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Review article

Radiation synovectomy revisited

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Abstract. Radiation synovectomy is a potential weapon in the therapeutic armamentarium of nuclear medicine. It is an attractive alternative to surgical or chemical synovectomy for the treatment of rheumatoid arthritis. In this article the clinical results obtained with radiation synovectomy from the 1950s through 1992 are summarized and reviewed. Even after taking into account the paucity of well-controlled trials and rigorous clinical follow-up, it is clear that radiation synovectomy is efficacious in controlling the symptoms of rheumatoid arthritis. However, the procedure is not widely used because of concerns about leakage of radioactivity from the treated joint, and the resulting high doses that can be delivered to nontarget organs. New approaches to the preparation of radiolabeled particles for use in radiation synovectomy promise to minimize this leakage and thus allow the full potential of this important radiotherapy to be realized.

Key words: Radiation synovectomy – Rheumatoid arthritis – Radiotherapy – Hydroxylapatite – Samarium-153

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Introduction

Scope

In the language of warfare, nuclear medicine is under attack from diagnostic modalities such as magnetic resonance imaging and ultrasonography. In this particular battle these other modalities enjoy considerable advantages since they are not encumbered by the perceived risks of ionizing radiation. However, the nuclear medicine arsenal contains unique weapons which can be used to kill cells and thereby affect the progression of disease. When viewed from this perspective it is clear that the growth and future of nuclear medicine depends to a large extent upon the development of new radiotherapies.

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While nuclear medicine therapies are most often associated with cancers [1], the cytotoxic effects of particulate emissions can in fact be used to control a variety of pathological conditions [2, 3]. One such therapy involves the injection of beta-emitting radiopharmaceuticals into a joint in order to counteract and control synovial inflammation. This procedure is referred to as radiation synovectomy, and it is applied most often in the treatment of rheumatoid arthritis [4–6]. However, radiation synovectomy can in principle also be applied to a variety of pathological states including inflammatory diseases such as purulent arthritis or tuberculosis, post-traumatic conditions, osteoarthritis, hemophilic synovitis, synovial chondromatosis, and pigmented villonodular synovitis (PVS) [6, 7].

Thus, radiation synovectomy holds considerable promise for the growing field of therapeutic nuclear medicine. The procedure requires only the injection into the synovial cavity of a radiopharmaceutical with the appropriate nuclear, chemical, and biochemical characteristics. It is regularly practiced in Australia and Canada, and it is used in a few European centers. On a global basis, radiation synovectomy is not extensively performed, and in the United States the technique is virtually nonexistent.

The primary disadvantage of existing radiation synovectomy procedures is the unacceptable radiation doses delivered to non-target organ systems due to leakage of radioactive material from the cavitiy [8]. This leakage problem is compounded by the fact that the radiopharmaceuticals currently employed in radiation synovectomy are inorganic colloids. Egress of these colloids from the joint can lead to significant radiation exposure to the liver, spleen, and draining inguinal lymph nodes [9]. Thus, today, the promise of radiation synovectomy, for both nuclear medicine and for patients, remains unfulfilled.

Advances in radiopharmaceutical design and synthesis have created the opportunity to generate new classes of radiation synovectomy agents which will exhibit minimal leakage from the treated joint [10–12]. Given these advances, and their likelihood for expanding the utility and practice of radiation synovectomy, it is appropriate to revisit radiation synovectomy to review what is known about the procedure and its clinical efficacy.

This review article focuses on the use of radiation synovectomy in the treatment of rheumatoid arthritis. In the discussion of clinical results, however, some attention is given to the other important inflammatory arthropathies (hemophilic synovitis and PVS). Previous review articles have treated various aspects of radiation synovectomy, but most of these articles are several years old [4–7, 13, 14] or do not discuss clinical outcomes [15]. In this review we attempt to survey all relevant clinical articles which appeared in the literature through the end of 1992. We have limited ourselves to those articles that reported at least some long-term follow-up. We additionally provide an overview of radiation synovectomy agents, their mechanism of action, and a description of their ideal characteristics. In this context we discuss radionuclides, particles, and labeling techniques. Consideration is also given to animal models and dosimetry. We apologise in advance to any authors whose work we may have inadvertently omitted.

Background

More than two million people in the United States alone suffer from rheumatoid arthritis. The major cause of pain and physical disability for these individuals comes from destruction of the diarthroidal or synovial joints. For many patients the disease will involve the hands (metacarpophalangeal joints), and more than half will have affected knee joints. Untreated, the joint linings become increasingly inflamed (synovitis). This inflammation leads directly to proliferate and degenerative changes in the joints which occur by means of an infiltrating granulation tissue (pannus) that degrades the articular cartilage [16]. For the rheumatoid patient, this destruction of the articular cartilage can result in great pain and immobility [17, 18].

