Article published online: 2022-05-21

Original article

Radiosynovectomy of Painful Synovitis of Knee Joints Due to Rheumatoid Arthritis by Intra-Articular Administration of ^{177}Lu-Labeled Hydroxyapatite Particulates: First Human Study and Initial Indian Experience

Ajit S. Shinto, K. K. Kamaleshwaran, Sudipta Chakraborty[1], K. Vyshakh, S. G. Thirumalaisamy[2], S. Karthik[3], V. N. Nagaprabhu[4], K. V. Vimalnath[1], Tapas Das[1], Sharmila Banerjee[1]

Departments of Nuclear Medicine and [2]Orthopedics, KMCH, Coimbatore, [1]Isotopes Applications and Radiopharmaceuticals Division, BARC, Mumbai, Maharashtra, [3]S.K. Global Ortho and Trauma Centre, Coimbatore, [4]Department of Rheumatology, PSGIMSR, Coimbatore, Tamil Nadu, India

Abstract

The aim of this study is to assess the effectiveness of Radiosynovectomy (RSV) using ^{177}Lu-labeled hydroxyapatite (^{177}Lu-HA) in the treatment of painful synovitis and recurrent joint effusion of knee joints in rheumatoid arthritis (RA). Ten patients, diagnosed with RA and suffering from chronic painful resistant synovitis of the knee joints were referred for RSV. The joints were treated with 333 ± 46 MBq of ^{177}Lu-HA particles administered intra-articularly. Monitoring of activity distribution was performed by static imaging of knee joint and whole-body gamma imaging. The patients were evaluated clinically before RSV and at 6 months after the treatment by considering the pain improvement from baseline values in terms of a 100-point visual analog scale (VAS), the improvement of knee flexibility and the pain remission during the night. RSV response was classified as poor (VAS < 25), fair (VAS ≥ 25-50), good (VAS ≥ 50-75) and excellent (VAS ≥ 75), with excellent and good results considered to be success, while fair and poor as failure and also by range of motion. Three phase bone scan (BS) was repeated after 6 months and changes in the second phase of BS3 were assessed visually, using a four-degree scale and in the third phase, semiquantitatively with J/B ratio to see the response. Biochemical analysis of C-reactive protein (CRP) and fibrinogen was repeated after 48 h, 4 and 24 weeks. In all 10 patients, no leakage of administered activity to nontarget organs was visible in the whole-body scan. Static scans of the joint at 1 month revealed complete retention of ^{177}Lu-HA in the joints. All patients showed decreased joint swelling and pains, resulting in increased joint motion after 6 months. The percentage of VAS improvement from baseline values was 79.5 ± 20.0% 6 months after RS and found to be significantly related to patients' age (P = 0.01) and duration of the disease (P = 0.03). Knees with Steinbrocker's Grades 0 and I responded better than those with more advanced changes (Steinbrocker's Grades III and IV) in terms of VAS improvement (75% vs. 45.8%) (P < 0.001). The overall success rate (VAS ≥ 50) was 80%. Remission of pain during the night was achieved in 100%, and knee flexibility was improved in 80%. The changes in the blood pool phase before RSV were 3.2 ± 0.7 and after the therapy 1.4 ± 0.7 (P < 0.001). The J/B ratio was: Before RSV 2.4 ± 0.3; after treatment 1.0 ± 0.2 (P < 0.05). CRP concentration 4 and 24 weeks after the therapy was significantly lower than before treatment. The fibrinogen level was not different before and after RSV. RSV side-effects assessed for the whole follow-up period were minor and not significant. RSV with ^{177}Lu-HA was safe and effective in patients with knee joint chronic painful synovitis of rheumatoid origin. It exhibited significant therapeutic effect after 6 months follow-up period with no significant side-effects. The preliminary investigations reveal that ^{177}Lu-labeled HA particles hold considerable promise as a cost-effective agent for RSV. More elaborate and controlled clinical trials are necessary to evaluate the therapeutic efficacy and safety of the agent compared with the treatment with other radionuclides and glucocorticosteroids.

Access this article online

Quick Response Code:

Website: www.wjnm.org

DOI: 10.4103/1450-1147.153908

Keywords: ^{177}Lu, hydroxyapatite, knee joint synovitis, radiation synovectomy

Address for correspondence:
Dr. Ajit S. Shinto, Department Nuclear Medicine, KMCH, Coimbatore - 641 014, Tamil Nadu, India. E-mail: ajitshinto@gmail.com

Introduction

Rheumatoid arthritis (RA) is a chronic disease that is mainly characterized by asymmetric erosive synovitis, particularly affecting peripheral joints.[1] Functional disability in patients with RA is the consequence of joint deformity, which is the result of pannus invasion of the articular cartilage, capsule, ligaments, and subchondral bone.[2] Current treatment for RA is based on a pharmacological approach,[3] physical therapy,[4] and patient education.[5] Synovectomy through the use of chemicals, radiation or by surgical means has been adopted as therapeutic options in RA.[6,7] Most chemical synovectomy is performed using intra-articular injection (IAI) of glucocorticosteroids, the most effective of which has been shown to be triamcinolone hexacetonide.[8] Radiation synovectomy (RSV) (also called radiosynoviorthesis or radiosynovectomy) is a local IAI of radionuclides in the form of radiolabeled colloidal or particulates. First used by Fellinger and Schmid[9] in 1952, the technique has been applied for over 50 years in the treatment of resistant synovitis in individual joints after the failure of long-term systemic pharmacotherapy and intra-articular steroid injections. It has been found that RSV relieves joint pain, improves joint flexibility and reduces joint effusion in about 60-80% of the cases.

