CLINICAL SCIENCE

EFFECTIVENESS OF RADIATION SYNOVECTOMY WITH SAMARIUM-153 PARTICULATE HYDROXYAPATITE IN RHEUMATOID ARTHRITIS PATIENTS WITH KNEE SYNOVITIS: A CONTROLLED RANDOMIZED DOUBLE-BLIND TRIAL

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doi: 10.1590/S1807-59322009001200008

Santos MF, Furtado RNV, Konai MS, Castiglioni MLV, Marchetti RR, Natour J. Effectiveness of radiation synovectomy with samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled randomized double-blind trial. Clinics. 2009;64(12):1187-93.

OBJECTIVES: The aim of the present study was to investigate the effectiveness of Samarium^{153}-particulate hydroxyapatite radiation synovectomy in rheumatoid arthritis patients with chronic knee synovitis.
METHODS: Fifty-eight rheumatoid arthritis patients (60 knees) with chronic knee synovitis participated in a controlled double-blinded trial. Patients were randomized to receive either an intra-articular injection with 40 mg triamcinolone hexacetonide alone (TH group) or 40 mg triamcinolone hexacetonide combined with 15 mCi Samarium^{153}-particulate hydroxyapatite (Sm/TH group). Blinded examination at baseline (T0) and at 1 (T1), 4 (T4), 12 (T12), 32 (T32), and 48 (T48) weeks post-intervention were performed on all patients and included a visual analog scale for joint pain and swelling as well as data on morning stiffness, flexion, extension, knee circumference, Likert scale of improvement, percentage of improvement, SF-36 generic quality of life questionnaire, Stanford Health Assessment Questionnaire (HAQ), Lequesne index, use of non-steroidal anti-inflammatory drugs or oral corticosteroids, events and adverse effects, calls to the physician, and hospital visits.
RESULTS: The sample was homogeneous at baseline, and there were no withdrawals. Improvement was observed in both groups in relation to T0, but no statistically significant differences between groups were observed regarding all variables at the time points studied. The Sm/TH group exhibited more adverse effects at T1 ($p<0.05$), but these were mild and transitory. No severe adverse effects were reported during follow-up.
CONCLUSION: Intra-articular injection of Samarium^{153}-particulate hydroxyapatite (15 mCi) with 40 mg of triamcinolone hexacetonide is not superior to triamcinolone hexacetonide alone for the treatment of knee synovitis in patients with rheumatoid arthritis at 1 y of follow-up.

KEYWORDS: Rheumatoid arthritis; Intra-articular injection; Radiosynoviorthesis; Radiation synovectomy; Samarium.

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 chemical, radioisotopic, or surgical means has been adopted as a therapeutic option in RA.[6,7] Most chemical synovectomy is performed using intra-articular injection (IAI) of glucocorticosteroids, the most effective of which has

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Received for publication on June 28, 2009
Accepted for publication on September 17, 2009

been shown to be triamcinolone hexacetonide (TH).[8]

Radiation synovectomy (RS) (also called radio-synoviorthesis or radiosynovectomy) is a local IAI of radionuclides in colloidal form for radiotherapy. First used by Fellinger et al.[9] in 1952, the technique has been applied for over 50 y in the treatment of resistant synovitis in individual joints after the failure of long-term systemic pharmacotherapy and intra-articular steroid injections. Radioisotopes with emission of β radiation have the capacity to diminish the inflammatory process and ablate the inflamed synovial membrane (pannus) with subsequent fibrosis.[10] Three radionuclides are currently in use: Yttrium-90 (^{90}Y-silicate/citrate), Rhenium-186 (^{186}Re-sulfide), and Erbium-169 (^{169}Er citrate), which have been indicated for large, medium, and small joints, respectively.[10] These radionuclides are indicated for treatment of joint pain arising from arthropathies, including RA, spondyloarthropathy, other inflammatory joint diseases (Lyme disease, Behçet's disease), persistent synovial effusion, hemophilic arthritis, calcium pyrophosphate dihydrate arthritis, pigmented villonodular synovitis, and undifferentiated arthritis.[10,12]

In clinical practice, RS is a procedure that has been widely used for several decades, mainly in European countries, Australia, and Canada,[11] especially for patients with refractory synovitis, (synovitis that fails to respond to at least one intra-articular injection with corticosteroids).[12]

Despite the established use of RS in clinical practice, there are few randomized, controlled studies using this technique in relation to the most often used radioisotopes: ^{186}Re, ^{169}Er and ^{90}Y.[7,10,12-24] Samarium^{153}-hydroxyapatite (^{153}SmPHYP) is considered another option for RS[25,26]; however, there are few well-conducted studies in the literature using ^{153}SmPHYP for the treatment of chronic synovitis. Therefore, we decided to develop a randomized controlled double-blinded study that aimed to investigate the effectiveness of ^{153}SmPHYP in RS for chronic knee synovitis in patients with RA.