One therapeutic approach to this disease involves the use of chemicals to atteck and destroy the inflamed synovium (chemical synovectomy). However, the agents employed are highly toxic (osmic acid, nitrogen mustard) and capable of damaging the joint [19]. Repeated injections of corticosteroids are also considered to be systemically toxic [20]. In severe cases, surgery is employed to removed the inflamed joint lining (surgical synovectomy) [21]. However, the difficulty of removing all the diseased synovium often leads to regrowth with recurrence of symptoms (if the operation is successful, freedom from symptoms usually lasts 2–5 years) [22]. When the symptoms reappear, surgical reintervention is often contraindicated because of fibrosis and scar tissue which have resulted from the previous surgery.

Radiation synovectomy agents

Mechanism of action

Radiation synovectomy agents consist of small particles which have been tagged with, or which incorporate, beta-emitting isotopes. The accepted biological mechanism by which these agents function involves their rapid phagocytosis by synoviocytes which then distribute evenly over the surface of the synovium. This presumed even distribution of the radioactive synoviocytes on the surface of the synovium leads to the commonly held belief that only isotopes which emit high-energy beta particles can be used to treat large joints, while isotopes which emit lower energy beta particles can be used to treat smaller joints [5]. Thus, yttrium-90 agents are most commonly used to treat the knee because of the deep penetration of its energetic beta particle (mean tissue penetration of 3.6 mm), while rhenium-186 agents are suggested for intermediate-sized joints (mean tissue penetration of 1.2 mm), and erbium-169 agents are suggested for the smallest joints (mean tissue penetration of 0.3 mm) [5] (Table 1). It should be noted at the outset that these commonly accepted generalizations would be obviated if the radioactive synoviocytes actually distribute evenly within the synovium, rather than on the surface of the synovium.

Ideal agent characteristics

Based on this commonly accepted mechanism, an ideal radiation synovectomy agent should have the following characteristics:

1. The radionuclide upon which the agent is based should have a beta particle energy sufficient to penetrate and ablate the enlarged synovial tissue, but not so great as to damage underlying articular cartilage or overlying skin. Any accompanying radiation should not generate an unacceptable, extraneous radiation dose to the patient.
2. The radionuclide should be attached to a particle that is sufficiently small to be phagocytized, but not so small that it might leak from the joint before being phagocytized; the appropriate size range is usually considered to be from 2 to 5 μm [23]. The binding between the radionuclide and particle should be irreversible throughout the course of the radiotherapy; this length of time is determined by the physical half-life of the particular isotope employed.
3. The particle should be biodegradable. Persistence in the joint of nonbiodegradable materials can itself give rise to granulomatous tissue.
4. Finally, any biologically induced degradation of the agent should ideally release the radionuclide in a chemical form that rapidly egresses from the body.

Radionuclides

Many isotopes have been suggested, and several have been tested, in both animal models and humans as the basis for potential synovial ablative agents (Table 1). All of the isotopes listed in Table 1 are beta emitters

Table 1. Radioisotopes suggested for use in radiation synovectomy agents

Isotope	Half-life (days)	Beta energy (max) (MeV)	Range in soft tissue (mm) Max	Mean	Gamma energy (KeV)
^{165}Dy	0.1	1.29 (83%) 1.19 (15%)	5.7		95 (4%)
^{115m}In	0.2	0.86 (4%)			336 (47%)
^{176m}Lu	0.2	1.3 (35%) 1.2 (65%)			None
^{156}Sm	0.4	0.7 (51%) 0.4 (44%)			None
^{188}Re	0.7	2.12 (72%) 1.96 (25%)	11.0		155 (15%)
^{166}Ho	1.2	1.85 (51%) 1.77 (48%)	8.5		81 (6%)
^{105}Rh	1.5	0.57 (75%) 0.25 (20%)			319 (19%)
^{153}Sm	1.9	0.67 (78%) 0.81 (21%)	2.5		103 (28%)
^{198}Au	2.7	0.96 (99%)	3.6	1.2	411 (96%)
^{90}Y	2.7	2.28 (100%)	11.0	3.6	None
^{186}Re	3.7	1.07 (74%) 0.93 (21%)	3.6	1.2	137 (10%)
^{175}Yb	4.2	0.47 (87%)			396 (7%)
^{177}Lu	6.7	0.48 (78%)	1.7		208 (11%)
^{169}Er	9.4	0.34 (45%) 0.35 (55%)	1.0	0.3	None
^{32}P	14	1.71 (100%)	7.9	2.6	None
^{51}Cr	27.8	0.47 (EC-145%)			320 (10%)

with average particle energies and concomitant soft tissue penetrations ranging from 0.34 MeV and 0.33 mm for ^{169}Er to 2.27 MeV and 3.6 mm for ^{90}Y. The half-lives of these isotopes range from 2.3 hours (dysprosium-165) to 27.8 days (chromium-51). Some can be generator produced (^{90}Y, ^{188}Re), while others require an on-site reactor (^{165}Dy). Because of the high energies of their beta emissions, ^{32}P and ^{90}Y are the two isotopes most widely used today as the basis for radiation synovectomy agents; however, these isotopes do not emit imageable gamma rays and thus it is impossible to obtain quantitative dosimetric information on patients treated with agents based on ^{32}P or ^{90}Y.