In RSV, the ionizing radiation, especially β^-, emitted by intra-articularly administered radionuclide ablates the inflamed synovial membrane (pannus) with subsequent fibrosis and in this way reduces join effusions.[10] An ideal agent for RSV would be one which the radionuclide is irreversibly attached to preformed particles of appropriate size.[10-13] The ideal size of such particles is reported to be 1-10 μ and hence that they are small enough to be phagocytized, but not so small that they may leak out of the cavity before phagocytizing resulting in high dose delivered to nontarget organs.[10,11,14] In addition, the particles should be bio-degradable, and the biological half-life of such particles should be longer than the physical half-life of the radio nuclide tagged with them.[10-13] Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], one of the preferred particulates for use in RSV applications,[11-13,15-19] is a naturally occurring mineral form of calcium apatite, mainly found in bone and teeth thus it is commonly used as a filler to replace amputated bone.[20] The material has excellent biocompatibility and biodegradability.[11-13,15-20] Hydroxyapatite particles of appropriate size labeled with β^-emitting therapeutic radioisotopes such as, ^{90}Y, ^{166}Ho, ^{153}Sm, ^{177}Lu and ^{169}Er have shown desirable biological properties in animal models and some of them have been found to be effective for RSV in human patients.[11-13,15-19]

Lu-177 has emerged as a pivotal radionuclide in the field of *in vivo* radionuclide therapy could be considered owing to its suitable nuclear decay characteristics ($T_{1/2}$ = 6.65 days, Eβ [max] =497 keV, Eγ =113 keV [6.4%], 208 keV [11%]).[11,21,22] The presence of gamma photons of imagable energy with low abundance provides the additional benefit of carrying out simultaneous scintigraphy. Lu-177 can be produced in large quantity with adequately high specific activity in a research reactor with moderate thermal neutron flux owing to the high thermal neutron capture cross-section of ^{176}Lu ($\sigma = 2090 \times 10^{-28}$ m^2).[11,21,22] Moreover, relatively longer half-life of the radioisotope provides logistic advantage during its transportation to distant nuclear medicine centers. Therefore, RSV agents based on ^{177}Lu will be economically more viable compared to most of the other agents so far in clinical use.[15]

The aim of this study was to assess the clinical utility of using ^{177}Lu-labeled HA particles, prepared at hospital radio pharmacy using ready-to-use kits, for the RSV of chronic synovitis of knee joints. To the best of our knowledge, the present article would be the first report on clinical utilization of ^{177}Lu-labeled HA particles in RSV. Moreover, the efficacy of RSV in RA patients with advanced radiographic knee damage has not been extensively studied.[23] In this study, the authors also tried to analyze the factors that may have influenced the response to RSV in such patients after a single injection of ^{177}Lu-HA for a follow-up period of 6 months.

Materials and Methods

Production of ^{177}Lu

Lutetium-177 was produced by thermal neutron irradiation of isotopically enriched lutetium target (lutetium oxide 82% enriched in ^{176}Lu; obtained from Trace Science International, Canada) at a thermal neutron flux of 1.2×10^{14} n/cm^2.s for a period of 21 days. The irradiated target was radiochemically converted to $^{177}LuCl_3$ solution after dissolving in 0.01 M suprapure HCl (Merck, Germany).[21] Assay of ^{177}Lu activity produced was carried out by high-resolution gamma ray spectrometry using an HPGe detector (Canberra Eurisys, France) coupled to a 4K multichannel analyzer system after radiochemical processing. ^{152}Eu reference source used for energy as well as efficiency calibration of the detector was obtained from Amersham Inc., USA. Radionuclidic purity of ^{177}Lu was ascertained using the same system.[21]

HA particles

HA particles used in this study were synthesized and characterized following the procedure reported earlier.[12,13,18] The particle size distribution of HA particles was carried out by using a laser diffraction particle size analyzer (LA-950, HORIBA, Japan). More than 95% of the

particles were found to be in the size range of 1–10 μm, with 4.33 μm being the median of distribution.

Preparation of the radiopharmaceutical

Lutetium-177-labeled HA particles suitable for administration into patients were formulated at the hospital radio pharmacy using cold kits. Cold kits of HA particles were prepared by mixing 5.0 ± 0.2 mg of HA particles (1–10 μ size range) with a suitable buffering agent, such that addition of 1 mL of water for injection into the kit vial results in a suspension of HA particles in a suitable buffer solution of pH ~ 8.5. For radiolabeling with ^{177}Lu, 1 mL of water for injection was added to the kit vials followed by addition of ~ 400 GBq (10 mCi) of ^{177}Lu activity as $^{177}LuCl_3$ solution. The contents of the kit vials were mixed thoroughly for 30-min using vortex mixture at room temperature and subsequently set aside for 60-min without any futer agitation. The pH of the reaction mixture was found to be ~ 7–8. Subsequently, the supernatant was carefully separated from the precipitated ^{177}Lu-labeled HA particulates. The radiolabeled HA particles obtained as precipitate were subjected to a further washing using 1 mL of sterile, pyrogen free normal saline to ensure the removal of free ^{177}Lu activity. Finally, the radiolabeled particulates were suspended in sterile normal saline, autoclaved and used for animal studies or human clinical applications after measurement of dose. The yield and radiochemical purity of the ^{177}Lu-labeled HA particles were determined by following the procedure already reported.[13]

