials,[9] their physical properties are not necessarily ideal for RSO. For example, ^{90}Y emits beta radiation that has a relatively wide range of soft tissue penetration, which risks irradiation of adjacent non-synovial tissue. ^{186}Re and ^{90}Y have short half-lives (2.7 and 3.7 days respectively), which create storage and logistical limitations and may not consistently deliver sufficient irradiation at the synovial target site.[14]

TIN-117M: A NOVEL RADIONUCLIDE

Tin-117m is a unique radionuclide without the disadvantages of high-energy beta-emitting radionuclides (*Table 1* compares physical properties of tin-117m with other therapeutic radionuclides).[16] As such, tin-117m is particularly well suited for RSO, including in dogs and horses. Instead of high-energy beta particles with a wide tissue penetration range (50-5,000 µm), tin-117m emits abundant conversion electrons (see Definitions), a low-energy particle with a short, non-diminishing penetration range of approximately 300 µm in tissue (*Figure 1*). Tin-117m has a $t_{½}$ of nearly 14 days, providing an ideal duration of effect spanning several half-lives to achieve therapeutic results and to enable short-term stability during storage and handling. To illustrate, *Figure 2* shows >99% dose retention in the joint of a dog three days following intra-articular injection with homogenous tin-117m colloid (HTC).[17] No other radionuclide with the properties of tin-117m exists.[18]

Table 1: Comparison of radionuclides commonly used for radiosynoviorthesis[16]

Radionuclide	Half-life (days)	Maximum energy (keV)	Maximum tissue penetration (mm)	Therapeutic emission	Diagnostic emission (keV)
Yttrium-90	2.7	2,280	11.0	beta	None
Rhenium-186	3.7	1,070	4.4	beta	gamma (137)
Erbium-169	9.4	350	1.1	beta	None
Tin-117m	13.6	158	0.3	conversion electrons	gamma (159)

keV = kiloelectron volt

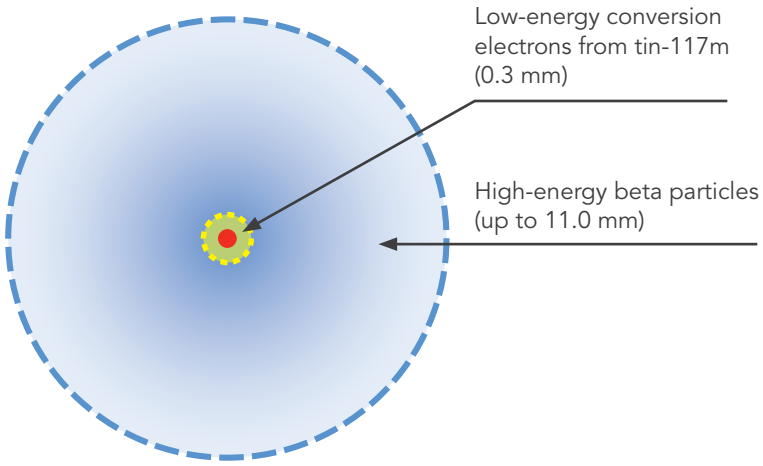

Figure 1. The diagram compares the radiation dose range of conversion electrons emitted by Tin-117m (300 µm, green zone) with beta-radiation emitted by radionuclides such as yttrium-90 and erbium-169 (up to 11,000 µm, blue zone). The ultra-narrow, discrete radiation range of tin-117m enables more precise dosimetry and avoidance of adverse effects on adjacent tissues that can occur with beta-emitting radionuclides.