Particles

The first agents developed for use in radiation synovectomy were colloidal suspensions; radiocolloids prepared with gold-198 [24], ^{186}Re [25], ^{90}Y [26], and ^{32}P [27, 28] were utilized for treatment of the hips, elbows, shoulders, and knees, and radiocolloids prepared with ^{169}Er [29] were used to treat the metacarpophalangeal cavities. While the majority of clinical studies with these agents report that radiation synovectomy is effective in producing remission of symptoms, leakage of the radioisotope from the cavity is a consistent problem and often results in an unacceptably high radiation dose to nontarget organs. In the case of ^{198}Au radiocolloid, anywhere from 5% to 48% of the dose delivered to the target cavity eventually leaked through the draining lymph glands found in the groin [30]. These small (10 g) organs are estimated to have received from 50 to 150 Gy during the treatment. ^{90}Y radiocolloids (prepared as citrates, hydroxides, silicates, and labeled resins) [31] were found somewhat less likely to leak from the treated cavities, but radiation doses to the draining lymph nodes are still estimated to be often in excess of 100 Gy [32]. This excessive leakage is believed to result from lack of control of the size of the radiocolloidal particles; it is presumed that the very small particles (fines) leak from the treated joint [23].

^{186}Re-labeled sulfur colloid has been available for radiation synovectomy in Europe for many years [25, 33–37]. More recently Sledge and co-workers have attempted to develop a similar preparation of ^{188}Re-labeled sulfur colloid for use in radiation synovectomy [38]. Their initial efforts utilized ^{186}Re as a model for ^{188}Re, and they obtained favorable results in the normal and arthritic rabbit models. However, the formulation of this radiopharmaceutical is prohibitively labor intensive.

In more recent years the field has advanced to the labeling of macroaggregates of insoluble particles in an attempt to control particle size and therefore minimize leakage. ^{165}Dy-labeled ferric hydroxide macroaggregate (FHMA) was the first such macroaggregate evaluated, and it did indeed generate much reduced radiation doses to nontarget organs [9, 22, 39–42]. However, this reduced radiation dose is more a function of the short half-life of the isotope than it is of the larger particle size of FHMA [43]. More recently, these studies have been repeated using ^{90}Y in place of the short-lived ^{165}Dy; in normal rabbits leakage from the joint is about 7% for both ^{90}Y-FHMA and ^{90}Y-labeled calcium oxylate [44].

The major problem inherent to the above particles is that the biological fate of whatever chemical forms of these labeled materials that leak from the joint primarily involves trapping by the reticuloendothelial system (RES) (as exemplified by the amount of leaked label found in lymph nodes and liver). In an effort to develop a radiolabeled particle that would not be trapped by the RES, several groups have championed the use of liposomes as carriers for radiation synovectomy [45–48]. The advantage of lipid vesicles resides in the fact that radionuclides in a variety of chemical forms can be incorporated as labels; lipophilic compounds can be entrapped in the lipid bilayers while water-soluble molecules can be encapsulated between the bilayers. Thus, a radionuclide might be incorporated into a chemical form which is designed to be rapidly eliminated from the body in the case that either the label or the labeled particle leaks from the target cavity. Initial experiments in animal models indicate that loss of activity from the target cavity is faster and more extensive for liposomes than for the radiocolloids; it appears that the synovial fluid is a hostile environment for liposomes. However, the full potential of this approach has not yet been completely evaluated, in part because of the difficult and time-consuming procedures required to prepare radiolabeled liposomes [45–48].

Labeling techniques

All of the above procedures to generate labeled colloidal or macroaggregated particles involve coprecipitation of the radioisotope and the particle. This means that two goals are being sought in a single-step process: (a) to generate only particles within the desired size range and (b) to quantitatively and irreversibly radiolabel the particles. Unfortunately, many reaction parameters which favor result "a" also disfavor result "b", and vice versa. These types of "one-step" syntheses involve outdated technology that is not well suited to simultaneously achieving both goals "a" and "b". A more rational and productive approach involves (1) the prior production of a particle of exactly the desired size, shape, density, porosity, etc., followed by (2) a second step the only function of which is to quantitatively radiolabel the preformed particle [49, 50]. In general, such "two-step" syntheses allow independent optimization of crucial radiopharmaceutical characteristics, and in this context they have been used in the development of radiolabeled monoclonal antibodies [50]. In terms of potential radiation synovectomy agents, this "two-step" approach has been used to prepare radiolabeled hydroxylapatite particles [10–12] which appear very promising in animal studies.

Hydroxylapatite [$Ca_{10}(PO_4)_6(OH)_2$] is the major component of skeletal bone matrix. This inorganic material has proven to be biodegradable in animal model studies [11]. The disappearance of material from tissue occurs over periods of days to weeks and by 1–2 months is virtually eliminated from the body. Particles in the desired size range have been prepared and the chemical nature of this substrate is such that it is easily labeled by a variety of lanthanide metal ions and bone seeking phosphonate complexes [10].