In vitro stability studies of ^{177}Lu-HA

In vitro stability of ^{177}Lu-labeled HA particles was studied in normal saline as well in human serum. For this, the radiolabeled particles were suspended in 1 mL of normal saline and freshly isolated human serum. The suspensions were stored at 37°C for 21 days (>3 half-lives of ^{177}Lu) in case of saline and 48 h in case of serum. At the end of different time intervals, the radiochemical purities of the suspended ^{177}Lu-HA particles were determined by following the reported procedure.[13]

The radiochemical preparation showed excellent *in vitro* stability in saline up to a period of 21 days (>3 half-lives of ^{177}Lu) and in human serum up to 48 h studied, both at 37°C. The radiochemical purity of the preparation was found to be retained to the extent of > 99% up to the study period in both cases.

Biological studies of ^{177}Lu-HA in animal model

The biological behavior of ^{177}Lu-HA particles was ascertained by carrying out biodistribution and imaging studies in Wistar rats with arthritis affected knee joints. Induction of arthritis was carried out in male Wistar rats using complete Freund's adjuvant following the procedure reported earlier. ^{177}Lu-labeled HA particles (~2 MBq) suspended in 100 μL of saline was injected intra-articularly into the arthritis affected knee joints of each animal to monitor its biodistribution. 100 μL saline was injected into the other joint (control). The animals were sacrificed by CO_2 asphyxiation, at the end of 3 h and 7 days post-injection (p.i.). Three rats were used for each time point. The tissues and the organs were excised, washed with saline and the activity associated with each organ/tissue was measured in a flat-type NaI (Tl) scintillation counter. Distribution of the activity in different organs was calculated as percentage of injected activity (dose) (%ID) per organ from these data. For imaging studies, ~20 MBq of the radiolabeled preparation suspended in 100 μL of saline was injected into the arthritis affected joints. Sequential whole-body scintigraphic images were acquired in the single head digital Single-photon emission computed tomography gamma-camera at 30-min, 3 h, 1, 2, 4 and 7 days p.i. using a low-energy high-resolution collimator. All the animal experiments were carried out in compliance with relevant national laws relating to the conduct of animal experimentation.

The results of the biodistribution studies showed retention of >98% of the injected activity within the joint cavity even after 7 days p.i. Almost no activity was detected in blood and most of the major organ/tissue. The whole-body scintigraphic images of Wistar rats recorded at 30-min, 2 and 7 days after intra-articular administration of ^{177}Lu-HA preparation into the arthritis induced knee joints show that all the injected activity remained localized in the synovium even at 7 days postadministration. No activity could be detected in any other organs/tissue thereby confirming that practically no leakage of instilled particles had occurred. This observation has been corroborated with the results of the biodistribution studies.

Selection of patients

The examined group consisted of 10 patients with RA and chronic painful synovitis: 7 women and 3 men; between 28 and 50 years of age (the mean age was 41.2 ± 7.2 years). Indication for RSV was persistent knee joint effusion and painful synovitis that was recurrent in spite of local corticosteroid injections and optimal systemic treatment of disease with modifying drugs in a stable dose for a period not shorter than 4 weeks before RSV. IAI with corticosteroid was prohibited within 4 weeks before RSV. The mean duration of the disease was 18.7 ± 14 months (range: 3–48 months). All 10 knee joints (7 right and 3 left knees) studied, had a history of knee pain at exercise, severe enough to limit their normal physical activity over the preceding 3 months, while 5 out of the 10 knee joints (50%) had also night pain. The

knee flexibility was normal in 6 out of 10 joints (60%) and reduced < 20° in 2/10, between 20° and 40° in 1/10 and > 40° in 1/10 knees. Concentration of the C-reactive protein (CRP) was also measured in all patients by means of the immunoturbidimetric method (normal values: 0–5 mg/mL) and the fibrinogen level was ascertained using the coagulometric method (normal values: 1.8–3.3 g/L). Changes in the knee joints caused by RA were consistent with radiological Steinbrocker's classification.

Bone scintigraphy

A 3-phase bone scintigraphy (BS) was performed before therapy by intravenous injection of ^{99m}Tc-MDP (740 MBq) with detectors positioned over the knee joints in anterior and posterior projections in all phases of the examination, with a dual head gamma-camera (Siemens Symbia True Point) equipped with a low-energy high-resolution collimator. The first phase (blood flow phase) was obtained immediately after radio-tracer administration. Dynamic acquisition was performed over a period of 2-min with the time resolution of 2 s. The second phase (blood pool phase) was carried out at 5-min after injection with a 10-min static acquisition. Delayed, static images (the third phase or metabolic phase) were obtained 2.5–4 h after radiotracer administration.

