Therapeutic Application of Dysprosium-165-FHMA in the Treatment of Rheumatoid Knee Effusions

Robert J. English, Michael Zalutsky, Prasona Venkatesan, and Clement B. Sledge

Brigham and Women's Hospital, Boston, Massachusetts

Radiation synovectomy utilizing a variety of radionuclides has proven to be an effective technique in the treatment of rheumatoid arthritis. The recent introduction of the short-lived radionuclide, Dysprosium-165 (^{165}Dy), as a replacement for the longer-lived radiocolloids has reduced nontarget dosimetry caused by leakage of the agent from the articular cavity. A review of the methods and status of radiation synovectomy, and the application of ^{165}Dy-ferric hydroxide macroaggregates (FHMA) as an alternative therapeutic agent is described.

Synovitis of the knee is an inflammatory disease of the synovium that weakens the peripheral joint capsule and ligaments. The pain and disability of rheumatoid arthritis results from this inflammatory response in the lining of the afflicted joint. The chronic inflammation, or synovitis, leads to connective tissue overgrowing the articular surface, with eventual enzymatic destruction of the joint cartilage.

Approximately 5% of the world's population is afflicted with rheumatoid arthritis—affecting three times more women than men. Arthritic disorders are the second leading cause of time and earning losses in the United States, exceeded only by cardiovascular disease (*1*). Approximately 1% of the adult population has rheumatoid arthritis, and of these, 56% will ultimately have involvement of the knee joint (*2*).

A wide range of medical and surgical therapies directed at inhibiting the inflammatory process have been employed, with no success, in preventing joint deterioration. Conventional treatments include the use of anti-inflammatory agents, remission inducing agents, and immunosuppressive agents. Aspirin and nonsteroidal anti-inflammatory drugs block prostaglandin synthesis and thereby reduce inflammation; agents such as gold, penicillamine, and chloroquine are widely used to produce temporary remission and significantly reduce local inflammation. However, joint destruction eventually occurs with all treatments.

An alternative to medical management is surgical synovectomy; the excision of the inflamed synovium. While the procedure is effective in temporarily arresting the disease process and providing significant symptomatic relief, it is subject to a number of limitations. The anatomy of the knee joint, for example, makes it technically difficult to excise all of the inflamed synovium, and recurrence of the disease is common 2–5 yr after the procedure. Surgery is also a limited alternative because of its potential postoperative risks (i.e., hemorrhage, infection, anesthesia, etc.) and its notable expense. Associated with these drawbacks is the problem that not all patients meet the criteria of ideal surgical candidates, thus restricting some portions of the population from this management option.

A viable alternative to these methods of treatment is the radiation synovectomy. This method of treating persistent knee effusion was first reported in 1963 (*3*), with the application of an intra-articular injection of colloidal gold (^{198}Au). In the following decade, refinements of this technique, using a variety of agents, were employed predominantly in Europe. Consequently the treatment of chronic synovitis with radiocolloids became a routine procedure that contained its own set of limitations (i.e., leakage, high dosage).

Radiation synovectomy has been performed with a number of colloidal-sized particles labeled to a variety of long-lived radionuclides (Table 1). Although patients responded well to the agents, the problems of extra-articular leakage and resultant nontarget exposure, prevented widespread application (*4*). Because leakage was an inherent problem, the search for a short-lived, high energy beta emitting radionuclide was conducted. Since its introduction in 1977 (*5*), the radiocolloid ^{165}Dy-ferric hydroxide macroaggregate (FHMA) has demonstrated promising results in the treatment of knee effusions, while yielding nontarget dosimetry at those levels characteristic of diagnostic radiology procedures.