Animal models

The rabbit is commonly used in screening potential radiation synovectomy agents. Injection of the radiopharmaceutical into the knee joint of a normal rabbit is used to (1) quantify radioisotope leakage, (2) establish dosimetry, and (3) screen for damage to the underlying cartilage. Rabbits are also used to provide models of the rheumatoid arthritis disease process; since refined in 1971, ovalbumin antigen-induced arthritis in rabbits has been considered to be the most consistent and reproducible model [51–54]. This method involves sensitization by subcutaneous injection of ovalbumin with Freund's adjuvant at 0 and 3 weeks. Once the animal is sensitized, a chronic monoarticular arthritis lasting up to 30 weeks can be produced by the intra-articular injection of ovalbumin. The antigen is normally injected into both knees so that one knee can serve as a histological control. Special care must be taken to ensure (1) that leakage does not arise from intra-articular pressure due to the injection of too large a volume of fluid and (2) that the intra-articular injection into the rabbit knee is performed with fluoroscopic guidance [44]. Synovial inflammation which mimics the symptoms of arthritis can also be induced by injections of dextran sulfate [55] or large polysaccharide macromolecules such as carrageenan [56]. A combination of haluronate and poly-D-lysine has also been used to induce experimental arthritis in rabbits [45, 46].

None of the above procedures generates a true model of rheumatoid arthritis; all of these induced arthritic-like conditions will eventually resolve without treatment, and thus do not mimic chronic rheumatoid arthritis. In contrast, an article from Southern Illinois University (USA) presents the results of experiments in naturally arthritic swine [57]. The authors describe mycoplasmal

arthritis as being common in large herds and "enzootic (present at all times but only occuring in a small number of cases) in the SIU herd."

Dosimetry

It is difficult to calculate the absorbed dose to the synovium because of the variable synovial dimensions encountered in diseased joints and because of the presumed nonuniform distribution of the radioisotope on or within the synovium [5, 58]. Furthermore, simplistic dosimetry calculations often assume an unrealistic (monoenergetic) beta-particle emission profile in order to avoid the calculational complexities engendered by using a realistic (polyenergetic) beta-particle emission profile. A recent discussion [59] of absorbed dose profiles generated by radionuclides used in radiation synovectomy raises several interesting issues concerning the dose delivered to all joint components. The Monte Carlo method was used to calculate the radiation dosimetry within an arthritic synovial joint model based on a series of thin slabs of bone, cartilage, synovial tissue, and synovial fluid. This model (assuming complete retention of the radionuclide in the joint) permits calculation of absorbed dose profiles for several beta-emitting radionuclides as a function of disease state. These calculations predict that the absorbed dose to bone decreases with advancing rheumatoid arthritis due to the concomitant increase in synovial fluid volume and the number of synovial lining cells. However, patients with very advanced disease often have little or no remaining synovial tissue. Clinical results reflect this latter fact; patients with advanced rheumatoid arthritis do not benefit very much from radiation synovectomy, which is primarily a technique for the ablation of proliferating synovial membrane. Thus, while this Monte Carlo method provides an improved method of calculating local dosimetry, there are still clear difficulties involved in relating calculated dosimetry to clinical outcome.

While the goal of a radiation synovectomy procedure is ablation of the inflamed synovial tissue, very few studies have been performed to determine the dose required to effect this goal; this is true for all of the radionuclides used in radiation synovectomy (Table 1). The rationale for choosing a particular administered dose of a given isotope for a given joint is obscure. Despite this lack of theoretical underpinning, most published studies employ similar, historically derived, amounts of activity for any given radionuclide (see Tables 2 and 3).

In the earliest study with ^{198}Au [24], the rationale for administering between 0.5 and 0.7 mCi to the knee appears to have been based on the estimated dose delivered during previous work with x-ray therapy. A later study [60] compared two different doses of ^{198}Au (1 mCi vs 5 mCi). The results, however, did not demonstrate any statistical difference between the two groups of patients, even though there was a trend towards a better outcome with the higher dose. Other studies with ^{198}Au [61, 62] have employed a range of administered doses, where the administered activity was based on the size of the knee and the amount of effusion; however, the relationship used to calculate the administered dose from the size of the knee was not specified.

Studies with ^{90}Y usually employ an average administered activity of 5 mCi which has been calculated to give a radiation absorbed dose of approximately 100 Gy to a 100-g synovium [8]. Since this dose of ^{90}Y was shown to be efficacious in the treatment of rheumatoid arthritis patients [31], other investigators have used a "calculated ^{90}Y dose equivalent" when administering other radionuclides [8]. This empirical approach to calculating the administered dose of a new radionuclide appears to provide a basis for the initiation of new investigations with different radionuclides. However, given the weak to nonexistent theoretical underpinnings of these calculations, the investigator still bears the burden of determining what dose of a new radioisotope will actually prove efficacious.

Very few data have been accumulated on the dose absorbed by extra-articular tissues (liver, lung, regional lymph nodes); these doses are generated by the various chemical forms of the injected radiopharmaceutical which leak from a treated joint. The lack of quantitative data on extra-articular absorbed dose arises largely because the most commonly used isotopes in radiation synovectomy (^{90}Y and ^{32}P) do not emit gamma rays suitable for quantitative dosimetric studies. Dosimetry estimates from these radionuclides rely on bremsstrahlung imaging which is prone to attenuation errors. Radiation synovectomy studies using ^{165}Dy, which does have an imageable gamma emission, have provided useful information on lymph node dosimetry over the brief periods of time relevant to this short-lived isotope (half-life=2.3 h) [63].