Bone scans were routinely evaluated pretreatment to confirm synovitis and post treatment for response evaluation.[24,25] Assessment of the second phase additionally included the four-degree scale of blood pool changes: (1) Normal blood pool, (2) slightly increased blood pool, (3) markedly increased blood pool, and (4) severely increased blood pool. Semi quantitative evaluation of the third phase was performed by employing the region of interest method. The J/B ratio was calculated dividing the average number of counts per pixel in the region of the treated knee joint by the average number of counts in the distal part of the femoral shaft on the side of the affected joint.[24]

RSV injection and technique

RSV treatment was performed in all knee joints with precise intra-articular single knee injection of a typical dose of 333 ± 46 MBq of ^{177}Lu-HA under sterile conditions. Before joint puncture, local anesthesia was administered with 2% lidocaine hydrochloride. Aspiration of synovial fluid prior to the administration of the radiopharmaceutical was performed in order to avoid back flushing due to high hydrostatic pressure. Depo-Medrol (40 mg in 1 mL) was injected into the joint immediately before the injection of ^{177}Lu-labeled HA particles in order to reduce the risk of acute radiation induced synovitis and also to avoid skin radiation necrosis.[26] Subsequently, 333 ± 46 MBq (range: 259–370 Mbq) of ^{177}Lu-labeled HA particles dispersed in 1 mL of sterile, apyrogenic normal saline was administered intra-articularly, and then the needle was flushed with 2–4 mL of normal saline. In case of any uncertainty about the exact location of the tip of the needle, arthrography was performed to check the correct location. Immediately after injection, the knee was flexed to augment inter articular distribution and the range of flexion was recorded. An orthopedic bandage was applied as a semi rigid splint. Patient remained nonweight bearing for 4 h with leg supported. The treated joints were immobilized for about 48 h in order to prevent migration of radiolabeled particles to local lymph nodes. Radionuclide leakage along the needle track or any local and general side-effects were not observed in examined group of patients. Patients were allowed to go home 4 h p.i. advised to take rest. Imaging of activity distribution with a dual head gamma-camera showed appropriate homogeneously intra-articular distribution of the radionuclide within the joint space.

Follow-up evaluation

The analysis of RSV treatment outcome after 6 months follow-up, in all knees was based on detailed information from the patient, clinical examination and three phases BS. Treatment outcome was examined in terms of joint pain during exercise improvement measured with a 100-point visual analog scale (VAS) pain score, before and at 6 months after treatment. Any improvement of the knee pain was measured and calculated as a mean (±standard deviation [SD]) percentage change from the baseline VAS score. The RSV treatment outcome was assessed as excellent, good, fair and poor.[27,28] Excellent and good results were considered as treatment success, fair, and poor as treatment failure. Patients with excellent results had an improvement of VAS score equal or higher than 75%, patients with good response had VAS scores of 50–75%. Patients with a fair result had VAS scores 25–50%, while patients with a poor result, had no benefit from treatment, joint pain continued and VAS score was <25%. The presence or absence of pain during the night before and after RSV treatment was recorded according to patient's judgment and was used as another treatment response variable. The improvement of patient's knee flexibility was considered as an objective treatment response, measured by the angle of knee flexion (<20°, between 20° and 40°, >40°). We also compared RSV influences with patient's age, the duration of symptoms and the X-ray grading. Knee joints were assigned in groups according to the radiographic RA findings, using the Steinbrocker radiological grading system (Grades 0-IV).[22] Comparison of soft tissue two phase BS was also performed to see the decrease in inflammation. Obtained results were subjected to statistical analysis, which included the calculation of mean values and standard deviations of all studied parameters. Correlations between parameters were analyzed and the significance of correlation coefficients

was verified with the *t*-test. Differences in mean values of evaluated parameters were assessed by Student's paired *t*-test and the $P < 0.05$ was considered as significant.

Results

Preparation of radiopharmaceuticals

Lutetium-177 was produced with a specific activity of 20–25 mCi/μg and radionuclidic purity of 99.985 ± 0.005%. ^{177}Lu-labeled HA particles were prepared in high radiochemical purity of 99.2 ± 0.3% following the procedure described in the experimental section. The trace quantity of unlabeled $^{177}LuCl_3$ was washed off and radiochemically pure ^{177}Lu-HA was obtained for administration into patients.

Bone scintigraphy

All patients demonstrated increased tracer activity in the afflicted knee joints and representative images are shown in Figures 1 and 2.

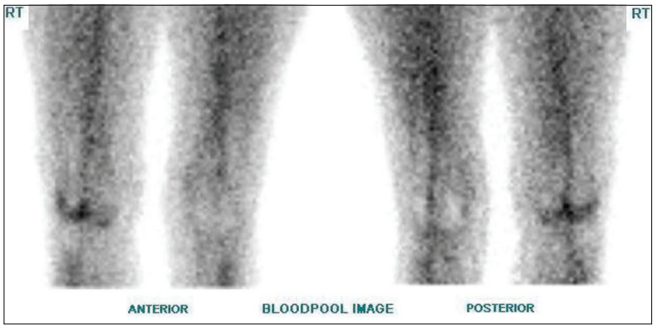

Figure 1: Representative anterior and posterior second phase blood pool images of 99mTc-MDP bone scan prior to the ^{177}Lu-HA therapy showing increased tracer pooling in the right knee joint suggesting active synovitis