PATIENTS AND METHODS

A controlled, randomized, double-blind prospective study was carried out comparing RS to ^{153}SmPHYP associated with TH versus IAI with TH alone for the treatment of knee synovitis in patients with RA.

Patients

This study included 58 consecutive patients (60 joints) with RA and chronic knee synovitis. Patients were recruited from the Rheumatology Outpatient Clinics at the Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil. The following were the inclusion criteria: diagnosis of RA (according to the ACR criteria) at least 6 mo prior to recruitment;[27] chronic monoarticular knee synovitis or oligoarticular arthritis with the knee being the more symptomatic joint for over 6 wks; age between 18 and 60 y; use of stable doses of oral corticosteroids for the previous 30 d and use of stable doses of DMARDs (disease modifying antirheumatic drugs) for the previous 3 mo; a score between 5 and 10 on a visual analog scale for pain (VAS, range 0-10 cm); reading and writing skills; and no risk of pregnancy (women with a history of hysterectomy, tubal ligation, or menopause). Written informed consent was obtained from all subjects, and the Ethics Committee approved the study. Exclusion criteria were as follows: patients with collagen diseases other than RA; pregnant or breast-feeding women; intra-articular knee injection in the previous 3 mo (or other joints); prior knee surgery or skin lesion; suspected septic arthritis or ruptured popliteal cyst (knee); urinary incontinence; any intervention in the knee in the previous 3 mo. Radiographs were performed with loads on the knees submitted to the procedure at the beginning of the study and later classified through "blinded" radiographic analysis according to the Kellgren-Lawrence scale for secondary osteoarthritis.[28]

After a period of 3 mo of follow-up, the patients could have their DMARDs modified. We opted for that flexibility in order to provide better clinical control of the disease and to increase the adherence of the patients.

Intervention

Lots with opaque sealed envelopes were used to randomly and equally allocate patients into two intervention groups: TH group, in which 30 patients (30 knees) received an IAI in the knee with 40 mg triamcinolone hexacetonide (TH) alone; and Sm/TH group, in which 28 patients (30 knees) received 40 mg TH combined with 15 mCi ^{153}SmPHYP. Both procedures were performed by the same researcher, and assessments were carried out by a blinded evaluator. In the case of bilateral synovitis, the knee with the higher visual analogue score (VAS) for pain was infiltrated. Inclusion of the same patient in the study for a second time was permitted if he/she fulfilled the inclusion criteria after three months from the initial intervention and exhibited arthritis in the contralateral knee. Inclusion a second time for the same knee was not permitted.

^{153}SmPHYP was provided by the "Instituto de Pesquisas Energéticas e Nucleares do Brasil" (IPEN). Both types of intervention were performed in the Nuclear Medicine Section following the bio-safety rules [10] for the use of radioactive material. Procedures were always performed

in the same fluoroscopy room. Threaded syringes were connected to a three-way tap and 50 x 8 mm needles were used to avoid reflux of the injected medication.

Procedure

Each patient underwent IAI guided by fluoroscopy while lying comfortably on their back. The knee was positioned at maximum extension with the needle entry point two centimeters from the upper-lateral angle of the patella subjected to eversion. Lidocaine (3 ml, 2%) with no vasoconstrictor was injected into the intra-articular region. Then, 3 to 5 ml of non-ionic iodated contrast medium was also injected. Distribution in the intra-articular recesses of the knee was viewed continuously by fluoroscopy. The Sm/TH group received 15 mCi injections of ^{153}SmPHYP diluted with 5 ml of 0.9% saline solution followed by 40 mg of TH. The TH group received 40 mg of TH alone.

A small amount of air was maintained in the syringe upon terminating infiltration so as to hinder subcutaneous reflux of the drugs. Systematic joint aspiration was performed prior to the injections in patients with synovial effusion. No patient had visual access to the procedure or preparation of the syringes.

All patients, regardless of group, remained at rest for four hours in a wheelchair in the Nuclear Medicine Section, and the knee was extended with the help of a splint.[26] Patients were then transported to their homes and were told to remain at rest with a splint on the infiltrated knee for 48 h, only getting up from the bed to attend to their physiological needs.

