Radiation Synovectomy with ^{166}Ho-Ferric Hydroxide: A First Experience

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Radiation synovectomy (RS) is indicated when conventional pharmacologic treatment of chronic synovitis has not relieved its symptoms. The use of radionuclides that are bound to ferric hydroxide (FH) particles has been shown to be effective and safe for this procedure. ^{166}Ho-FH macroaggregates offer promising properties for RS but there is a lack of clinical data. We investigated the efficacy and safety of ^{166}Ho-FH in a prospective clinical trial in patients suffering from chronic synovitis. **Methods:** Twenty-four intraarticular injections were performed in 22 patients receiving a mean activity of 1.11 GBq (range, 0.77–1.24 GBq) ^{166}Ho-FH. Blood activity measurements and monitoring of activity distribution were performed by whole-body gamma-camera imaging for control of leakage 3 and 24 h after injection of ^{166}Ho-FH. The patients were evaluated clinically before RS, 1 wk and 1 mo after the treatment, and thereafter in 3-mo intervals by assessing joint effusion, pannus, local pain, range of motion, and the patient's satisfaction. **Results:** In 18 of 24 treatments, no leakage to nontarget organs was visible, whereas small amounts of activity could be detected in the local inguinal lymph nodes in 6 patients and to the lungs and to the liver in 1 patient ($<$0.1%). In all cases leakage to the lymph nodes was $<$1%. Leakage to the blood was negligible. Clinically, 17 patients (71%) exhibited a complete or partial response. **Conclusion:** RS with ^{166}Ho-FH was safe and effective in patients with chronic synovitis of different origin. Controlled clinical trials are necessary to evaluate the therapeutic efficacy and safety compared with the treatment with other radionuclides and glucocorticosteroids.

Key Words: radiation synovectomy; ^{166}Ho-ferric hydroxide; leakage

J Nucl Med 2002; 43:1489–1494

An effusion of any joint is a painful sign of an acute or chronic inflammatory process. Chronic inflammation causes pannus formation and the destruction of the articular cartilage, leading to the progressive loss of joint function and significant disability. Treatment of chronic synovitis using radiation synovectomy (RS) aims to stop the inflammatory process causing pain, disability, and nonreversible structural damage to the joint (*1–3*). RS has been in clinical use for 50 y (*4*) primarily as an alternative to surgical treatment (*5*). Safety is one of the most important aspects when radionuclides are applied therapeutically. The use of ferric hydroxide (FH) particles as a carrier may offer some advantages over other carriers with respect to the frequency and degree of leakage (*6,7*). FH particles were often used in RS with ^{165}Dy (*6–11*), but the availability of this radionuclide is rather limited because of its short half-life. Furthermore, the short half-life of about 2 h requires well-scheduled treatment logistics. There is a lack of clinical data on ^{166}Ho, which has been marketed but not been approved yet for RS. ^{166}Ho has favorable physical properties (Table 1) with a maximum β-energy of 1.8 MeV, resulting in a mean and a maximum penetration in the inflamed synovial layer of 2.2 mm and 8.7 mm, respectively (*12*). The higher β-energy might be an advantage over the most commonly used radionuclide ^{90}Y, which is bound to colloids. The aim of this study was to report the first clinical experience with ^{166}Ho-FH.

MATERIALS AND METHODS

^{166}Ho-FH Preparation

^{166}Ho is produced by neutron activation of ^{165}Ho. Commercially available ^{166}Ho-FH macroaggregates (MAP Medical Technologies Oy, Tikkakoski, Finland) were used for RS. The red-brown colored, sterile, and isotonic suspension with sodium chloride solution was delivered ready for injection. Specific activity was 3–6 GBq/mg with a radiochemical purity of $>$99% as ^{166}Ho-FH macroaggregates. Analysis of particle size distribution showed, on average, 75% of particles in the range of 3–12 μm. No particles were smaller than 0.2 μm (Pirkko Penttilä, written personal communication, June 2002).

Estimation of Activity for Therapy

Earlier experience demonstrated a target dose of about 100 Gy to be necessary for the therapeutic effect of RS (*6*). The activity to be applied to obtain a dose of 100 Gy was derived from the following equation (*13*):

Received Dec. 11, 2001; revision accepted Jun. 24, 2002.