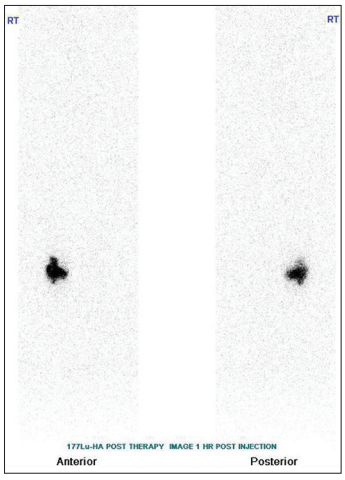

Figure 3: Lu-177 HA images of the same patient recorded immediate injection and 1 month post therapy, which depicts complete retention of the administered activity in the knee joint cavity

Retention of ^{177}Lu-HA in the knee joints

In all patients treated with ^{177}Lu-HA, no leakage of activity from the knee joint cavity to any other nontarget organs could be visible in the whole-body scans recorded using 208 keV gamma photon of ^{177}Lu up to 1 month postadministration of ^{177}Lu-HA. Figure 3 shows the representative static whole-body scan of the same patient recorded 1 h postadministration of ^{177}Lu-HA, indicating excellent localization of the agent in joint cavity. The images of the same patient recorded 1 month posttherapy are shown in Figure 4, which depicts near complete retention of the administered activity in the knee joint cavity. This excellent retention of the radiolabeled particulates in the joint cavity with almost no leakage of activity to any other nontarget organs is one of the major requirements of a successful RSV procedure. Routine whole-body sweep images were done1 h, 1 week and 1 month after IAI, for confirming bio distribution patterns; which showed no significant extra articular tracer leaching. In addition, the radiation dose to the gonads was negligible as all the injections were in the knee joints, which were far away from the gonads and no extra articular or inguinal node activity was present in any of the cases.

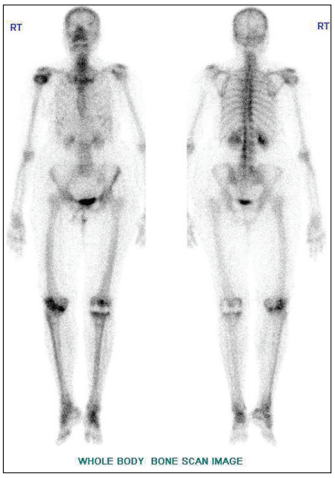

Figure 2: Representative third phase 99mTc-MDP whole-body scan of the same patient indicating increased tracer activity in the right knee joint

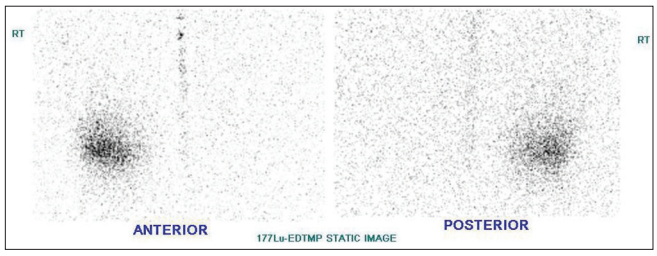

Figure 4: Static knee joint images taken 1 month post therapy, depicting near complete retention of the administered activity in the knee joint cavity

Efficacy of the treatment

Six months after RSV, the VAS improvement from baseline values of the knee pain for the whole group was 79.5% ±20.0%. For patients aged between 25–35 years and 35–50 years, the mean VAS improvement was 82.1% ±14.5% and 57.2% ±17.4%, respectively. There was a statistically significant difference ($P = 0.01$) between these two groups. Patients with symptoms lasting < 1 year, had a mean VAS improvement of 85.5% ±17.0%, significantly higher than the corresponding value of 58.4% ±18.6% of patients with the disease lasting for 1 or more years ($P = 0.03$).

Visual analog scale improvement for knees with Steinbrocker's Grades 0 and I, versus knees with more advanced (Steinbrocker's Grades III and IV) radiographic changes, was 75% versus 45.8% ($P < 0.001$). In a further analysis, concerning the radiographic changes, it seems that at 6 months after RSV treatment the success rate was 100% for knees without or with mineral osteoarthritis (OA) radiographic changes (Steinbrocker's Grades 0 and I) and 85% for knees with moderate OA radiographic changes (Steinbrocker's Grade II).However, in knees with advanced (Steinbrocker's Grades III and IV) degenerative changes, the RSV success rate was significantly reduced (52.2% in 6 months), compared to the joints with no or minimal radiographic changes.

The overall success rate of RSV as a percentage of knee joints studied is shown in Table 1. None of the patients showed complete failure (VAS improvement score 0%), one patient showed VAS improvement of 25–50% termed as failure. Three patients showed VAS improvement between 50% and 75%, seven patients showed VAS improvement of 75–100% among that complete response (VAS improvement score 100%) was seen in 2/10 knees.

