RHEUMATOLOGY RESEARCH JOURNAL

Vol. 5, No. 3, July 2020,
Webpage: http://rheumres.org
Email: editor@rheumres.org
ISSN:2476-5856
doi: 10.22631/rr.2020.69997.1098

Original Article Open Access

Feasibility and Toxicity of Intra-Articular ^{188}Re-tin Colloid Injection in Patients with Rheumatoid Arthritis with Three-Phase Positive Bone Scan and Refractory Knee Pain, a pilot study

Zahra Mirfeizi[1], Nasim Norouzbeigi[2], Maryam Sahebari[1], Mohammad Hassan Jokar[1], Zahra Rezaei Yazdi[1], Seyed Rasoul Zakavi[3], Sousan Shafiei[3], Atena Aghaee[3]*

[1]Rheumatic Diseases Research Center (RDRC), Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.[2]Nuclear Medicine Department, Razavi Hospital, Imam Reza International University, Mashhad, Iran.[3]Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that causes chronic synovial inflammation. Reactor-produced β−particle emitting radionuclides is a new therapeutic strategy in the management of RA. This study was conducted in 2019 and analyzed the toxicity and feasibility of ^{188}Re-tin colloid injection, Three-Phase Positive Bone Scan, and Refractory Knee Pain. Ten patients with RA were administered radiosynovectomy with ^{188}Re-tin colloid. The main complications after the intervention were assessed and compared with patients' pre-intervention condition. Patients showed alleviation of pain, tenderness, and morning stiffness after the administration of radiosynovectomy. Only one RA patient received a corticosteroid injection; the other 6 patients did not need a corticosteroid injection after radiosynovectomy. Intra-articular ^{188}Re-tin colloid injection seems to be an effective treatment modality for refractory knee joint pain in rheumatoid arthritis patients. Thus, it is suggested as a safe and effective strategy to apply.

Keywords: knee joint, pain, rheumatoid arthritis, ^{188}Re-tin

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that causes chronic synovial inflammation and leads to articular cartilage destruction. In later stages, RA usually causes loss of joint mobility and overt disability [1]. In recent decades, interest in using reactor-produced β particle-emitting radionuclides for developing therapeutic radiopharmaceuticals has grown [2]. Selecting a suitable radionuclide for a specific therapeutic application is related to many factors, such as the half-life of the radiopharmaceutical, nature of particulate emission and energy, and concomitant γ-ray emission characteristics [3]. Several short-lived reactors that produce radionuclides have been introduced, such as ^{90}Y, ^{188}Re, ^{186}Re, ^{153}Sm, ^{166}Ho and ^{105}Rh, and ^{155}Lu which is used for radionuclide therapies and seems to have more favorable features, especially considering the half-life, in comparison with ^{89}Sr or ^{32}P [4].

^{188} Rhenium tin-colloid (^{188}Re-tin) has been used for synovectomy in patients with chronic inflammatory knee joint pain refractory to conventional treatments and has achieved proper results [5]. The on-demand availability of ^{188}Re from the ^{188}W/^{188}Re generator is an important feature and facilitates in-hospital radiopharmaceutical production. Rhenium-188 and technetium-99 have similar chemical properties and are presented as a "theragnostic pair". Using and imaging ^{188}Re-tin agents for therapy is the same as imaging agents prepared with ^{99m}Tc, which is the most commonly used diagnostic radionuclide due to its favorable characteristics [6]. The properties of ^{188}Re enable the treatment of knee joint disease through its maximum tissue penetration of approximately 11 mm and its mean range of 3.8 mm [7]. In the current study, the toxicity and feasibility of ^{188}Re-tin colloid injection in the knees of patients with RA and refractory knee pain were analyzed.

Materials and Methods

This clinical trial study was conducted from 2017 to 2019 at Ghaem Hospital, affiliated with Mashhad

*Corresponding Author: Atena Aghaee, MD, IBNM, Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. PO-Box: 91766-99199, E-mail: aghaeeat@mums.ac.ir aghaeeat@gmail.com, Telefax: 5138400494.