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TABLE 1
Characteristics of Radionuclides for RS of Knee

Characteristic	^{166}Ho	^{165}Dy	^{90}Y
Half-life (h)	26.9	2.3	64.1
Maximum β-energy (MeV)	1.8	1.3	2.3
γ-Energy (keV)	48–58 (9.8%) 81 (6.2%) 1,379 (0.9%)	95 (4.0%) 361 (0.8%)	None
Particle size (μm)	1.2–12	0.8–12	1.5–3.5
Soft-tissue penetration (mm)			
Maximum range	8.7	5.6	10.8
Mean range	2.2	1.4	3.8

$$D_\beta = 0.85\ E_\beta aT = \frac{0.85\ E_\beta AT}{V},$$

where D_β = energy dose effected by β-rays in Gy, E_β = mean β-energy in MeV, A = activity in MBq, a = activity concentration/mL, T = effective half-life in h, and V = volume of the affected tissue in mL.

For ^{166}Ho (E_β = 0.66 MeV, T = 26.76 h):

$$D_\beta = \frac{15\ A}{V}\ \text{Gy/GBq}.$$

Therefore, the activity necessary to obtain a dose D_β is:

$$A = \frac{D_\beta \cdot V}{15}.$$

After injection of ^{166}Ho-FH the syringe was placed in a γ-counter to measure the remaining activity. Only <1% of the activities were shown to remain in the syringe.

Patient Population and Selection

All patients gave their written informed consent to the treatment protocol according to the Declaration of Helsinki. Patients were eligible when suffering from persistent synovitis of the knee refractory to systemic and local pharmacologic treatment, but without any evidence for infection, trauma, or joint instability. All patients had undergone multiple arthrocentesis or diagnostic arthroscopy of the affected knee with subsequent synovial fluid analysis. Systemic pharmacotherapy was defined as the use of nonsteroidal antiinflammatory drugs, glucocorticosteroids, and disease-modifying antirheumatoid drugs at a dosage suppressing systemic inflammatory activity for at least 4 mo. Patients were included when they fulfilled the criteria mentioned above, but without any evidence for an acute, polyarticular exacerbation of the underlying disease. Local management involved all drugs that were injected intraarticularly. None of the patients had received intraarticular glucocorticosteroids 2 mo before the study, but most of them had been treated orally with nonsteroidal antiinflammatory drugs. No patient was treated with intraarticular glucocorticosteroids or any other locally acting therapeutic agent during the study period. Radiographs were taken before inclusion and in case of clinical deterioration after treatment and were classified according to Larsen et al. (*14*). No subjects with a Larsen stage of >2 were included. The patients were followed-up clinically by 2 orthopedic surgeons. Clinical evaluations were performed before and 1 d, 1 wk, 1 mo, and in 3-mo intervals after RS and in between when necessary for the monitoring of drug therapy. Besides the assessment of standard clinical parameters (i.e., joint count, morning stiffness, global assessments of arthritis activity, erythrocyte sedimentation rate, or C-reactive protein), the evaluation included the assessment of local pain, pannus, range of motion, and joint effusion of the treated knee joint (clinically or sonographically). A score was derived from each of the clinical symptoms and signs for the assessment of treatment. Each parameter was classified into a scale ranging from normal (0 point) to severe (3 points). Using the point scale, the range of motion of the treated knee was classified as normal (>130°—i.e., 0 point), good (115°–130°—i.e., 1 point), fair (90°–115°—i.e., 2 points), and poor (<90°—i.e., 3 points). Patients' assessments were graded as excellent (complete relief of symptoms), good (almost complete relief of pain, little or no joint effusion, and improved or maintained range of motion), fair (only partial improvement in the majority of the parameters), or poor (no improvement in most parameters).

The use of any accepted form of contraception was obligatory for any fertile women when treated with ^{166}Ho-FH. Exclusion criteria for the treatment with ^{166}Ho-FH were pregnancy, any life-threatening or infectious disease, or the presence of a Baker's cyst of >2 cm in diameter or a valve mechanism of the respective joint. Systemic pharmacotherapy was defined as the use of nonsteroidal antiinflammatory drugs, glucocorticosteroids, and disease-modifying antirheumatoid drugs, whereas local management involved all drugs that were injected into the affected joint.