PHYSICAL CHARACTERISTICS FOR INTRA-ARTICULAR RADIONUCLIDE THERAPY

Successful treatment of rheumatoid arthritis in the knee is

TABLE 1. Radionuclides Used in Radiation Synovectomy

Isotope	Half-Life	Radiation	E max (meV)	Soft Tissue Maximum Penetration
^{198}Au	2.7 days	β	0.95	3.9 mm
		γ	0.41 (96%)	
^{90}Y	2.7 days	β	2.3	11.1 mm
^{169}Er	9.4 days	β	0.34	0.9 mm
^{186}Re	3.7 days	β	1.07	4.5 mm
		γ	0.14 (9%)	
^{165}Dy	140 min	β	1.3	5.7 mm
		γ	0.09 (9%)	

For reprints contact: Robert J. English, Div. of Nuclear Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

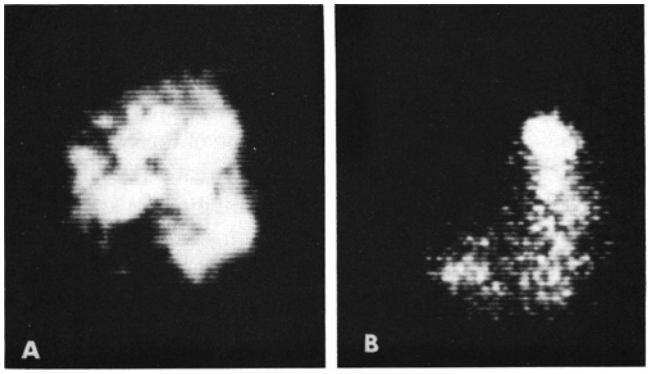

FIG. 1. (A) Anterior view of left knee after intra-articular injection of ^{165}Dy-FHMA. (B) Lateral view of ^{165}Dy-FHMA distribution in the knee.

based upon the premise that the destruction of the inflammatory synovium, or synoviolysis, is caused by irradiation of the serosa. After injection, the radioactive suspension becomes distributed in the joint in the shape of the synovium (Fig. 1), similar to that seen on an arthrogram. The ideal radionuclide will contain physical properties that ensure that the energy transfer from ionizing radiation is absorbed in the synovium only. Depending on the range of emission, the radiation may irradiate not only the synovium but also the cartilage and bone marrow (*6*). Consequently, the radiopharmaceutical of choice must not only have chemical characteristics that ensure lengthy localization, thus minimal leakage, but also retain those physical properties yielding target irradiations only.

The early applications of this technique utilized ^{198}Au colloid; however, the 411 keV gamma radiation is actually a parasitic radiation that irradiated tissues at a distance. For this reason ^{198}Au was abandoned in favor of rhenium-186, a radionuclide with a similar half-life and beta energy, but without the intense gamma emission.

With the abandonment of ^{198}Au, radiotherapists in Europe utilized a variety of radionuclides with specific targets matched to specific beta energies. Rhenium-186, with a 1.07 MeV beta energy and a maximum soft tissue penetration of 4.5 mm, was utilized in the treatment of the hips, shoulders, elbows, and wrists. Erbium-169, with a 340 keV beta energy and 0.9 mm penetration, was utilized in the finger joints. Treatment of the knee joint would be dominated for a decade with the application of yttrium-90 (^{90}Y), whose relatively short half-life (2.7 days) and energetic beta radiation (2.3 MeV) proved effective (*7*).

Whereas most investigators agreed that ^{90}Y is safer than ^{198}Au colloids, the inherent problem of leakage still prevented this technique from being favorably received within the orthopedic community (*8*). In 1977, Sledge, et al. (*9*) stated:

> "One is left with the impression that if leakage could be prevented or minimized there would be a procedure as effective as surgical synovectomy, but not requiring the time, facilities, and dangers of anesthesia and surgery."

In 1977, Hnatowich, et al. (*5,8*) introduced the treatment of synovitis with ^{165}Dy-FHMA, a beta emitter with little gamma emission and a maximum tissue penetration of 5.7 mm. With a half-life of only 139 min, it had been previously used in the treatment of gliomata (*10*). Dysprosium-165 is obtained at high specific activity by the neutron irradiation of dysprosium oxide for 8 hr (*8*). Dysprosium-165 met the following criteria of an acceptable radionuclide for synovectomy: 1) beta emission; 2) low (or no) gamma emissions; 3) sufficient beta energy; 4) maximum tissue penetrates $<$ 10 mm; and 5) a short half-life.