Received: 14 October 2019; **Accepted:** 24 April 2020

University of Medical Sciences, Mashhad, Iran. It was a pilot investigation to determine the feasibility of Intra-Articular ^{188}Re-tin colloid injection.

The study was approved by the Ethical Committee of Mashhad University of Medical Sciences under the approval code 8363557.

Ten RA patients with refractory knee joint pain were enrolled in this study. All patients had had at least one (range: 1-7) previous (>6 weeks prior) intra-articular corticosteroid injection and had suffered from arthritis for at least four years before treatment (range: 4-30 years). Moreover, all patients had experienced at least one previous intra-articular corticosteroid injection. In one patient, radiosynovectomy had been performed for both knees.

Patients were selected according to the inclusion criteria that comprised being more than18 years old and having RA, chronic knee pain and swelling despite oral corticosteroid therapy, a history of previous intra-articular corticosteroid injections (>6 weeks before therapy), and a positive 3-phase scintigraphy in the painful knee in a previous ^{99m}Tc-methylene bisphosphonate (bone) scan. Exclusion criteria were an age of <18 years, a history of recent intra-articular corticosteroid injections (i.e., <6 weeks prior to the study), a history of surgical or radionuclide synovectomy, baker cyst, tenderness, and redness in the injection area raising suspicions about inflammation or infection, elevated AST or ALT three times higher than the upper limit of the normal range, and serum Cr > 3 mg/dl.

Patients' pain was assessed using a patient-completed questionnaire on which pain was rated on the scale of 0 to 10 according to the Visual Analog Scale (VAS). The scores were checked and compared before and within six months after radiosynovectomy in three follow-up appointments after one week, three months, and six months of therapy.

Before each injection and at every follow-up visit, all patients underwent a laboratory evaluation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), and complete blood count (CBC) before radiosynovectomy. Follow-up appointments after treatment were scheduled at one week, three months, and six months. All ^{188}Re-tin colloid injections were performed after prepping by a single expert rheumatologist. Injections were given with all materials and processes maintained under total sterile conditions. Before radiotracer injection, a few drops of articular fluid were drained, and then the tracer was injected. The initial toxicities at one week and any complications in the first six months after therapy were investigated. The injection needle should have been fixed during the process. As the highest radiation exposure appears at the finger pulp, grasp-forceps were used to fix the injection needle during radiosynovectomy in the knee [8].

Patients' sleep disturbances before and after therapy were rated in the questionnaire using a ten-score scale and giving their sleep characteristics. Morning stiffness and its duration before and after therapy were assessed. Patients completed the self-assessment considering all these factors and revealed that their global assessment was good, fair, poor, or excellent before radiosynovectomy and at each follow-up appointment after therapy. The functional status of each patient according to ACR criteria was also checked before therapy and at each follow-up [9, 10].

Statistical Analysis

Statistical analysis was conducted using the SPSS software (v. 20.0, SPSS Inc. Chicago, IL, USA). Based on the results of normality tests (i.e. one sample Kolmogorov–Smirnov (K-S) test) continuous variables are presented as mean ± standard deviation (SD). Differences in proportions across the binary characteristics (i.e. gender) were assessed using a design-based chi-square test.

Results

In this study, eight women and two men aged between 25 and 71 years and suffering from RA participated, scoring their pain from 0 to 10 on the VAS scale, depending on its severity before radiosynovectomy therapy. While the mean value before treatment was six, the minimum value was four, and three patients scored their pain a 10.

Sleep disturbances before and after therapy were evaluated in the questionnaire using a ten-score scale, and patients' sleep characteristics were registered.

Morning stiffness and its duration before and after radiosynovectomy therapy were determined. Only one patient did not claim having morning stiffness before treatment; five patients complained of severe morning stiffness continuing more than 30 minutes. The results of other assessments are presented in Table 1.

