Homogeneous Sn-117m Colloid Radiosynovectomy: Results in Rat Models of Joint Disease

Cynthia Doerr[1], Nigel R. Stevenson[1], Gilbert R. Gonzales[1], Jaime (Jim) Simon[2], Alison Bendele[3], Suresh C. Srivastava[4], H. William Strauss[5]

1 R-NAV, The Woodlands, TX, USA, 2 IsoTherapeutics Group, Angleton, TX, USA, 3 Bolder BioPath, Boulder, CO, USA, 4 Brookhaven National Laboratory, Upton, NY, USA, 5 Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Introduction

Late stage osteoarthritic (OA) disease and rheumatoid arthritis (RA) cause severe, chronic joint pain that can be treated with radiosynovectomy (RSV). A limitation of RSV has been the suboptimal characteristics of the radiocolloids including leakage from the joint resulting in irradiation of tissues beyond the synovium. To overcome these limitations we developed a novel Sn-117m homogeneous colloid that has been tested in two animal inflammatory arthritis models for its effects. Sn-117m ($t_{½}$=14 d) decays by isomeric transition, producing both gamma rays at 159 keV, 86% abundance as well as monoenergetic conversion electrons (~140 keV; >110%) with a discreet range of about 290 µm, providing the therapeutic advantage of depositing energy in the synovial wall with minimal or no effect to surrounding tissue. Colloids used in RSV should be large enough to avoid leakage and small enough for macrophage engulfment (2-20 µm). We tested our Sn-117m colloid on two animal models.

Objective

In previous studies using a non-GLP OA rat model (n=79), three doses of Sn-117m colloid demonstrated average knee joint retention of 99.8%, safety, and efficacy. Our new objectives were to (1) validate the cGMP production of Sn-117m colloid, (2) validate the non-GLP OA rat model results in GLP conditions with better statistics (more rats per time point) with the two previously determined best doses, and (3) validate the use of Sn-117m colloid in a GLP RA rat model to demonstrate joint retention, safety, and effect.

Materials & Methods

Sn-117m colloid

A method was developed for manufacturing a particle suspension consisting of Sn-117m particles prepared using a patent pending homogeneous precipitation process which produces particles in a tight size distribution of ~10 µm. The Sn-117m colloid underwent cGMP production, sterilization, and stability testing at room temperature.

Rheumatoid arthritis and osteoarthritis rat models

Collagen induced RA rat models and surgically created meniscal tear OA rat models were established in Lewis rats as previously described [1,2]. The rats were randomized into the groups shown in Figure 1 where injections occurred in the right knee except for Group 4 which received injections in both knees. Rats were evaluated for biodistribution, blood chemistries, CBC, autoradiography, radiation field, radiation excretion, and histopathology at various time-points.

GLP Lewis Rat RA		Date of procedure/sacrifice					
		minus 10/3 days	0wk	1wk	4wk	6wk	10wk
	# animals		joint injection	sacrifice			
Group 1 (Control)	11	collagen inj	Cold tin	3	3	3	2
Group 2 nominally 2uCi	11	collagen inj	Tin-117m colloid	3	3	3	2
Group 3 nominally 10uCi	14	collagen inj	Tin-117m colloid	4	4	4	2
Group 4 Normal (no disease) nominally 10uCi	6		Tin-117m colloid both knees	2	2	2	
Total RA study	42						

GLP Lewis Rat OA		Date of procedure/sacrifice					
		minus 1 wk	0 wk	1wk	4wk	6wk	10 wk
	# animals		Joint Injection	sacrifice			
Group 1 (Model Control)	15	Surgery	None	4	4	4	3
Group 2--2uCi	31	Surgery	Tin-117m Colloid	10	10	11	
Group 3--10uCi	36	Surgery	Tin-117m Colloid	11	11	11	3
Group 4 Normal (no disease)	8	No surgery	Tin-Colloid both knees	2	2	2	2
Group 5 (Control)	20	Surgery	cold tin colloid	5	5	5	5
Total OA study	110						

Figure 1. Good Laboratory Practice OA and RA rat trial design.

Results

Sn-117m colloid

The Sn-117m colloid was reliably and reproducibly manufactured at ~10 µm, was sterile, free of endotoxin, and stable at room temperature through at least 2 half-lives (Figure 2). Particle size distribution (data not shown) remained unchanged at five weeks.

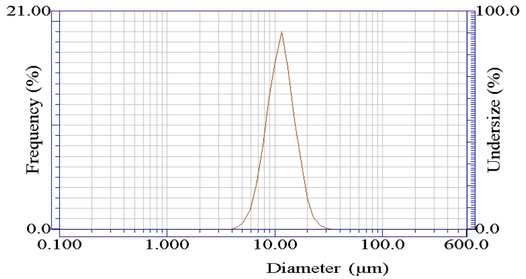

Figure 2. Horiba LA-300 laser light scattering instrument measurement of Sn-117m colloid particle size distribution after sterilization. The median particle size was 10.8 µm.

Rat models

❑Partial data from the OA model are available, and demonstrate that all animals retained normal activity throughout the study.

❑ In 34 animals with full biodistribution, excluding obvious missed injections (5 of 34 injections), joint retention of the colloid was 99.7%.

❑The urinary and fecal excretions were typically <2X background at 24 hours.

❑Radiation field measurements of 20 µCi injected into a rat knee were found to be 1.8 µR/hr at 1 m (Figure 3). When normalized to a dose of 1 mCi injected into the joint of a larger animal (dog, human, etc), this resulted in no more than 0.1 mR/hr at 1m, which is well below the commonly adopted release guideline of 0.5 mR/hr at 1m. This likely would result in less than 5 mSv (NRC criterion) to the pet owner.

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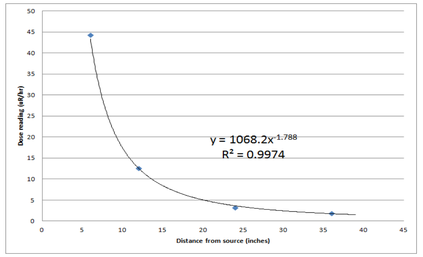

Figure 3. Radiation field measurement of 20 µCi at 1m is 1.8 µR/hr

Conclusion

Sn-117m colloid

Sn-117m homogeneous colloid could be reliably and reproducibly created under cGMP conditions using our proprietary methodology. The colloid is stable for at least two half-lives.

GLP OA rat model

These results demonstrated that this unique Sn-117m colloid, when accurately delivered intra-articularly, had exceptionally high retention in the joint space in an OA rat model. In general, isotope excretion in the urine and feces was at background within 24 hours. The radiation field in rats when extrapolated to anticipated doses used in dogs or humans are projected to be well below NRC release criteria. Full results of these OA and RA rat trials, which are incomplete at this time, will be reported at a later date.

These positive results have led to the initiation of a trial using tin-117m colloid in five normal dogs (completed) to demonstrate safety, as well as a trial using Sn-117m colloid in 48 client-owned dogs with naturally occurring elbow OA.

References

1. A.M. Bendele, J Musculoskel Neuron Interact 2001; 1(4):363-376
2. A.M. Bendele, J Musculoskel Neuron Interact 2001; 1(4):377-385