The injection was performed in this room with the patient in a supine position. The puncture site of the knee was sterilized by washing with iodine solution. If necessary, about 2 mL 1% lidocaine hydrochloride were instilled into the joint space before the application of activity when the effusion was small. ^{166}Ho-FH was injected into the joint space using a 1.2-mm needle by the lateral approach. The knee was then immobilized in extension. The patient was confined to rest for about 5 h to minimize movement, except for gamma-camera imaging. Patients were advised to avoid any stress to the immobilized treated joint for 4 d. Twenty-four intraarticular injections were performed in 22 patients (age range, 26–76 y) (Table 2) with either rheumatoid arthritis (RA; n = 10), psoriatic arthritis (PA; n = 6), villonodular synovitis (VNS; n = 5), or seronegative arthritis (SA; n = 3). Three patients (patients 14, 21, and 22) were lost for follow-up for unknown reasons.

Gamma-Camera Imaging

Imaging of the ^{166}Ho distribution was performed using a large-field-of-view gamma camera (Digital gamma camera; Picker International Inc., Cleveland, OH) adjusted to 81-keV ^{166}Ho γ-rays (6.2%). A low-energy, general-purpose collimator was used. Patients were scanned 3, 24, and, in single cases, 96 h after intraarticular injection of ^{166}Ho-FH.

Leakage was calculated by measuring counts over a region of interest (lymph nodes, liver region, lungs) in relation to whole-body counts corrected for decay and background activity.

Measurement of Blood Activity

Blood activity levels were determined from 8-mL blood samples taken before and about 1 and 24 h after therapy using a γ-counter (Cobra II 5003 Auto-gamma; Packard Instruments, Downers Grove, IL) calibrated for ^{166}Ho.

TABLE 2
Demographics and Clinical Patient Data

Patient no.	Sex	Age (y)	Diagnosis	Treated knee	Surgery	Medication	C-reactive protein (mg/dL) T_0	Clinical score		Patient's satisfaction
								T_0	T_1	
1	F	30	PA	L	Nil	NSAR, MTX	0.8	6	4	2
2*	F	42	RA	L	BCR	NSAR, SP, GC	5.1	6	1	2
3	F	34	RA	R	BCR	NSAR, MTX	4.6	6	1	3
4*	M	34	VNS	R	2× SE	Nil	0.5	8	0	3
5	F	41	PA	R	SE	NSAR, MTX, GC	6.8	6	2	3
6	M	29	RA	R	SE	NSAR	0.5	7	3	1
7	F	76	RA	R	BCR	NSAR, MTX, GC	1.1	6	2	3
8	F	54	VNS	R	SE	Nil	0.5	4	0	3
9	F	42	RA	R	SE	NSAR, L, GC	0.5	8	2	1
10	M	51	PA	R	SE	NSAR, MTX, GC	0.8	7	3	2
11	F	26	VNS	R	SE	Nil	0.5	6	4	2
12	M	31	VNS	L	SE	NSAR	0.7	6	0	2
13	M	33	SA	L	SE	Nil	1	3	0	3
14	F	74	RA	L	BCR	NSAR, MTX	1.5	7	n.a.	n.a.
15	M	28	SA	R	SE	NSAR	1	5	2	1
16	F	41	PA	L	SE	NSAR, MTX	6	6	2	1
17	M	54	RA	L	SE	NSAR, GC	8.9	6	5	2
18	M	63	VNS	L	SE	Nil	0.5	9	0	1
19	F	31	RA	R	SE	GC, SP	1.9	6	0	1
20	F	70	RA	L	SE	NSAR, GC, L	3.4	5	3	2
21	M	41	PA	R	SE	NSAR, GC	0.5	4	n.a.	n.a.
22	M	57	RA	L	SE	NSAR, GC	2.5	9	n.a.	n.a.
23	M	37	SA	R	SE	NSAR	0.5	4	0	1
24	M	34	PA	R	SE	NSAR	0.5	7	2	1

*Both knee joints were treated.

T_0 = before radiation synovectomy; T_1 = 1 y after RS; PA = psoriatic arthritis; NSAR = nonsteroidal antirheumatics; MTX = methotrexate; RA = rheumatoid arthritis; BCR = Baker's cyst resection; SP = salazopyrine; GC = glucocorticoids; VNS = villonodular synovitis; SE = synovectomy; L = leflunomide; SA = seronegative arthritis; n.a. = not available.