During the post-therapy period, one patient required an increase in the dose of oral corticosteroid one week after therapy; the analgesic dose was increased in one patient and decreased in two patients. All patients had a significant reduction in pain except one who did not report any changes one week after radiosynovectomy. At the one-week evaluation, all patients but one presented with improved quality of sleep, and morning stiffness was remarkably decreased; five patients declared that they had no morning stiffness.

Table 1. Clinical profiles and patient status after radiosynovectomy.

Patient condition	Increase (N)	No change (N)	Decrease (N)
Corticosteroid consumption	1	6	-
Analgesic consumption	1	4	2
Pain reduction	-	1	6
Sleep disturbance	-	1	6
Morning stiffness	-	2	5
Range of motion	7	-	-
Improved global assessment	6	-	1

Range of motion was also increased at least 20 degrees in 7 patients in the first week after therapy. Patients also declared that their global assessment was significantly improved. No change was noted in the laboratory tests of the patients one week after radiosynovectomy.

After three months, three patients did not attend the follow-up appointment scheduled after radiosynovectomy. Only one of the seven visited patients had needed intra-articular corticosteroid injection, which had been performed two months after radiosynovectomy.

At the evaluation three months after ^{188}Re-tin colloid injection, the dose of analgesics was decreased in two patients but not changed in five other cases.

At the three-month follow-up after therapy, all seven patients reported a reduction in pain of at least 2 scores, and in six patients, sleep disturbance was improved. One other patient had a two-degree increment in sleep disturbance.

Morning stiffness was similar to the pre-therapy state in three patients and decreased in four patients. The range of mobility of the affected knee joint was increased three months after radiosynovectomy compared with the pre-treatment state.

In summary, the pain and subsequent need for analgesics, morning stiffness, and motion range impairment did not increase during the three months following radiosynovectomy.

Three patients recorded an improvement in their global assessment, and four patients reported that their global assessment had not changed compared with the pre-treatment evaluation.

A comparative study of changes in patients' clinical manifestations at the one-week and three-month follow–up visits after treatment revealed that patients' conditions were better than before treatment.

No alteration in laboratory test results, including serum liver enzymes, serum creatinine, and CBC, was noticed.

In a six-month evaluation of patients' conditions, four patients underwent intra-articular injection 45 days before their appointment.

The analgesic dose was not increased in any of the patients, but the pain scores of 8 patients had increased 1 to 3 points compared with the previous follow-up (i.e. three months after therapy). Morning stiffness was improved compared with all previous assessments. The global assessment showed improvement in all patients except one who had a worse global assessment than at the previous follow-up appointments. No alteration in laboratory data was noticed six months after injection.

None of the patients complained of increased pain or tenderness after therapy. In total, no side effects were reported during the entire follow-up period.

Discussion

This study reports that symptoms were alleviated in RA patients who experienced radiosynovectomy. The results revealed a reduction in morning stiffness, increase in range of motion, and a palliative effect on pain after the intervention were observed. Sleep disturbance was also improved in RA patients after radiosynovectomy. The satisfactory outcomes achieved during this investigation encouraged the team to continue the process and set it up as a conventional therapeutic strategy. Many other investigations have found this method to be helpful for patients' amelioration, and radiosynovectomy is increasingly being used as a therapeutic approach, particularly for rheumatoid disease. Complete reduction of knee joint swelling has been seen in some patients in multiple studies. Furthermore, in many investigations, pain relief was observed in RA patients after radiosynovectomy [8]. These results are similar to the results of the present study. Many researchers indicated acceptable results during two years of patient follow-up; knee joint swelling was reduced almost completely in about half of the cases, pain relief was achieved in most of the patients, and stretching deficiency was corrected (12). Some researchers have reported a good rate of improvement after 3-4 years [11, 12]. The follow-up in the current study was less than two years; thus, not all results can be compared. Nevertheless, the primary results were fairly similar. According to the high interest in radiosynovectomy that has grown during the last decades, ^{188}Re application has been developed for managing several diseases [7]. The development of other radionucleotides persuaded a group of researchers to compare Re-188 and Lutetium-177; they reported that despite the good effects of Re-188, Lutetium-177 can be an appropriate alternative with more acceptable results for RA patients [13].