Evaluation

Patients were evaluated by a blinded physician at baseline (T0) as well as 1, 4, 12, 32, and 48 weeks after intervention (T1, T4, T12, T32, and T48, respectively). The following instruments were applied during all assessment sessions: VAS for joint pain and swelling (range: 0-10 cm), knee goniometry (flexion and extension), morning stiffness, knee circumference (cm), Likert scale of improvement (a lot of improvement, little improvement, unchanged, a little worse, much worse) according to the patient and the evaluator, percentage of improvement, Lequesne index,[29] calls to the physician, hospital visits, and adverse effects and events.

The following assessment instruments were applied through T12: Brazilian version of the Functional subscale of the Stanford Health Assessment Questionnaire (HAQ),[30] Brazilian version of the SF-36 generic quality of life questionnaire,[31] Lequesne index,[29] and use of non-steroidal anti-inflammatory drugs and oral corticosteroids.

The number of sodium diclofenac tablets and oral prednisone doses were counted at each time point, and average daily doses for these drugs were assessed. Patients were considered withdrawals if they interrupted the follow-up in the first month of the study; had altered DMARDs; or experienced an interruption of their disease for a period of two weeks or more. During the three-month follow-up period, the DMARDs were maintained stable, whereas prednisone and diclofenac doses could be altered according to need. After this period, there was flexibility for the following items: physiotherapy, acupuncture, infiltrations, and change in DMARDs according to the needs and activity of the disease.

Statistical Analysis

Data are presented as mean ± standard deviation. Chi-square analysis was used to evaluate differences between categorical variables. The Mann-Whitney test was used for analysis of non-parametric numerical variables. ANOVA analysis was performed to compare numerical variables repeated over time. The significance level was set at $p<0.05$. The Tukey multiple comparison test was performed for intra-group analysis. ANOVA with non-parametric repeated measurements was used in the analysis of ordinal data of the Likert scale. Data were analyzed according to the intention-to-treat principle and patients with missing data had the previous evaluation data repeated.

RESULTS

The sample was made up of 58 patients (60 knees). Two patients participated in the study twice and were randomized twice (once for each knee). The second randomization was for the contralateral knee and occurred three months after the intervention for the first knee. The data displayed in the tables refer to the number of knees and not the number of patients. There was no statistically significant difference between groups regarding joint, functional class, demographic, or disease-related variables at baseline (T0) (Table 1).

The radiological assessment was done according to the Kellgren-Lawrence scale[28] and no difference was found between the groups, even when the groups were stratified into five degrees (0 to 4) according to this scale (Table 1).

Three patients were absent from the T32 reevaluation (2 from the Sm/TH group and 1 from the TH) and four were absent from the T48 reevaluation (1 from the Sm/TH Group and 3 from the TH group).

In the **intra-group** analysis in relation to T0 (initial time), there was a statistically significant improvement at

Table 1- Characteristics of the sample at baseline

	Sm/TH Group (n=30)	TH Group (n=30)	p#
Age, years (Mean±SD)	54.8 (±8.04)	54.4 (±7.4)	0.491
Gender (Women/ Men)	25:5	27:3	0.447
Race (White)	24	20	0.11
Disease duration, years (Mean±SD)	12.07 (±9.4)	13.2 (±12)	0.677
Rheumatoid Factor (positive) (%)	19 (63.3%)	20 (66.7%)	0.787
Functional class II: III	9:21	13:17	0.284
DMARDS (%)	28 (93.3%)	27 (90%)	0.640
Methotrexate (%)	24 (80%)	23 (76.6%)	0.754
Chloroquine diphosphate (%)	4 (13.3%)	4 (13.3%)	1.000
Sulfasalazine (%)	1 (3.3%)	2 (6.7%)	0.554
Leflunomide (%)	6 (20%)	8 (26.7)	0.542
Infliximab (%)	0 (0%)	1 (3.3%)	0.313
Time from past infiltration of the knee (months) Mean±SD	12.4 (±15.4)	15.4 (±16.9)	0.954
Kellgren-Lawrence Classification			
Grade 0	1	3	0.269
Grade 1	5	8	
Grade 2	6	9	
Grade 3	14	9	
Grade 4	4	1	

TH group: triamcinolone hexacetonide (TH); Sm/TH group: ^{153}SmPHYP + TH; SD=standard deviation; #*p* = Pearson's chi-square, Mann-Whitney test

all evaluation times for the VAS for pain and swelling; at T1 for morning stiffness; at T1, T4, and T12 for joint flexion; at T1 and T4 for joint extensions; and from T4 to T48 for knee circumference in both groups (Table 2). In the **inter-group** analysis throughout the evolution of the study, no differences were observed between groups regarding the local variables (VAS for pain and swelling, morning stiffness, knee flexion, extension, and circumference) (Table 2).