The outcome results in terms of VAS for joint improvement related to the three phase BS changes are shown in Table 2. VAS improvement for knees with moderately increased blood pooling (score 3), versus severely increased (score 4) scintigraphic changes, was 76.5% versus 59.4% ($P < 0.001$). In a further analysis, concerning the scintigraphic changes, it seems that at 6 months after RSV treatment the success rate was 90% for knees with moderately increased blood pooling and 75% for knees with severe grade blood pooling. However, in knees with more increased blood pooling, the RSV success rate was significantly reduced (70% in 6 months), compared to the joints with mild or moderate scintigraphic changes. After 6 months, the improvement in knee pain correlated with the decrease in soft tissue pooling in the treated joints. More the improvement in VAS score, more decrease in blood pooling compared to pretherapy scintigraphic changes noted. Changes in the third phase of BS3 (the J/B ratio) were: Before the therapy 2.4 ± 0.3; after treatment 1.0 ± 0.2 ($P < 0.05$). It was also statistically significant pre and posttreatment.

At 6 months after RSV treatment, night pain was absent in 5 out of the 5 knees (100%). Knee flexibility was improved on 3/4 knees (75%) at 6 months and not improved in 1 patient. Specifically knee flexibility was reduced to <20°, between 20° and 40° and > more than 40° in 2/4, 1/4 and 1/4 cases (for direct comparison with abnormal knee flexibility before RSV). The side-effects during the follow-up period were minimal: No side-effects occurred including thromboses or skin radiation necrosis.

Mean concentrations of CRP (mg/l) were: Before therapy 67.3 ± 10.5, 48 h after therapy 43 ± 18.4, 4 weeks after therapy 35.8 ± 12.5, 24 weeks after therapy 16.5 ± 6.4. Mean levels of fibrinogen (g/l) were respectively: 5.3 ± 0.6; 5.0 ± 0.5; 4.7 ± 0.6; 4.3 ± 0.8. CRP concentration 4 and 24 weeks after the therapy was significantly lower than before treatment. The fibrinogen level was not different before and after RSV.

Discussion

This study demonstrated that ^{177}Lu-HA can be potentially used as a viable option for radiosynovectomy of the knee joints. The choice of this radiopharmaceutical was made

Table 1: Percentage of VAS improvement before and after therapy

Number of joints	Excellent VAS≥75-100	Good VAS≥50-75	Fair VAS>25-50	Poor VAS<25	Success	Failure
10	7	2	1	0	9	1

VAS: Visual analog scale

Table 2: Results of three-phase bone scan and acute phase reactants before and after therapy

	Number of patients	Three-phase bone scan		CRP (mg/dl)	Fibrinogen (g/l)
		Second-phase	Third-phase		
Before therapy	10	3.2±0.7	2.4±0.3	67.3±10.5	5.3±0.6
6 Months after therapy	10	1.4±0.7	1.0±0.2	16.5±6.4	4.3±0.8
P value		*P*<0.001	*P*<0.05	*P*<0.05	NS

NS: Not significant; CRP: C-reactive protein

based on the optimal penetration of beta radiation in the synovia. Bio distribution of ^{177}Lu-HA can be easily studied scintigraphic imaging utilizing the gamma photons emitted by ^{177}Lu. Histopathological findings in the early phase after intra-articular administration of ^{177}Lu-HA reveal reduction in the quantity and size of the synovial villi, decreased hyperemia and the thickness of the synovia. In the late phase after RSV, synovial fibrosis is predominantly seen. The beta radiation, because of its short penetration distance, reaches only structures in the intermediate vicinity of the joint cavity, while the gamma photons co-emitted by ^{177}Lu-HA can reach more remote organs. In this connection, the radiation dose to the gonads is the main topic. The highest dose results from a RSV of the hip joint. For RSV of other joints, the dose to the gonads is clearly smaller because of the greater distance to the gonads and a lower activity injected. For an activity of 150 MBq of ^{177}Lu administered at the hip, the maximal gamma radiation dose to the gonads was estimated as 3.5 mSv.[28]

Based on the *in vitro* stability studies and bio distribution studies performed in animal models, it has been observed that ^{177}Lu-HA is highly stable and leakage from the synovial site is negligible.[13,15] Based on the posttherapy whole-body imaging studies conducted on human patients, we have seen that when the treated joint was immobilized, activity in the lymph nodes was undetectable and leakage was negligible even at 1 month post therapy. Significant intra-articular retention at 1 month also suggests excellent *in vivo* stability of the preparation in human.

According to our prospective study, the RSV overall success rate (VAS ≥ 50%) was 80% at 6 months, indicating a high short-term beneficial effect in pain remission of knee joints. Markou and Chatzopoulos[23] studied Yttrium-90-silicate radiosynovectomy treatment of painful synovitis in knee and they published results after 6 months, the RSV overall success rate (VAS ≥ 50%) was 83.8% at 6 months, indicating a high short-term beneficial effect in pain remission at exercise of OA knee joints. We also find similar response with ^{177}Lu-HA. An equally significant beneficial effect of RSV in complete remission of the joint pain during the night was found in 100% of the joints. Our results in this case is also correlated with that of Markou and Chatzopoulos,[23] which showed night pain remission of 88.6%. Improvement of knee flexibility, as we have shown, has also been reported by others[29] and is probably associated with the ablation of the synovial membrane, reduction of knee effusion and pain remission.