TREATMENT CONSIDERATIONS

The drawback common to all clinical application of radiation synovectomy is the significant leakage of radioactive material from the injected joint, with subsequent accumulation in certain organs of the body (*9*). The introduction of ^{165}Dy-FHMA is performed with an intra-articular injection. Following administration of a local anesthetic, the lateral patella is pulled laterally, and the puncture made at the mid-patella enters the joint space beneath the surface (Fig. 2). After satisfactory placement of the 20-gauge needle, 270–300 mCi of ^{165}Dy-FHMA, in a high specific activity, is injected and followed by a flush of 1% lidocaine. Upon removal of the needle, the knee is immobilized with a splint, and appropriate radiation monitoring and safety procedures are conducted.

At 24 hr, static images of the liver, pelvis, two calibrated standards, patient background, and room background are acquired. These data are collected with a scintillation camera interfaced with a computer that uses a 20% symmetrical window centered over the 90 keV gamma photo peak. Counts are acquired through a low-energy general purpose parallel-hole collimator and stored on a 128 $\times$ 128 matrix. Because of the

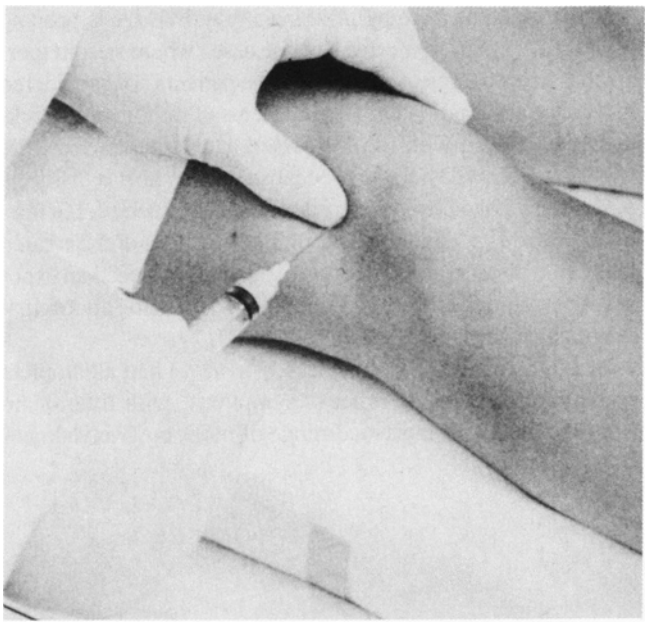

FIG. 2. Intra-articular injection technique for administration of beta-emitting radionuclides.

therapeutic dose administered, the knee is shielded with a 0.25-in. lead to reduce the scatter originating from the target region. The standards, calculated percentages of the injected dose, are imaged at a distance equal to that distance from the injected knee to the pelvis. Counts from regions of interest in each image are calculated as a percentage of the injected dose.

Our current population has yielded a mean leakage to the liver of 0.5% of the injected dose. This corresponds to a mean liver dose of ~ 2.5 rads. An abdominal CT scan may provide a liver dose of ~ 3.0 rads. The mean leakage to the blood was ~ 0.3% of the injected dose, corresponding to a total body dose of ~ 0.4 rads.

When compared to the radionuclides used for radiation synovectomy in the past, ^{165}Dy has demonstrated a reduction in patient exposure. Assuming that 5 mCi of ^{90}Y is required for effective synovectomy and correcting for half-life and average beta energy, it may be estimated that ~ 270 mCi of ^{165}Dy is required (*9*). Dolphin calculated that a 1% leakage of a 10 mCi dose of ^{198}Au would deliver a radiation dose of 4.5 rads to the liver, and for 5 mCi of ^{90}Y, the figure would be ~ 5.4 rads (*11*). Dysprosium-165 offers a reduction of ~ 50% in exposure to the liver, bringing these nontarget exposure rates within the level of diagnostic radiology procedures.

For those patients who were immobilized after ^{165}Dy-FHMA therapy, the average lymph node radiation absorbed dose was 13.4 rads. The one patient who was not confined to bed, posttreatment, received a lymph node dose of 83 rads (*12*). These data are in contrast to ^{198}Au therapy where doses as high as 15,000 rads have been reported, and doses of 5,000 rads are not uncommon (*13*). Williams, et al. reported doses to the lymph nodes of between 1,000–12,200 rads after treatment with ^{90}Y radiocolloid (*14*).