There were no statistical differences between the groups for the following variables: Likert scale of improvement according to patient and evaluator, percentage of improvement, HAQ (Table 3) and SF-36 questionnaires, Lequesne index (Table 3), use of non-steroidal anti-inflammatory drugs and oral corticosteroids (Table 4), calls to the physician and hospital visits.

Side effects were divided into two groups: ***adverse effects*** were those cited by either the patient or evaluator as likely related to the procedure; ***events*** were situations of any nature cited by either the patient or evaluator. Twenty-two adverse effects were registered in the evolution of the patients, the most frequent of which was post-injection flare (6.7% of the initial sample) with an average duration of 2.25 d (1 to 4 d) after infiltration that did not persist through to the T1 evaluation. The Sm/TH group exhibited more adverse effects than the TH group at T1 ($p<0.015$), but in the evaluations T4 to T48 the number of adverse effects was similar in both groups. Three of the five adverse effects (60%) in the TH group occurred before the T1 evaluation.

Table 2 - Assessment of clinical parameters

Time Points (weeks)	Sm/TH Group (n=30) Mean±SD	TH Group (n=30) Mean±SD	Inter-group p**
	VAS for pain (0-10 cm)		0.607
T0	6.8 (1.4)	6.8 (1.4)	
T1	**2.3 (2.4)***	**2.0 (2.1)***	
T4	2.9 (2.6)*	2.6 (2.6)*	
T12	3.4 (2.8)*	3.0 (2.5)*	
T32	4.5 (3.0)*	4.3 (3.2)*	
T48	3.8 (3.2)*	3.8 (3.3)*	
	VAS for swelling (0-10 cm)		0.179
T0	3.9 (2.0)	3.8 (1.8)	
T1	**1.6 (1.7)***	**1.0 (1.4)***	
T4	1.1 (1.1)*	0.9 (1.4)*	
T12	1.3 (1.3)*	0.7 (1.0)*	
T32	1.6 (1.5)*	1.2 (1.4)*	
T48	1.5 (1.7)*	1.0 (1.6)*	
	Morning stiffness		0.413
T0	14.2 (14.9)	32.5 (55.2)	
T1	**4.8 (12.9)***	**1.9 (5.8)***	
T4	6.2 (13.9)	4.1 (11.5)	
T12	6.6 (22.0)	2.2 (5.0)	
T32	12.2 (26.2)	26.9 (76.6)	
T48	8.8 (15.5)	11.5 (33.3)	
	Knee flexion (grade)		0.661
T0	116.1 (14.6)	115.03 (14.5)	
T1	**119.4 (16.7)***	**121.97 (16.3)***	
T4	120.5 (15.3)*	123.17 (16.4)*	
T12	120.4 (12.5)*	121.93 (16.9)*	
T32	117.6 (15.1)	120.3 (16.9)	
T48	118.0 (15.2)	119.7 (18.0)	
	Knee extension (grade)		0.096
T0	7.7 (8.5)	3.1 (5.3)	
T1	**4.0 (5.9)***	**1.8 (4.0)***	
T4	3.5 (5.2)*	1.9 (4.0)*	
T12	4.4 (5.8)	3.0 (7.3)	
T32	6.5 (8.3)	3.3 (6.0)	
T48	6.6 (8.7)	3.6 (6.8)	
	Knee circumference (cm)		0.875
T0	40.0 (3.8)	39.9 (3.3)	
T1	**38.4 (7.3)**	**39.3 (3.9)**	
T4	39.3 (4.0)*	38.9 (3.8)*	
T12	39.7 (3.8)*	39.1 (4.3)*	
T32	39.6 (4.0)*	39.2 (4.2)*	
T48	39.3 (4.1)*	38.9 (4.5)*	

TH group: triamcinolone hexacetonide (TH); **Sm/TH group**: ^{153}SmPHYP + TH; **VAS:** visual analog scale; **SD**=standard deviation; **ANOVA for repeated measurements; **p< 0.05* (intra-group p in relation to T0): Tukey multiple comparison test