The mean VAS improvement observed at 6 months was inversely related to patients' age, duration of symptoms and the radiographic grading of OA. Similarly to other studies, RSV seemed to be less beneficial in older patients, in cases of long duration of the disease and in advanced OA stages (Steinbrocker's Grades III and IV).[23,30,31] The examined group of patients seems to be homogenous in terms of disease entities and the intensity of the inflammatory process in the knee joints. Considering indications for RSV, it should be kept in mind, that the response to the therapy is incomplete in patients with advanced articular changes (degree III and IV of Steinbrocker's classification), joint instability or synovial hypertrophy exceeding penetration rate of beta radiation.

In our study, not only clinical evaluation was considered, but also the concentration of acute phase proteins, in particular CRP, which decreases significantly after RSV, and scintigraphic evaluation (particularly in the blood pool phase). One of the conditions, that qualify a patient for RSV, is the presence of inflammatory changes in BS3.[26] In this paper, we have tried to assess the therapeutic effectiveness of RSV, by means of BS3. BS3 plays a crucial role in the diagnosis of early articular changes. In more advanced stages its role is complementary to radiographical investigations in the assessment of prognosis and therapy efficacy.[32] Similar to other authors,[32,33] we have observed a considerable normalization of the blood pool and to a lesser degree of metabolism after RSV. This observation proves BS3 to be a useful diagnostic tool that truly reflects joint changes.

Repeated RSV treatment procedures may be applied in the same joint after a minimum interval of 6 months, according to EANM guidelines.[26] Single RSV treatment, response usually has a delay of onset of 3–6 months and lasts up to 24 months. For this reason, we followed-up our patients for 6 months. The co-administration of glucocorticoids immediately after the ^{177}Lu-HA injection is considered to have a beneficial effect as early as the 1st week and up to 4 months and is used to reduce the risk of acute radiation induced synovitis, due to ^{177}Lu injection.[3] The RSV side-effects and complications observed were minimal and not significant as is usually expected.[34]

Conclusion

Preliminary clinical investigations were carried out on the efficacy of ^{177}Lu-labeled HA particles in RSV after intra-articular administration of 333 ± 46 MBq does of the agent in a small group of patients suffering from recurrent joint effusions and chronic synovitis of knee joints. The study indicated the potentiality of the agent as a viable and cost-effective radiopharmaceutical for use for the treatment of chronic RA of knee joints. The significant pain relief and improved mobility observed in all patients treated was encouraging. RSV efficacy can be confirmed by imaging and biochemical tests. Moreover, there is minimal radiation risk involved in the procedure and can

be performed on outpatient basis. Since, the number of centers performing radiation synovectomy is increasing all over the world, ^{177}Lu-HA showed the potential to emerge as a promising and cost-effective candidate considering its large-scale production feasibility and logistic advantage for transportation to distant places.