An investigation on the same population administered P-32 to their participating patients and demonstrated knee improvement [8] with similar results as those of the current study. They indicated that swelling was diminished, and an increase in joint motion in the patients' follow-up evaluations was observed. They also reported that pain was relieved after radiosynovectomy with P-3 for 3 months, which is very close to the results of the current study. Other studies have revealed that radionuclides remained in the synovium after radiosynovectomy, while radionucleotides injected in the colloidal form cannot be transported by lymphatic vessels, exposing other organs to radiation (11).

The present data indicated that patients' amelioration rate was improved after radiosynovectomy. Many studies have illustrated that the response rate of radiosynovectomy is dependent upon the grade of synovitis. They have indicated the importance of disease stage in rheumatoid arthritis' response to treatment, so intervention in the early stage is essential for an optimal response [14].

One of the main limitations of the current study is the lack of classification based on disease stages. The main challenge of this type of study is the lack of a gold standard for evaluation of the objectives. Specialists should depend only on comparable parameters. A common scale for evaluation is a subjective scoring by the patient or four levels, e.g. excellent effect, good, moderate, and no effect to worsening [15]. This subjective scoring scale, but not a grading type, was used in this study.

One of the important issues in radiosynovectomy that should be considered during radiation exposure is toxicity. Investigations have shown that the possibility of toxicity on a patient's whole body is quite slight [8].

Studies have reported neither systemic nor local effects of radioisotopes. No leakage was observed during P-32 treatment [16]. No toxicity in the RA patients of the current investigation was observed. Nonetheless, the standard protocol was applied to protect the medical staff involved in the process. Although toxicity of the peripheral blood was not reported after any treatment, there is an important challenge to avoid possible leakages in some cases. The best solution is 48 h immobilization of the patient after therapy, which can reduce the leakage rate of radio-colloids by more than 2% [17]. Accordingly, this protocol was applied in the current study to avoid leakage.

Radiation exposure to the medical staff could result in some challenges. A France group demonstrated that the finger pulp had the highest radiation exposure, especially at the left thumb and forefinger. The radiation effects can be avoided by fixing the injection needle [18].

To the best knowledge of the authors, there is no similar project in Iran which has applied intra-articular ^{188}Re-tin colloid injections in patients with RA. As this was a pilot project, there were some limitations in gathering and reporting descriptive data. There is also lack of information about the patients who did not arrange follow-up appointments.

Conclusion

Radiosynovectomy performed by intra-articular injection of rhenium^{188} colloid seems to be an effective treatment modality for refractory knee joint pain in rheumatoid arthritis patients without any complications or radiation-induced toxicities. Thus, it can be suggested as a cost-effective, safe alternative procedure.

Acknowledgments

None.

Conflict of interest

Authors declare that they have no conflicts of interest.

References

1. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. ***JAMA*** 2018; 320(13):1360-72. doi: 10.1001/jama.2018.13103.
2. Qaim SM. Nuclear data for medical radionuclides. ***J Radioanal Nucl Chem*** 2015; 305(1):233-45. doi: 10.1007/s10967-014-3923-2
3. Qaim SM, Spahn I. Development of novel radionuclides for medical applications. ***J Labelled Comp Radiopharm*** 2018; 61(3):126-40. doi: 10.1002/jlcr.3578.
4. Van de Voorde M, Van Hecke K, Cardinaels T, Binnemans K. Radiochemical processing of nuclear-reactor-produced radiolanthanides for medical applications. ***Coordination Chem Rev*** 2019; 382:103-25. doi: 10.1016/j.ccr.2018.11.007.
5. Shamim SA, Kumar R, Halanaik D, Kumar A, Shandal V, Shukla J. *et al.* Role of rhenium-188 tin colloid radiosynovectomy in patients with inflammatory knee joint conditions refractory to conventional therapy. ***Nucl***

Med Commun 2010; 31(9):814-20. doi: 10.1097/MNM.0b013e32833d6869.