DISCUSSION

Radiation synovectomy utilizing ^{165}Dy-FHMA is proving to be an effective alternative to those cases where steroid therapy has proven ineffective and to those patients not considered ideal surgical candidates. The problems of radionuclide leakage encountered with the long-lived agents has posed little problem with ^{165}Dy-FHMA because of the short half-life, a particle system whose leakage doses do not exceed 1.2% over 24 hr, and a strict adherence to immobilization of the treated knee. Radiation exposure from leakage has produced an exposure level equivalent to that found in CT and some abdominal diagnostic radiology procedures.

At a 1-yr follow-up of 55 knees, 34 (62%) had a complete or an almost complete relief of symptoms, with little or no joint effusion, and improved range of motion. Twelve knees (22%) had a partial symptomatic relief, and nine knees (16%) did not show any improvement. None of the treated knees showed any loss of range of motion, while all knees with improved results had an increased flexation-extention arc.

In radiation synovectomy, destruction of the synovium appears to be complete because the particle that carries the radionuclide is actively taken up by the lining of the knee. Once the synovium is removed, regeneration occurs after a period of months. If it should become inflamed again, as happens in surgical synovectomy after ~ 3 yr, this less complicated and less expensive procedure can again be employed.

Although it is still in an investigational status, treatment of synovitis utilizing ^{165}Dy-FHMA has demonstrated improved practical application over previous radionuclide therapy methods, and shows significant promise as an alternative method of rheumatoid joint therapy.

REFERENCES

1. Petersdorf RG, Adams RD, Braunwald E, et al. *Principles of Internal Medicine.* Vol. 2. New York: McGraw-Hill, 1983:1978.

2. Radiation synovectomy: Promising tool for treating arthritic joint. LF Blacuer, ed. In *Focus,* Harvard University, March 7, 1985.

3. Ansell BM, Crook A, Mallard JR, et al. Evaluation of intra-articular colloidal gold (^{198}Au) in the treatment of persistent knee effusions. *Ann Rheum Dis* 1963;22:435–39.

4. Ingrand J. Characteristics of radio-isotopes for intra-articular therapy. *Ann Rheum Dis* 1973;32:3–9.

5. Sledge CB, Noble J, Hnatowich DJ, et al. Experimental radiation synovectomy by ^{165}Dy ferric hydroxide macroaggregate. *Arthritis Rheum Dis* 1977;320:1334–42.

6. Gumpel JM, Farrah HEA, Williams ED. Use of yttrium-90 in persistent synovitis of the knee. *Ann Rheum Dis* 1974;33:126–28.

7. Dunscombe PB, Bhattacharyya AK, Dale RG. The assessment of body distribution of yttrium-90 ferric hydroxide during radiation synovectomy. *Br J Rad* 1976;49:372–73.

8. Hnatowich DJ, Kramer RI, Sledge CB, et al. Dysprosium-165 ferric hydroxide macroaggregates for radiation synovectomy. *J Nucl Med* 1978; 19:303–08.

9. Sledge CB, Noble J, Hnatowich DJ, et al. Experimental radiation synovectomy by Dy-165 ferric hydroxide macroaggregate. *Arthritis Rheum* 1977;20:1334–42.

10. Ojemann RG, Brownell GC, Sweet WH. Possible radiation therapy of cephalic neoplasms by perfusion of short-lived isotopes. II. Doserosium-165. *Neurochisurgica* 1961;4:41.

11. Dolphin GW. Biological hazards of radiation. *Ann Rheum Dis* 1973; 32:23–28.

12. Zalutsky MR, Venkatesan PP, English RJ, et al. Radiation synovectomy with Dy-165 FHMA: Lymph node uptake and radiation dosimetry calculations. *J Med Biol* (in press).

13. Virkkunen M, Krusius FE, Keiskanen T. Experiences of intra-articular administration of radioactive gold. *Acta Rheum Scand* 1967;13:81.

14. Williams ED, Caughey DE, Hurley PJ, et al. Distribution of yttrium-90 ferric hydroxide colloid and gold-198 colloid after injection into knee. *Ann Rheum Dis* 1976;35:516–20.