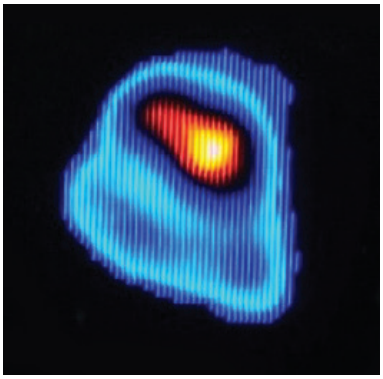

Figure 2. Scintigraphy of an HTC-injected canine elbow shows high dose-retention of the homogenous colloid with minimal uptake in the draining lymph node three days after administration. Retention at this time point was measured at >99% in synovial tissue, indicating a continuous therapeutic effect consistent with the 14-day half-life of tin-117m. *(Image courtesy of Jimmy Lattimer, DVM.)*

In addition to conversion electrons, tin-117m emits gamma radiation, a zero-mass quantum of light and electromagnetic radiation that results from nuclear decay of a radionuclide. Gamma radiation is non-therapeutic but readily detectable in tissue by imaging methods such as scintigraphy. By emitting gamma radiation at 159 kilo-electron volts (keV), tin-117m can be used diagnostically to detect the distribution and duration of its presence in tissue of treated patients. This application is similar to that for technetium-99m (^{99}mTc), a widely used systemic radionuclide with gamma emissions of 140 keV that is used in diagnostic procedures, including evaluation of bone structure and function.

Due to its unique therapeutic and diagnostic (theranostic) properties as a conversion electron- and gamma-emitter with an optimal $t_{½}$, tin-117m has attracted interest as a radiopharmaceutical and also now as a medical device in the colloid form. Favorable results were reported in phase I and II clinical trials where tin-117m was used to treat metastatic bone pain in human patients.[19-21] Investigators noted the value of the gamma emission component of tin-117m, which provides an objective basis for diagnostic monitoring, disease staging, dosage estimates, and assessing response to therapy.[21,22]

A homogenous colloid of tin-117m

Serene, LLC has developed a patented preparation of tin-117m specifically for RSO and other potential applications in veterinary and human medicine. Tin-117m is manufactured using methods that produce yields sufficient to be scaled up for manufacturing therapeutic dosages in commercial quantities.[18] The tin-117m radionuclide is combined with a homogenous colloid.[18] The radionuclide particles are small enough to be phagocytized by synovial macrophages but large enough to avoid leakage outside the joint prior to phagocytosis. In situ retention of the HTC in laboratory animals has been measured out to five $t_{½}$ (i.e., 68 days), a duration sufficient for therapeutic efficacy. The HTC has demonstrated safety and efficacy following RSO of experimental OA in rats and dogs and safety in normal canine elbow joints (*Figure 3*).

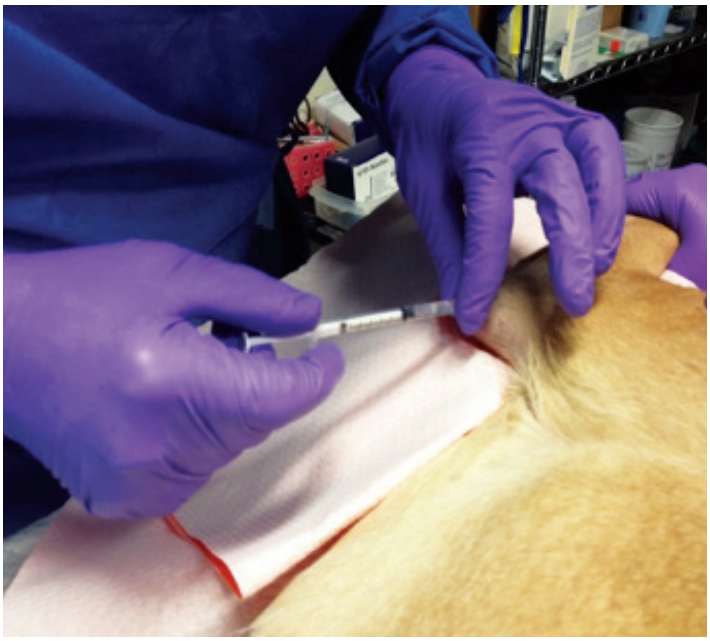

Figure 3. Experimental intra-articular injection of the radionuclide tin-117m into the caudolateral aspect of a canine elbow, positioned at 45-degree flexion, between the lateral condyle of the humerus and the triceps tendon. Following injection the joint is put through a range of motion to disperse the radiocolloid throughout the synovial surface. *(Photo courtesy of Cynthia Doerr, MD.)*