References

1. Wilder RL. Rheumatoid Arthritis. Epidemiology, pathology and pathogenesis. In: Shumacher HR, Klippel JH, Koopman WJ, editors. Primer on Rheumatic Diseases. 10th ed. Atlanta: Arthritis Foundation; 1993. p. 86-9.
2. Eberhardt K, Johnson PM, Rydgren L. The occurrence and significance of hand deformities in early rheumatoid arthritis. Br J Rheumatol 1991;30:211-3.
3. Emery P. Treatment of rheumatoid arthritis. BMJ 2006;332:152-5.
4. Hicks JE, Gerber LH. Rehabilitative management of rheumatic diseases. In: Hicks JE, Nicholas JJ, Swezey RL, editors. Handbook of Rehabilitative Rheumatology. Atlanta: American Rheumatism Association; 1998. p. 81-110.
5. Jennings F, Toffolo S, de Assis MR, Natour J. Brazil patient knowledge questionnaire (PKQ) and evaluation of disease-specific knowledge in patients with rheumatoid arthritis. Clin Exp Rheumatol 2006;24:521-8.
6. Gray RG, Gottlieb NL. Intra-articular corticosteroids. An updated assessment. Clin Orthop Relat Res 1983;177:235-63.
7. Heuft-Dorenbosch LL, de Vet HC, van der Linden S. Yttrium radiosynoviorthesis in the treatment of knee arthritis in rheumatoid arthritis: A systematic review. Ann Rheum Dis 2000;59:583-6.
8. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol 1994;33:461-3.
9. Fellinger K, Schmid J. Local therapy of rheumatic diseases. Wien Z Inn Med 1952;33:351-63.
10. Schneider P, Farahati J, Reiners C. Radiosynovectomy in rheumatology, orthopedics, and hemophilia. J Nucl Med 2005;46 Suppl 1:48S-54.
11. Chinol M, Vallabhajosula S, Goldsmith SJ, Klein MJ, Deutsch KF, Chinen LK, *et al*. Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: Potential radiopharmaceuticals for radiation synovectomy. J Nucl Med 1993;34:1536-42.
12. Unni PR, Chaudhari PR, Venkatesh M, Ramamoorthy N, Pillai MR. Preparation and bioevaluation of 166Ho labelled hydroxyapatite (HA) particles for radiosynovectomy. Nucl Med Biol 2002;29:199-209.
13. Chakraborty S, Das T, Banerjee S, Sarma HD, Venkatesh M. Preparation and preliminary biological evaluation of ^{177}Lu-labelled hydroxyapatite as a promising agent for radiation synovectomy of small joints. Nucl Med Commun 2006;27:661-8.
14. Deutsch E, Brodack JW, Deutsch KF. Radiation synovectomy revisited. Eur J Nucl Med 1993;20:1113-27.
15. Abbasi I, Ishfaq M, Sohaib M. Preparation and pre-clinical study of ^{177}Lu-labelled hydroxyapatite for application in radiation synovectomy of small joints. Q J Nucl Med Mol Imaging 2011;55:458-68.
16. Davis MA, Chinol M. Radiopharmaceuticals for radiation synovectomy: Evaluation of two yttrium-90 particulate agents. J Nucl Med 1989;30:1047-55.
17. Clunie G, Lui D, Cullum I, Edwards JC, Ell PJ. Samarium-153-particulate hydroxyapatite radiation synovectomy: Biodistribution data for chronic knee synovitis. J Nucl Med 1995;36:51-7.
18. Pandey U, Mukherjee A, Chaudhary PR, Pillai MR, Venkates M. Preparation and studies with 90Y-labelled particles for use in radiation synovectomy. Appl Radiat Isot 2001;55:471-5.
19. Chakraborty S, Das T, Chirayil V, Lohar SP, Sarma HD. Erbium-169 labeled hydroxyapatite particulates for use in radiation synovectomy of digital joints – A preliminary investigation. Radiochim Acta 2014. [In Press].
20. Harbert JC. Radio colloid therapy in joint diseases. In: Harbert JC, editor. Nuclear Medicine Therapy. New York: Thieme Medical; 1987. p. 169-86.
21. Pillai MR, Chakraborty S, Das T, Venkatesh M, Ramamoorthy N. Production logistics of ^{177}Lu for radionuclide therapy. Appl Radiat Isot 2003;59:109-18.
22. Das T, Pillai MR. Options to meet the future global demand of radionuclides for radionuclide therapy. Nucl Med Biol 2013;40:23-32.
23. Markou P, Chatzopoulos D. Yttrium-90 silicate radiosynovectomy treatment of painful synovitis in knee osteoarthritis. Results after 6 months. Hell J Nucl Med 2009;12:33-6.
24. Chrapko B, Zwolak R, Nocun A, Golebiewska R, Majdan M. Radiation synovectomy with 90Y colloid in the therapy of recurrent knee joint effusions in patients with inflammatory joint diseases. Rheumatol Int 2007;27:729-34.
25. Arzu Gencoglu E, Aras G, Kucuk O, Atay G, Tutak I, Ataman S, *et al.* Comparison of Tc-99m HIG and three-phase Tc-99m MDP bone scintigraphy for evaluating the efficacy of Yttrium-90 silicate radionuclide synovectomy. Clin Nucl Med 2003;28:277-85.
26. Clunie G, Fischer M, EANM. EANM procedure guidelines for radiosynovectomy. Eur J Nucl Med Mol Imaging 2003;30:BP12-6.
27. Taylor WJ, Corkill MM, Rajapaske CN. A retrospective review of yttrium-90 synovectomy in the treatment of knee arthritis. Br J Rheumatol 1997;36:1100-5.
28. Stucki G, Bozzone P, Treuer E, Wassmer P, Felder M. Efficacy and safety of radiation synovectomy with Yttrium-90: A retrospective long-term analysis of 164 applications in 82 patients. Br J Rheumatol 1993;32:383-6.
29. Jahangier ZN, Moolenburgh JD, Jacobs JW, Serdijn H, Bijlsma JW. The effect of radiation synovectomy in patients with persistent arthritis: A prospective study. Clin Exp Rheumatol 2001;19:417-24.
30. Farahati J, Schulz G, Wendler J, Körber C, Geling M, Kenn W, *et al.* Multivariate analysis of factors influencing the effect of radiosynovectomy. Nuklearmedizin 2002;41:114-9.
31. Kresnik E, Mikosch P, Gallowitsch HJ, Jesenko R, Just H, Kogler D, *et al.* Clinical outcome of radiosynoviorthesis: A meta-analysis including 2190 treated joints. Nucl Med Commun 2002;23:683-8.
32. Colamussi P, Prandini N, Cittanti C, Feggi L, Giganti M. Scintigraphy in rheumatic diseases. Best Pract Res Clin Rheumatol 2004;18:909-26.
33. Türkmen C, Zülflkar B, Taşer O, Tokmak H, Kílíçoglu O, Mudun A, *et al*. Radiosynovectomy in hemophilic synovitis: Correlation of therapeutic response and blood-pool changes. Cancer Biother Radiopharm 2005;20:363-70.
34. Kampen WU, Matis E, Czech N, Soti Z, Gratz S, Henze E. Serious complications after radiosynoviorthesis. Survey on frequency and treatment modalities. Nuklearmedizin 2006;45:262-8.

How to cite this article: Shinto AS, Kamaleshwaran KK, Chakraborty S, Vyshakh K, Thirumalaisamy SG, Karthik S, *et al.* Radiosynovectomy of Painful Synovitis of Knee Joints Due to Rheumatoid Arthritis by Intra-Articular Administration of ^{177}Lu-Labeled Hydroxyapatite Particulates: First Human Study and Initial Indian Experience. World J Nucl Med 2015;14:81-8.

Source of Support: Nil, **Conflict of Interest:** None declared