Clinical evaluation of new agents

Prior to initiating clinical evaluations it must be established by both in vitro and in vivo assays that the radiolabel is irreversibly bound to the particulate carrier. If the radiolabel dissociates from the particle because of poor labeling chemistry, poor labeling technique, or some biological action, then the radioisotope could be transported throughout the body. This could result in an unacceptably high whole-body dose to the patient.

A well-designed clinical protocol for radiation synovectomy should not only address proper administration of the agent but also include measures to monitor the patient for leakage and to minimize any extra-articular dose. One such protocol, as adopted by English et al. [22], involves imaging the patient some time after the

administered dose and keeping the patient's joint immobile until an assessment is made that the agent is secure within the synovial cavity and any movement would not induce leakage of the material. Although the radiation synovectomy procedure discussed herein is based on treating a knee, the concepts should be applicable to other joints.

The administration of any radiation synovectomy agent into a rheumatoid joint requires extreme care to ensure that all of the radioactive dose is deposited within the synovial cavity and remains there after the needle is withdrawn. Any misadministration of material will cause the agent to be injected into the bloodstream or the lymphatic system, resulting in accumulation of the agent in the liver, lungs, and lymph nodes.

Introduction of the radiolabeled agent into the knee is performed after administration of a local anesthetic to the area. Care must be taken not to induce perforations in the synovial membrane.The lateral patella is pulled laterally, and the puncture is made with a 20-gauge needle at the midpatella to enter the joint space beneath the surface. Delivery of the agent into the synovium is followed by a flush of 1% lidocaine to transfer the remaining activity in the needle into the cavity. There are two recommended procedures for performing this delivery:

1. The first involves removing the syringe from the needle after delivering the agent, leaving the needle in place in the joint. A second syringe containing the lidocaine flush is then attached to the joint needle, and the flush is delivered before finally withdrawing the needle from the joint. A disadvantage of this technique is that it could potentially induce leakage of radioactive material from the joint if the joint exhibits high hydrostatic pressure; such external leakage can unnecessarily expose both the physician and the patient to radiation. Some investigators initially remove as much synovial fluid as possible from the inflamed joint before administering the agent, in part to avoid any backflushing of material.
2. A preferable technique involves the use of a three-way stopcock with both the radiation synovectomy agent syringe and the lidocaine flush syringe attached. After the needle is inserted into the patient's joint, the stopcock is turned to allow the delivery of the radioisotope; then the stopcock is turned to allow administration of the flush. This technique is more efficient and precludes potential radiation contamination by backflushed agent.

In either of the above techniques, the use of a syringe shield for the radiation synovectomy agent is recommended in order to minimize physician hand exposure.

English recommends that the treated joint be kept immobile until images are obtained several hours later. The use of a splint and bed confinement are suggested to minimize any potential extra-articular leakage from the joint. This group has reported that, with ^{165}Dy-FHMA, the average lymph node radiation absorbed dose was 13.4 cGy in patients immobilized after treatment, compared to 83 cGy in one patient who was not confined to bed posttreatment [43].

The patient should be imaged after treatment in order to monitor for extra-articular leakage. Images should be obtained within a time frame suited to the particular radioisotope employed. Use of very short-lived isotopes requires images to be obtained within several hours after treatment in order to avoid an inaccurate reading due to decay. Longer-lived isotopes allow imaging to be performed when convenient. Static images of the liver, pelvis, calibrated standards, patient background, and room background should be acquired in order to accurately assess patient dosimetry. Direct imaging of the treated joint for the purposes of local dosimetry should only be done if the gamma camera has been completely calibrated. Use of shorter-lived radioisotopes in radiation synovectomy involves tens to hundreds of millicuries of activity which may tax the limits of many cameras currently in use. Since the goal of the imaging procedure is to assess extra-articular leakage, the treated joint should be shielded to reduce scatter originating from the target region. Standards, prepared as calculated percentages of the adminstered dose, should be imaged at a distance from the camera equal to that distance from the injected knee to the pelvis. Finally, blood and urine samples should be obtained from the patient every few hours after treatment and counted for activity; these samples are important for assessing the chemical form of any leaked radioactivity (i.e., whether leakage involves the radiolabeled particle or the free radiolabel).

Clinical results

Clinical results abstracted from 64 literature references are presented in Tables 2 and 3. Tabulated parameters include type of disease, number of patients (when available, otherwise number of joints), type of joint injected, isotope and carrier, amount of activity, and insofar as they are available, the qualitative results of long-range (at least 1 year) follow-up.

The first reported use of radiolabeled colloids to treat arthritis was in 1952 [64]. Since then, hundreds of patients have been injected with a variety of isotopes of different beta energies and physical half-lives; most of the studies have been reported within the past 10 years. With the exception of some early reports of potentially adverse effects due to the accompanying radiation [65, 66], the procedure has been found to exhibit few side-effects [65, 67], to be of minimal toxicity when compared to other therapies [68], and to provide significant relief of the deleterious symptoms experienced by arthritic patients in a majority of cases.