RESULTS

Biokinetics and Biodistribution: Determination of Leakage

Leakage to the blood was not detectable in 22 of 24 treatments and was <0.1% in 2 subjects (patients 6 and 23), which is negligible (Table 3). In 18 of 24 treatments, no leakage to nontarget organs was visible (Figs. 1A and 1B), whereas small amounts of activity could be detected in the local inguinal lymph nodes in 6 patients (Figs. 2A and 2B). No patient exhibited leakage to the lymph nodes in early imaging 3 h after tracer application, but leakage was found in 6 subjects 24 h after tracer application. In all cases, leakage accounted to <1% of the total activity applied after the injection of ^{166}Ho-FH. In 1 patient (patient 23), leakage to the liver, lungs, and lymph nodes (<0.1%) was observed.

Clinical Course

Seventeen of 24 treatments (71%) resulted in a persistent (1 y) response to RS (Table 2). Three patients were lost for follow-up and could not be fully evaluated. The local clinical score improved significantly ($P < 0.05$) from a median of 6 (range, 9–2) before treatment to a median of 2 (range, 3–0) after treatment. Effusions decreased from a pretherapeutic median of 1.25 (range, 3–0) to a median of 0 (range, 0–1) after treatment. One year after treatment any effusion or pannus was absent in 19 and 16 patients, respectively. Thirteen patients showed gradual increase in the range of motion in the affected knee joint according the classification given above. Seventeen patients felt no local pain in the treated knee joint 1 y after treatment. Treatment failed to induce any relevant clinical improvement in 2 patients (Table 2).

Adverse Effects

Adverse effects were experienced by 7 patients. One patient reported a self-limiting period of nausea, and 6 others had local adverse effects. Effusion, local pain, or tenderness was most commonly observed after tracer injection, with a maximum duration of 8 d (Table 3). Thereby, 3 patients did not require any medication or intervention, 2 patients were treated locally with cold compresses, and 1 subject (patient 6) underwent arthrocentesis 1 wk after RS because of the painful local tenderness. Cytologic analysis of the 30-mL effusion revealed a reactive inflammatory pattern without any evidence of bacterial infection.

TABLE 3
Biokinetics and Biodistribution After Administration of ^{166}Ho-FH Macroaggregates

Patient no.	Applied activity (MBq)	Activity distribution	Blood	Urinary bladder	Leakage to lymph nodes	Liver	Local adverse reaction
1	1,056	Homogeneous	Nil	Nil	Nil	Nil	Pain
2	998	Homogeneous	Nil	Nil	Nil	Nil	Nil
3	1,020	Homogeneous	Nil	Nil	Nil	Nil	Nil
4	1,100	Inhomogeneous	Nil	Nil	Yes	Nil	Nil
5	1,025	Homogeneous	Nil	Nil	Yes	Nil	Nil
6	1,110	Homogeneous	<1%	Nil	Nil	Nil	Effusion, pain
7	1,075	Homogeneous	Nil	Nil	Nil	Nil	Nil
8	1,086	Homogeneous	Nil	Nil	Nil	Nil	Nil
9	1,112	Homogeneous	Nil	Nil	Nil	Nil	Effusion
10	1,076	Homogeneous	Nil	Nil	Nil	Nil	Effusion, pain
11	1,202	Homogeneous	Nil	Nil	Nil	Nil	Nil
12	1,109	Homogeneous	Nil	Nil	Nil	Nil	Effusion
13	1,167	Homogeneous	Nil	Nil	Yes	Nil	Nil
14	1,163	Homogeneous	Nil	Nil	Nil	Nil	Nil
15	950	Inhomogeneous	Nil	Nil	Nil	Nil	Nil
16	1,004	Homogeneous	Nil	Nil	Yes	Nil	Nil
17	1,056	Inhomogeneous	Nil	Nil	Nil	Nil	Effusion
18	1,100	Homogeneous	Nil	Nil	Nil	Nil	Nil
19	1,093	Homogeneous	Nil	Nil	Yes	Nil	Nil
20	1,005	Homogeneous	Nil	Nil	Nil	Nil	Nil
21	1,068	Homogeneous	Nil	Nil	Nil	Nil	Nil
22	1,015	Homogeneous	Nil	Nil	Nil	Nil	Nil
23	1,041	Homogeneous	<1%	Yes	Yes	Yes	Nil
24	769	Homogeneous	Nil	Nil	Nil	Nil	Nil

Activities in blood, urinary bladder, and lymph nodes are given as percentage of injected activities (3 or 24 h after injection [or both]); nil denotes <0.1%.