Clinically important features of tin-117m
Several features of tin-117m make it well suited for RSO and an improvement over other therapeutic radionuclides:

- Localized administration: Intra-articular dosing is suitable for outpatient use.
- Non-beta emitter: Avoids high-energy irradiation of non-synovial tissue, extra-articular diffusion, or systemic distribution.
- Emits low-energy conversion electrons: Minimizes potential for synovial scarring and eliminates collateral tissue damage.
- Gamma radiation emitter: Gamma energy of 159 keV is suitable for diagnostic imaging and is similar to the commonly used diagnostic radionuclide Tc-99m (140 keV).
- Half-life of 14 days: Enables sufficient tissue retention for therapeutic efficacy over several weeks.
- Practical handling characteristics: Ease of handling, hospital containment and shipping using standard radiological safety and packaging practices.

RADIOSYNOVIORTHESIS IN VETERINARY MEDICINE

Radiotherapy has had various applications in companion animal medicine. For example, the beta-emitter iodine-131 (^{131}I) has been used systemically to treat feline hyperthyroidism since the 1990s and is considered the treatment of choice for that condition.[23] Palliative and curative radiation therapy is now commonly used at veterinary oncology referral centers,[24] and radionuclides are also used for bone scanning in animals. Not surprisingly, successful RSO in human patients has created interest in using this method in companion animals and horses as a treatment for synovitis. Experimental RSO in horses has been attempted at university centers both in Europe and the U.S.[15,25,26] Investigators in those studies used the beta-emitting radionuclides holmium-166 (^{166}Ho) or samarium-153 (^{153}Sm). However, high-energy emissions from either radionuclide resulted in some transient, periarticular soft-tissue injury and minor extra-articular joint leakage.[15,25,26] In a small Australian study, ^{90}Y was administered concurrently with methylpredisolone acetate to four horses with severe chronic synovitis and hemarthrosis.[27] Median return to normal joint use was seven months, with two of the horses developing recurrent hemarthrosis.

In experimental studies with thulium-170 and ^{90}Y, healthy dogs were used as models for comparing results of canine and human RSO.[28-30] Results indicated that RSO in dogs is feasible and generally well tolerated. However, the studies found that excessive dosages of beta-emitting radionuclides can reduce glycosaminoglycan synthesis in articular cartilage and result in extra-articular leakage of radiocolloid particles as late as nine months after intra-articular administration. Such outcomes reflect the importance in clinical applications of using well characterized radionuclides that emit radiation within well-defined parameters. Successful RSO in relatively small canine joints was noteworthy given the commonplace occurrence of canine elbow dysplasia and associated OA, a small-joint pathology that would be difficult to treat surgically.[31]

A safe and effective RSO radionuclide

Based on widespread clinical and experimental experience with beta-emitting radionuclides, a safe and effective radiocolloid suitable for RSO has the following characteristics:[9,21]

- A limited, discrete emission penetration depth that corresponds to the thickness of the synovium (i.e., avoids irradiation too shallow for clinical effect or that extends beyond the synovial layer to affect non-target tissue).
- An intermediate radionuclide $t_{½}$ that is long enough to provide a reasonable shelf life (ease of shipping logistics) and to produce a therapeutic effect but short enough to avoid excessive exposure.
- A homogenous colloid that binds the radionuclide so that it cannot escape beyond the joint.
- Suitable colloid particle size for synovial phagocytosis and in situ retention.
- Gamma emission for purposes of diagnostic imaging.
- Manufacturing capabilities that allow scaling up for cost-effective production.
- A clinical profile that demonstrates a high degree of efficacy and safety.

Because a non-beta emitting, homogenous tin-117m radiocolloid satisfies all of these criteria, it is considered to be uniquely suited for RSO treatment.[18] Further evaluation in canine, feline, and equine models is expected to affirm its suitability for synovitis treatment combined with diagnostic confirmation of therapeutic response.

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