It is worth noting that evaluations of the therapeutic effects of radiation synovectomy are largely based upon improvements in measurable patient parameters (range

Table 2. Clinical results of radiation synovectomy used for the treatment of rheumatoid arthritis

Reference	Year	No. of Patients (no. of joints)	Type of joint	Isotope	Vehicle	Activity range	Stage I[a] response	Stage II[a] response	Stage III-IV[a] response	Overall response[b]
29	1977	36 (201)	Digits	^{169}Er	Citrate collid	0.5–1.0 mCi	62.5% good–excellent	51.2% good–excellent	56.3% good–excellent	56–58% good–excellent
68	1979	32 (83)	Digits	^{169}Er	Citrate colloid	0.25–0.5 mCi				60% good–excellent
75	1979	7 (70)	Digits	^{169}Er	Citrate colloid	N/A[c]				79% good–excellent
76	1979		Digits	^{169}Er	N/A	N/A				54.6% good–excellent
77	1977		Digits	^{169}Er	N/A	N/A				67% effective
70	1992	32 (45)	Knee, hip, elbow, shoulder	^{90}Y	Silicate colloid	2.2–5.4 mCi	100% good	89% good	42% good	74% good
26	1975	28	Knee	^{90}Y	Citrate colloid	N/A				100% improvement
79	1985	27 (42)	Knee	^{90}Y	Silicate colloid	5 mCi	71% improvement	31% improvement	29% improvement	35% improvement (21 months)
32	1971	20 (22)	Knee	^{90}Y	Resin colloid	3–6 mCi	100% good–excellent	83% good–excellent	100% good–excellent	91% good–excellent
80	1990	142	Knee	^{90}Y	N/A	4–5 mCi	81% good–very good	81% good–very good	63% good–very good	63–81% good–very good
81	1990	16 (16)	Knee	^{90}Y	Silicate colloid	5 mCi				56% improvement
84	1979	54	Knee	^{90}Y	Ferric hydrate colloid	4–5 mCi				77.8% good–very good
85	1985	20 (23)	Knee	^{90}Y	Silicate colloid	5 mCi	53% good–excellent	0% good–excellent		35% good–excellent
76	1979		Knee	^{90}Y	N/A	4 mCi				54.6% good–excellent
86	1976	29 (48)	Knee	^{90}Y	Silicate colloid	N/A				85% improvement
87	1975	(40)	N/A	^{90}Y	N/A	3–6 mCi				43% effective
88	1991	(16)	Knee	^{90}Y	Silicate colloid	5 mCi				56% good

Table 2. (Continued)

Reference	Year	No. of Patients (no. of joints)	Type of joint	Isotope	Vehicle	Activity range	Stage I[a] response	Stage II[a] response	Stage III-IV[a] response	Overall response[b]
89	1983	93 (169)	Knee, shoulder	^{90}Y	N/A	N/A				60% good
90	1983	(28)	Knee	^{90}Y	N/A	N/A				54% good
91	1982	(106)	Knee	^{90}Y	N/A	N/A				Similar to other studies
92	1978	(131)	Knee	^{90}Y	Silicate colloid	N/A				50% good–excellent (24 months)
93	1977	15	Knee	^{90}Y	N/A	N/A				40% excellent
94	1976	(46)	Knee	^{90}Y	N/A	N/A				50% good–very good (6 years)
95	1975	(48)	Knee	^{90}Y	N/A	N/A				60% good–excellent
96	1985	41 (61)	Knee	^{90}Y	Silicate colloid	N/A				73% successful
97	1981	137	Knee	^{90}Y	N/A	N/A				76% improvement
71	1978	16 (19)	Knee	^{90}Y	N/A	N/A				79% slightly effective–effective
98	1992	133	Knee	^{165}Dy	FHMA	270 mCi	68% good	59% good		62% good
99	1988	>200	Knee	^{165}Dy	FHMA	270 mCi				80% improvement
22	1986	(55)	Knee	^{165}Dy	FHMA	270–300 mCi				84% improvement
100	1988	17	Knee	^{165}Dy	FHMA	270 mCi	100% fair–good	80% fair–good		85% fair–good
101	1985	44 (53)	Knee	^{165}Dy	FHMA	N/A				90% fair–excellent
102	1987	97 (121)	Knee	^{165}Dy	FHMA	270 mCi	72% good	53% good		61% good
103	1987	111 (135)	Knee	^{165}Dy	FHMA	270 mCi	80% good	60% good		66% good
104	1986	93 (108)	Knee	^{165}Dy	FHMA	270 mCi	71% good	59% good	33% good	61% good
105	1984	44 (53)	Knee	^{165}Dy	FHMA	270 mCi	90% good–excellent	35% good–excellent	25% good–excellent	60% good–excellent
106	1991	69 (103)	Elbow	^{186}Re	N/A	2 mCi	89% good–very good	76% good–very good	56% good–very good	83% good–very good
76	1979		Wrist, elbow, shoulder, ankle, hip	^{186}Re	N/A	N/A				50%–60% good–excellent