Table 3 - Knee function according to the Lequesne and HAQ questionnaires

Time Points (weeks)	Sm/TH Group (n=30) Mean±SD	TH Group (n=30) Mean±SD	Inter-group p**
	Lequesne index		0.889
T0	16.6 (3.2)	17.2 (2.8)	
T1	11.8 (4.5)*	11.0 (5.0)*	
T4	11.6 (4.8)*	11.2 (5.0)*	
T12	12.0 (4.4)*	11.6 (5.1)*	
T32	13.2 (4.8)*	13.4 (4.7)*	
T48	13.2 (4.4)*	13.1 (4.5)*	
	HAQ		0.077
T0	1.3 (0.5)	1.6 (0.5)	
T1	1.0 (0.5)*	1.2 (0.5)*	
T4	1.0 (0.5)*	1.2 (0.6)*	
T12	1.2 (0.5)*	1.4 (0.7)*	

TH group: triamcinolone hexacetonide (TH); **Sm/TH group**: ^{153}SmPHYP + TH; **SD**=standard deviation; **ANOVA for repeated measurements; *$p< 0.05$ (p intra-group p in relation to T0): Tukey multiple comparison test

Table 4 - Use of number of sodium diclofenac tablets and oral prednisone (doses)

Time Points (weeks)	Sm/TH Group (n=30) Mean±SD	TH Group (n=30) Mean±SD	Inter-group p**
	NSAIDS, tablets/day (Mean±SD)		0.782
T0	0.63 (1.07)	0.63 (0.99)	
T1	0.63 (0.99)	0.64 (0.87)	
T4	0.80 (1.01)	0.77 (0.97)	
T12	0.80 (1.04)*	1.07 (1.15)*	
	Prednisone, mg/day (Mean±SD)		0.064
T0	5.1 (6.0)	7.1 (5.3)	
T1	**5.3 (5.8)**	**6.6 (5.7)**	
T4	5.9 (5.5)	7.5 (5.0)	
T12	5.5 (5.4)	7.6 (5.3)	

TH group: triamcinolone hexacetonide (TH); **Sm/TH group**: ^{153}SmPHYP + TH; **NSAID**= non-steroidal anti-inflammatory drug; **SD**=standard deviation; **ANOVA for repeated measurements; *$p< 0.05$ (p intra-group p in relation to T0): Tukey multiple comparison test

A femur fracture occurred in one patient from the Sm/TH group with risk factors for osteoporosis. This fracture was considered a casual event and occurred after 11 mo of follow-up. There were no statistically significant differences between groups regarding events throughout the study (Table 5).

One patient from the Sm/TH group required re-infiltration of the knee with TH after 8 mo, and 2 patients from the TH group required re-infiltration of the knee after three and eight months from the intervention due to the recurrence of arthritis (p= 1.00). After three months, 27 patients (14 from the Sm/TH group and 13 from the TH group**;** p= 0.795) modified the use of DMARDs due to activity of their disease.

Table 5 - Distribution of the types of adverse effects and events between groups

ADVERSE EFFECTS	Sm/TH Group (n=30)	TH Group (n=30)
Post-injection flare (T1)	2	2
Urticaria (T1)	2	0
Pruritus (T1, T4)	2	0
Chills (T1)	1	0
Headache (T1)	2	0
Rash on face (T1)	1	0
Sweating (T1)	1	0
Hot flashes (T1)	2	1
Hypertensive peak (T1, T4)	1	1
Insomnia (T4)	0	1
Swelling of lower limbs (T12)	1	0
Increased instability (T12,T48)	2	0
EVENTS	Sm/TH Group (n=30)	TH Group (n=30)
Polaciury (T1)	0	1
Urinary tract infection (T1)	1	0
Acute sinus condition (T4)	0	1
Asthma episode (T4)	0	1
Vaginal Candidiasis (T32)	0	1
Femur fracture (T48)	1	0
Detached retina (T48)	0	1

TH group: triamcinolone hexacetonide (TH); **Sm/TH group**: ^{153}SmPHYP + TH; **SD**= standard deviation