DISCUSSION

RS is an established, locally acting treatment for chronic synovitis refractory to intraarticular glucocorticosteroids. Clinically, previous randomized studies showed beneficial outcomes for patients treated with either ^{90}Y or ^{198}Au (*1,5*). A recent double-blind study comparing ^{165}Dy-FH and ^{90}Y demonstrated that the former was at least equally effective but caused less leakage (*7*). This may be due to the carrier used—that is, FH particles (*15*). However, the use of ^{165}Dy requires a reactor nearby for the delivery of this short-lived radionuclide ($t_{1/2}$ = 140 min). For that reason we have investigated ^{166}Ho-FH for the use of RS. Among 4 radionuclides—that is, ^{32}P, ^{90}Y, ^{165}Dy, and ^{166}Ho—the latter was found to be an attractive candidate for RS because of its physical characteristics (*12,16*). With the exception of hemophiliac joint disease, ^{32}P has been abandoned almost completely from RS because of its unfavorable biophysical characteristics. On the basis of the penetration range of the β-particles it would be feasible for the physician to select any of the remaining 3 radionuclides, whereby ^{90}Y penetrates significantly farther than 4 mm in tissue. The amount of radioactivity the physician must prescribe to deliver the desired dose depends on which radionuclide is selected. For ^{166}Ho, which imparts 6.76 mGy/MBq at a depth of 4 mm in tissue, an injected activity of at least 740 MBq is required. On the basis of these dosimetric calculations and the fact that a previous MRI-based study demonstrated that the thickness of an inflamed synovial layer might exceed 4 mm by far, reaching a mean of about 7 mm, activities of about 1 GBq should be applied to ablate an inflamed synovial layer (*8*).

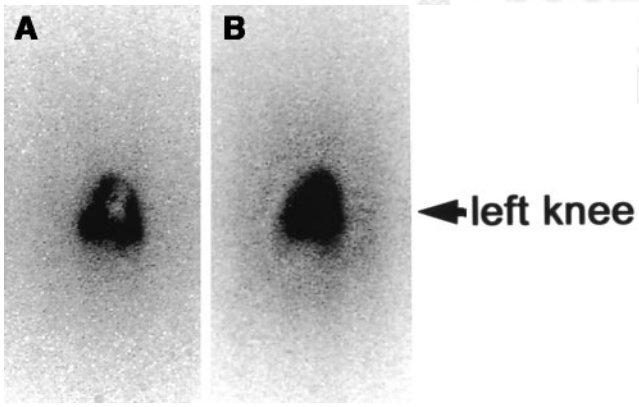

FIGURE 1. Patient 2. (A) Deposition of ^{166}Ho-FH in left knee joint (anterior view) 3 h after intraarticular tracer injection without evidence of leakage. (B) Absence of any leakage 24 h after tracer injection (anterior view).

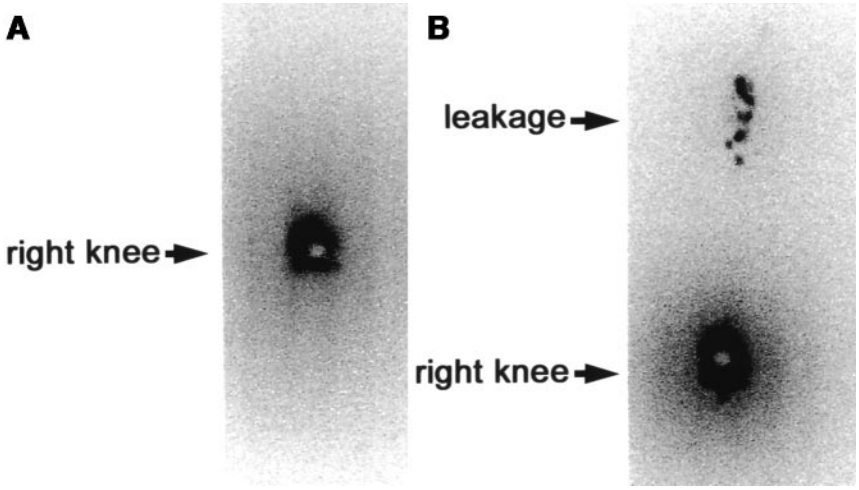

FIGURE 2. Patient 5. (A) Deposition of ^{166}Ho-FH in right knee (anterior view) 3 h after intraarticular tracer injection without evidence of leakage. (B) Leakage to inguinal lymph nodes 24 h after tracer injection (anterior view).