Table 2. (Continued)

Reference	Year	No. of Patients (no. of joints)	Type of joint	Isotope	Vehicle	Activity range	Stage I[a] response	Stage II[a] response	Stage III-IV[a] response	Overall response[b]
108	1982	111 (217)	Knee, ankle, elbow, hip, wrist, digits	^{32}P	Chromic phosphate colloid	0.3–6.0 mCi	73%–74% good			84% some benefit–good
85	1985	57 (63)	Knee	^{198}Au	Colloid	5 mCi	55% good–excellent	37% good–excellent		51% good–excellent
114	1989	50 (91)	Knee	^{198}Au	Colloid	5–7 mCi				70% satisfactory–effective
61	1975	81 (81)	Knee	^{198}Au	Colloid	4–10 mCi				81% good–excellent (6 months)
24	1963	24 (30)	Knee	^{198}Au	Colloid	0.5–0.7 mCi				77% some benefit–good
62	1967	90 (156)	Knee, elbow, shoulder, digits	^{198}Au	Colloid	1–10 mCi				79% beneficial
84	1979	101	Knee	^{198}Au	Colloid	4–5 mCi				71.3% good–very good
115	1990	260	N/A	^{198}Au	Colloid	N/A				Good
60	1988	46 (60)	Knee	^{198}Au	Colloid	1–5 mCi				Better with 5 mCi
76	1979		Wrist, elbow, shoulder, ankle, hip	^{198}Au	N/A	N/A				50%–60% good–excellent
116	1991	10	Knee	^{198}Au	N/A	N/A				73% beneficial
94	1976	(46)	Knee	^{198}Au	N/A	N/A				50% good–very good
117	1975	40	Knee	^{198}Au	N/A	N/A				90% good
97	1981	137	Knee	^{198}Au	N/A	N/A				76% improvement
71	1978	21 (33)	Knee	^{198}Au	N/A	N/A				88% slightly effective–effective

[a] Response to treatment in patients classified according to the American Rheumatism Association's staging criteria (Steinbrocher)
[b] All follow-up results are at 1 year unless otherwise noted
[c] Data not available

of motion of joint, size of knee effusion, degree of crepitus, circumference of knee at midpatella, and pain). In recent years, magnetic resonance imaging of the knee has been applied to more objectively assess the effects of radiation synovectomy treatments, but insufficient data are currently available to allow evaluation of this technique. Radiodiagnostic imaging has often been attempted in efforts to evaluate the amount of disease progression or to monitor the result of treatment, but to date this technique has not proven useful [69].

Radiation synovectomy has primarily been employed in the treatment of patients who have some form of

Table 3. Clinical results of radiation synovectomy used for the treatment of other inflammatory diseases

Reference	Year	No. of Patients (no. of joints)	Type of joint	Isotope	Vehicle	Activity range	Disease	Response[a]
70	1992	40 (58)	Knee, hip, elbow, shoulder	^{90}Y	Silicate colloid	2.2–5.4 mCi	Osteoarthropathy	43% good
78	1989	8 (8)	Knee	^{90}Y	Silicate colloid	5 mCi	Pigmented villonodular synovitis	50% improvement (32 months)
79	1985	6 (6)	Knee	^{90}Y	Silicate colloid	5 mCi	Osteoarthritis	Some improvement
80	1990	58	Knee	^{90}Y	N/A	4–5 mCi	Psoriatic arthritis, ankylosing spondyl-arthritis, collagenosis, anteroarthritis, hemophilia, gonarthrosis	80% favorable
82	1990	(50)	Knee, elbow, ankle	^{90}Y	N/A	N/A	Hemophilia	84% improvement (34 months)
83	1991	35 (58)	Knee, ankle, elbow, shoulder	^{90}Y	Silicate colloid	5 mCi	Hemophilic arthropathy	81% improvement (2–12 years)
89	1983	14 (24)	Knee, shoulder	^{90}Y	N/A	N/A	Other chronic synovitis	60% good
97	1991	57	Knee	^{90}Y	N/A	N/A	Other inflammatory joint diseases	76% improvement
107	1990	10 (10)	Knee, ankle, elbow, shoulder	^{186}Re	Colloid	2–5 mCi	Hemophilia	90% excellent
109	1990	(51)	Knee, elbow, shoulder, ankle	^{32}P	Chromic phosphate colloid	0.25–1.0 mCi	Hemophilia	96% some benefit
110	1985	14 (22)	Knee, elbow, shoulder, ankle	^{32}P	Chromic phosphate colloid	0.5–1.0 mCi	Hemophilia	91% some benefit
111	1982	4 (6)	Knee, elbow	^{32}P	Chromic phosphate colloid	0.25–1.0 mCi	Hemophilia	100% improvement
112	1991	220	Knee	^{198}Au	Colloid	10 mCi	Hemophilia	97% improvement
113	1990	15 (15)	Knee	^{198}Au	Colloid	5 mCi	Hemophilia	80% good–excellent
107	1990	33 (40)	Knee, ankle, elbow, shoulder	^{198}Au	Colloid	2–5 mCi	Hemophilia	85% good-excellent
118	1993	64	Knee	^{198}Au	N/A	N/A	Hemophilia	82% fair–good
97	1981	57	Knee	^{198}Au	N/A	N/A	Other inflammatory joint diseases	76% improvement