6. Lepareur N, Lacœuille F, Bouvry C, Hindré F, Garcion E, Chérel M. *et al*. Rhenium-188 labeled radiopharmaceuticals: current clinical applications in oncology and promising perspectives. ***Front Med (Lausanne)*** 2019; 6:132. doi: 10.3389/fmed.2019.00132.
7. Dash A, Knapp Jr FR. An overview of radioisotope separation technologies for development of 188 W/188 Re radionuclide generators providing 188 Re to meet future research and clinical demands. ***RSC Advances*** 2015; 5(49):39012-36. doi: 10.1039/c5ra03890a.
8. Knut L. Radiosynovectomy in the therapeutic management of arthritis. ***World J Nucl Med*** 2015; 14(1):10-15. doi: 10.4103/1450-1147.150509.
9. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y. *et al*. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. ***Arthritis Res Ther*** 2016; 18(1):251. doi: 10.1186/s13075-016-1151-6.
10. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. ***Arthritis Rheum*** 1992; 35(5):498-02. doi: 10.1002/art.1780350502.
11. Jodłowska-Cicio K, Telesińska-Jasiówka D, Bielińska A, Korkosz M. The use of radiosynovectomy in the rheumatologic practice. ***Forum Reumatol*** *2017*; 3(1): 18-23.
12. Özkan E. Radionuclide Pain Palliation Treatment and Radiosynovectomy. In: *Radionuclide Treatments.*Edited by Cigdem Soydal. IntechOpen; 2017:51-60.
13. Shamim SA, Arora G, Jha P, Gupta P, Behera A, Mukherjee A. *et al*. Comparison of Lutetium-177 tin colloid and Rhenium-188 tin colloid radiosynovectomy in chronic knee arthritis. ***Nucl Med Commun*** 2020; 41(8):721-26. doi: 10.1097/MNM.0000000000001210.
14. Mödder G. Radiosynoviorthesis (radiation synovectomy). In: *Clinical nuclear medicine.* Edited by Ahmadzadehfar H, Biersack HJ, Freeman LM, Zuckier SL, 2 edn. Springer, Cham; 2020: 1015-1024.
15. Liepe K. Efficacy of radiosynovectomy in rheumatoid arthritis. ***Rheumatol Int*** 2012; 32(10):3219-24. doi: 10.1007/s00296-011-2143-0.
16. Soroa VE, Velázquez Espeche MdH, Giannone C, Caviglia H, Galatros G, Fernández D. *et al*. Effects of radiosynovectomy with p-32 colloid therapy in hemophilia and rheumatoid arthritis. ***Cancer Biother Radiopharm*** 2005; 20(3):344-48. doi: 10.1089/cbr.2005.20.344.
17. Zuderman L, Liepe K, Zöphel K, Andreeff M, Kotzerke J, Luboldt W. Radiosynoviorthesis (RSO): influencing factors and therapy monitoring. ***Ann Nucl Med*** 2008; 22(9):735-41. doi: 10.1007/s12149-008-0167-7.
18. Ignas DM, Doria AS, von Drygalski A, Blanchette VS, Chang EY, Dover S. *et al*. Use of ultrasound for assessment of musculoskeletal disease in persons with haemophilia: Results of an International Prophylaxis Study Group global survey. ***Haemophilia*** 2020; 26(4):685-93. doi: 10.1111/hae.14006.