Our study revealed that by the use of ^{166}Ho-FH leakage occurred in only about one fourth of the patients, which is comparable with ^{165}Dy-FH (*6,7*). The frequency of leakage must be related to the sensitivity of its method of determination. Leakage detection has relied on less sensitive measurements of bremsstrahlung in studies with ^{90}Y (*3*). It is notable that with the use of ^{166}Ho-FH, leakage was $<$1% of the applied activity in our study. Our dosimetric findings are comparable with those of a recent study using ^{166}Ho-chitosan complexes (*17*). Maximum leakage reached about 1% of the applied activity 24 h after treatment in both studies. In our study leakage did not increase further over time up to 96 h after RS. Leakage was restricted to the lymph nodes in 6 patients in our study, whereas only 1 exhibited leakage to other nontarget organs as well—that is, the liver and the lungs. Song et al. (*17*) restricted their dosimetric measurements to the pelvic, abdomen, and brain region and did not relate it to any anatomic structure. Radiation exposure to the lymph nodes calculated as equivalent doses to the lymph nodes reached a maximum of about 9 Gy compared with a maximum of 100 Gy using ^{198}Au- or ^{90}Y-labeled colloids (*3,5,18*). The causes of leakage remain to be elucidated. It is widely accepted that mobilization should be avoided for some hours after injection because of the increase in both the probability and the degree of leakage. However, in our study 3 of the patients with leakage were confined to prolonged bed rest. Other reasons include changes in the pH of the synovial fluid that might facilitate leakage because of dissociation of the tracer from the carrier substance (*6*). Under normal conditions, synovial fluid volumes do not exceed 0.2–0.5 mL even in large joints. The pH varies with a range of 7.2–7.8. However, under inflammatory conditions, pH may decrease and the volume of synovial fluid may change significantly and, consequently, affect the in vivo stability of the tracer. In vitro studies showed a high stability of the tracer under a variety of experimental conditions (with and without the addition of lidocaine) at both physiologic and pathologic pH (Ingrid Schweeger, oral personal communication, October 2001). Furthermore, blood activities of ^{166}Ho were not detectable in 22 of 24 treatments and were $<$0.1% in 2 patients, which argues against any significant dissociation of the radionuclide–carrier complex, although we did not administer glucocorticoids. The distribution of FH particles with a predominance of particles measuring $>$1.2 μm contributes to reduce leakage and is a major advantage over (^{90}Y) colloids. It is noteworthy that by the use of ^{166}Ho leakage to the lymph nodes constitutes the only relevant exposure but is lower than with ^{90}Y-labeled colloids.

These initial clinical results suggest that RS with ^{166}Ho-FH was also effective. The median clinical score as an integrated marker of clinical variables improved significantly by decreasing from 6 to 2. It is notable that the evaluation of therapeutic effects is based primarily on improvements in these measurable patient variables. However, it has been shown recently that these changes are closely related to independent variables—for example, blood-pool activity in 3-phase scintigraphy (*19*) or changes in synovial enhancement in MRI (*8*). Overall, in our study, which included patients with synovitis of different origin, the response rate 1 y after RS was 71%, corresponding to numerous previous studies with lanthanide radioisotopes and other radionuclides used for RS (*3,5,7,10*). This is remarkable because our observation period extended over 1 y, which is longer than that of many published trials (*19*). It should be stated that proper patient selection is essential by the exclusion of patients with primarily degenerative joint disease or advanced joint disease (Larsen stage of $>$2) because these patient groups responded significantly worse to RS (*20*).

The therapeutic efficacy of RS may also depend on intraarticular activity distribution (*21*). In our study, all but 3 patients showed a homogeneous intraarticular activity distribution.

The short-term outcome does not always reflect long-term outcome because signs of local inflammation occur sometimes after RS. In our study, 6 of 24 treatments were associated with minor adverse effects, mainly pain or effu-

sion with a maximum duration of 7 d, requiring arthrocentesis in only 1 patient. In terms of frequency and intensity, this is comparable with the findings of previous studies although we did not apply corticosteroids.

CONCLUSION

RS is an effective and easy-to-perform treatment option in selected patients suffering from chronic synovitis refractory to standard pharmacologic treatment. This pilot trial suggests a beneficial safety profile of ^{166}Ho-FH for RS of the knee joint. Further controlled clinical trials are necessary to evaluate whether the advantageous physical properties of ^{166}Ho-FH translate into improved clinical outcome when compared with the most commonly used radionuclide ^{90}Y or glucocorticoids alone.

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