DISCUSSION

The effectiveness and cost benefit of RS for patients with chronic synovitis have not yet reached a consensus in the medical literature. Despite the fact that RS has a higher cost than IAI with GC, the benefit of its use is the impression of a greater response, longer duration of response in comparison to chemical synovectomy through corticosteroid use, and its use as an option for treatment of refractory synovitis.[10,12] In our study, ^{153}SmPHYP was chosen because it is available for use in our country and for its properties. ^{153}SmPHYP is a radionuclide with a half-life of 46.3 h and β^- energy of 0.29 MeV, resulting in a maximum penetration of 3.1 mm and therapeutic penetration of 0.7 mm into soft tissue.[25,26] The ^{153}SmPHYP compound emits a small amount of gamma radiation, which is suitable for imaging by gamma camera equipment and is associated with low levels of leakage after injection, safe, and good tolerance.[25,26,34] There is also a possible fibrotic action of this compound on the pannus, enabling more lasting control over inflammation. Therefore, use of this radioisotope is theoretically superior to the use of TH alone.

There are few controlled, randomized trials in the literature comparing RS with IAI of glucocorticosteroids. ^{186}Re is used for synovectomy of medium-sized joints and

has been assessed in controlled, randomized prospective and retrospective trials that demonstrate its superiority to IAI of glucocorticosteroids.[19,20,24] So far, there is no consensus about the superiority of RS with ^{169}Er (used in small joints) over IAI of glucocorticosteroids.[21,22] Synovectomy by ^{90}Y has been studied in some controlled trials and has been shown to be superior to IAI of saline solution,[10,13-15] but studies comparing it to IAI of glucocorticosteroids have had conflicting results.[16-18] A systematic review regarding RS with ^{90}Y concluded that there is no clear evidence of greater efficacy of ^{90}Y over IAI of glucocorticosteroids despite its frequent use in cases of refractory synovitis.[7] New radioisotopes such as Dysprosium-165 Ferric Hydroxide Macroaggregate (^{165}Dy) and Holmium-166 (^{166}Ho) have been developed, but their effectiveness and superiority have not yet been proven in clinical trials.[32,33]

The only controlled, double-blinded study of ^{153}SmPHYP similar to the present study was carried out by O' Duffy et al. (1999), who found no difference between the groups studied.[26] However, sixty patients with different inflammatory arthropathies participated in this study and few assessment instruments were used.[26] In the present study, only patients with RA participated and more objective instruments were used, rather than just scores, including those that assess inflammation, function, quality of life, subjective improvement, and adverse effects and events. The present study also found no statistically significant differences between groups for the diverse variables studied.

A trial with the same experimental design as the present study demonstrated through magnetic resonance a statistically greater reduction in synovitis of the knee in the group using IAI of TH alone in a three-month follow-up.[34] However, it only analyzed evolution through an imaging method and for a much shorter follow-up period. Nonetheless, the findings of that study corroborate the impression that the addition of ^{153}SmPHYP to TH does not increase the effectiveness of the glucocorticosteroids when injected into the intra-articular region.[34]

Studies on ^{153}SmPHYP for RS describe no side effects attributed to the radioisotope.[25-26] The present study found more adverse effects in the Sm/TH group than in the TH group, but the difference was only significant in the T1 evaluation *($p<0.015$)* and the effects were mild with a short duration and spontaneous remission. Most of the side effects were systemic and were also described for IAI of glucocorticosteroids.[6] Post-injection flare occurred at an equal frequency in both groups, with an average duration of 2.25 d (1 to 4 d), and these effects did not persist until T1 evaluation.

In the present comparison study of RS with ^{153}SmPHYP associated with TH and IAI of TH alone, no difference was found, which confirms the results of the study by O' Duffy et al.[26.]

The results show that RS with ^{153}SmPHYP associated with TH is not superior to IAI of HT alone, and that the positive effects may be attributed to the concomitant use of HT.[13-16,18]

Some theories may explain the similar results between the groups studied: ^{153}SmPHYP penetration may not have been effective for the knee, which is a large joint, or its dosage may have been too small.

We conclude that IAI of ^{153}SmPHYP at a dosage of 15 mCi associated with TH was not superior to administration of TH alone for the treatment of synovitis of the knee in RA patients with a one-year follow-up. There is a need for studies with longer follow-up periods in order to more completely evaluate the benefit of ^{153}SmPHYP in these patients' knees. ^{153}SmPHYP may be useful in medium-size joint, such as wrists, elbows, and ankles, because it exhibits tissue penetration similar to ^{186}Re, which is also used in these joints.[35] Thus, further studies assessing higher doses in the knees and similar doses in medium-sized joints are important for determination of the true effectiveness of RS through ^{153}SmPHYP.

ACKNOWLEDGEMENTS

This work was supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil).

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