[a] All follow-up results are at 1 year unless otherwise noted

inflammatory arthropathy. By far, the largest number of patients have been treated for symptoms of rheumatoid arthritis. This type of radiotherapy also has been very successfully employed in controlling the recurrent bleeding that arises from hemophiliac synovitis and in treating pigmented villonodular synovitis (Table 3). The latter condition has been most successfully controlled by a combination of prior surgical debulking followed by the injection of a radiotherapeutic colloid [Sledge CB, personal communication].

Generally, radiation synovectomy has not been as successful in controlling the symptoms of patients suffering from osteoarthropathy [70, 71]. One possible explanation for this observation can be derived from the accepted biological mechanism of action of radiation synovectomy agents (vide supra). Radiation effectively controls the deleterious proliferation of inflamed synovial membrane. In those cases where the patients' symptoms arise as a result of advanced cartilage destruction or bone-on-bone interactions, the synovial membrane is likely to be virtually nonexistent. This effect also can be seen in those studies wherein rheumatoid arthritis patients were divided into groups exhibiting earlier (inflamed proliferating synovium, little cartilage damage) and later (no synovium, extensive cartilage damage) stages of disease. Patients who were treated at earlier stages of the disease invariably responded more favorably than those treated at late to end-stage disease (Table 2).

All of the clinically used radiation synovectomy agents show some leakage. Estimates range from only a few percent to as much as 25% [31]. Leakage has been particularly difficult to quantify in those cases where the isotope used was ^{32}P or ^{90}Y. These radioisotopes are both pure beta emitters with no accompanying gamma emissions that might be used to quantify biodistributions and dosimetry. In some cases, bremsstrahlung imaging has been employed to evaluate the radiation synovectomy agent leakage from the synovial cavity, but this procedure is highly subject to attenuation error and is virtually impossible to perform quantitatively [72, 73].

The number of knees treated far exceeds the numbers of the other possible arthritic joints (digit, elbow, shoulder, hip, ankle, wrist). To some extent this results from the nature of the radiopharmaceuticals commercially available for radiation synovectomy. These agents are based upon ^{32}P and ^{90}Y which have beta particle emissions with a maximum energy of approximately 2 MeV. This makes them unsuitable for use in all but the largest joints due to the potential for necrosis of the skin overlying the joint.

Overall, the survey of clinical literature summarized in Table 2 leads to the unmistakable conclusion that radiolabeled particles successfully control the deleterious effects of proliferating synovium in rheumatoid arthritis. In spite of the fact that in the majority of studies neither the carrier particle, nor the radiolabel, nor even the combination of the two could be considered optimal, the technique of radiation synovectomy proved capable of effectively controlling the symptoms of this chronic and progressively debilitating disease. Leakage of radioactivity from the treated joint, when it occurred, did not result in serious toxicological consequences. This observation takes on special import when viewed in the context of the inherent stress and hazard associated with surgical synovectomy, or in the context of the severe toxicological impacts on major organ systems associated with some of the more potent disease-modifying antirheumatic drugs such as methotrexate, gold-based drugs, and D-penicillamine [74].

Summary

Over the last several decades a number of radiolabeled materials have been clinically evaluated as potential radiation synovectomy agents. No one single material or one single formulation has yet proven optimal, but these evaluations have made it possible to define the characteristics which an ideal radiation synovectomy agent should exhibit. The size of the particles that compose the agent should fall within a defined range which minimizes the likelihood of leakage from the treated joint. The particle itself should be biodegradable and generate no deleterious effects within the treated joint. Most importantly, the particle and its associated radiolabel should be kinetically matched; i.e., the physical half-life of the radioisotope should be commensurate both with the stability of the binding between isotope and particle, and with the rate at which the particle undergoes biodegradation. While no currently used radiation synovectomy agent displays all of these characteristics, new developments in radiopharmaceutical design and synthesis are leading to improved materials which more closely approach this ideal description [10].

The development of new radiation synovectomy formulations, using rational and controlled chemical procedures to radiolabel biodegradable particles, serves the common intere ts of rheumatologists, nuclear medicine practitioners, and patients. The advent of these new radiopharmaceuticals should prompt clinicians to take a renewed interest in the potential of radiation synovectomy. The nonradioactive treatment modalities currently available to clinicians often fail to control the debilitating symptoms of chronic rheumatoid arthritis and are themselves associated with considerable costs and/or severe side-effects. As this survey of the literature shows, even when conduced with suboptimal agents, radiation synovectomy provides effective treatment of affected joints on an individual basis with little or no associated systemic or radiation toxicity. Thus, the title of this article is appropriate and timely for both nuclear medicine and rheumatology – radiation synovectomy should be revisited.

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