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ORIGINAL ARTICLE

Effectiveness of radiation synovectomy with Yttrium-90 and Samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled, randomized, double-blinded trial

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Abstract The aim of the present study was to investigate the long-term effectiveness of and tolerance to Yttrium-90 and Samarium-153-particulate hydroxyapatite radiation synovectomy in patients with rheumatoid arthritis (RA) and chronic knee synovitis. Eight-four patients (90 knees) with chronic knee synovitis and RA (according to the American College of Rheumatology criteria) participated in a controlled, double-blinded trial. Patients were randomized to receive an intra-articular injection with either 5 mCi Yttrium-90 plus 40 mg of triamcinolone hexacetonide (Y/TH Group), 15 mCi Samarium-153 hydroxyapatite plus 40 mg of triamcinolone hexacetonide (Sm/TH Group), or 40 mg triamcinolone hexacetonide alone (Control Group). Blinded examination at baseline, 1, 4, 12, 32, and 48 weeks post-intervention included a visual analog scale for joint pain and swelling, morning stiffness, range of motion, knee circumference, Likert scale, percentage of improvement, Stanford Health Assessment Questionnaire, Lequesne index, use of non-steroidal anti-inflammatory drugs and corticosteroids, events and adverse effects, calls to the physician, and hospital visits. There were three withdrawals prior to the injections. Regarding the pain, there was a significantly better response in the Y/TH Group versus the Sm/TH Group at T1 ($p=0.025$) and versus TH alone at T48 ($p=0.026$). The Sm/TH group had more adverse effects ($p=0.042$), but these were mild and transitory. For the pain parameter alone, Yttrium-90 radiosynovectomy associated to TH proved superior to Samarium-153 hydroxyapatite radiosynovectomy associated to TH at T1 and to synovectomy with TH at T48. No other statistically significant inter-group differences were detected.

Keywords Intra-articular injection · Radiation synovectomy · Rheumatoid arthritis · Samarium · Yttrium

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Introduction

Rheumatoid arthritis (RA) is a progressive, chronic, systemic, inflammatory disease of a multi-factor origin [1]. Current treatment involves medication [2,–6] and joint procedures such as intra-articular injection (IAI) and preventive or deformity-repairing surgery [7, 8].

IAIs with GC (corticosteroids) are generally indicated in cases of RA with persistent monoarthritis or oligoarthritis [9]. There is scientific evidence of the superior effectiveness of and tolerance to IAI over the systemic use of GC in cases of mono- and polyarthritis [10, 11]. Controlled studies have demonstrated that triamcinolone hexacetonide (TH) is the corticosteroid with the least solubility, longest intra-articular duration, and greatest effectiveness for intra-articular use in RA [9, 12,–18]. Radioisotopic synovectomy, radiation synovectomy, radiosynovectomy, or radiosynoviorthesis (RS) is another local treatment option and consists of an IAI procedure in which the injected drug is a radioisotope with mainly β radiation emission that has the ability to penetrate the synovial layers, leading to fibrosis of the synovial membrane and consequent atrophy of the rheumatoid pannus [19].

There are a number of beta radiation-emitting drugs used for RS, either together with corticosteroids or alone. The mostly used are Yttrium-90 (^{90}Y), Erbium-169 (^{169}Er), and Rhenium-186 (^{186}Re) [20]. RS is indicated for patients for whom there was failure of at least one IAI with corticosteroids [20]. It is mainly employed in RA due to the exuberant pannus caused by the disease, but is also used in hemophilic arthritis, arthrosis caused by the deposition of calcium pyrophosphate crystals, pigmented villonodular synovitis, and persistent synovitis following the placement of a prosthesis. This procedure may also be indicated in cases of incomplete arthroscopic synovectomy or those with refractory synovitis following prosthetic surgery in order to treat residual synovitis [19–22].

The radioactive product is chosen based on the joint to be treated. ^{90}Y is very penetrating and energetic and is used exclusively in the knee, where the synovial pannus has a greater thickness (mean and maximal tissue penetration of 3.6 mm and 11 mm, respectively; maximal β energy emission of 2.25 MeV). ^{169}Er is far less energetic and penetrating, which allows its use on small joints, such as interphalangeal and metacarpophalangeal joints (mean and maximal tissue penetration of 0.3 mm and 1.0 mm, respectively; maximal β energy emission of 0.34 MeV). ^{186}Re has intermediate characteristics and is used on joints such as the wrist, elbow, ankle, shoulder, and hip (mean and maximal tissue penetration of 1.2 mm and 3.7 mm, respectively; maximal β energy emission of 1.07 MeV and little gamma emission) [19, 23]. A large number of investigations have reported the effectiveness of RS performed with ^{90}Y, but most are older studies of poor methodological quality [24–32, 48, 49]. In literature reviews, Jones et al. [33] and Heuft Dorenbosch et al. [7] concluded that there was no scientific evidence of the superiority of ^{90}Y over IAI with corticosteroids.

Samarium-153 particulate hydroxyapatite (^{153}SmPHYP) is a radioisotope linked to hydroxyapatite that has mainly β radiation emission and was developed for intra-articular use in RS. It has a half-life of 46.3 h and a β radiation emission capacity of 0.29 MeV, resulting in mean and maximal tissue penetration of 0.7 mm and 3.1 mm, respectively [34]. As it also has γ radiation, conventional γ camera equipment allows the assessment of its distribution in organs and tissues [35]. The size of the hydroxyapatite particles allows them to be phagocytized by synoviocytes following their intra-articular injection [35]. The effectiveness of ^{153}SmPHYP for the treatment of knee synovitis has been assessed in open studies [36] and controlled studies [37, 38] which have not demonstrated any superiority over TH. However, only the study by Dos Santos et al. (2009) [38] was made up of a homogeneous sample involving only patients with RA.

Therefore, the aim of the present study was to investigate the effectiveness and tolerance to RS with ^{153}SmPHYP and ^{90}Y in patients with chronic knee synovitis and rheumatoid arthritis, comparing this procedure to IAI with TH.

Methods

A controlled, randomized, double-blind prospective trial was carried out comparing RS with ^{90}Y associated to TH versus RS with ^{153}SmPHYP associated to TH versus IAI with TH alone for the treatment of knee synovitis in patients with RA.

Patients

Eight-four patients (90 knees) with chronic knee synovitis and RA participated in the study. Patients were recruited from the Rheumatology Outpatient Clinics of the Universidade Federal de São Paulo, São Paulo, Brazil. The following were the inclusion criteria: diagnosis of RA (according to the American College of Rheumatology criteria) at least 6 months prior to recruitment [39]; chronic knee synovitis, with the knee as the most symptomatic joint for over 6 weeks; age between 18 and 60 years, use of stable doses of oral corticosteroids in the previous 30 days, and use of stable doses of disease-modifying anti-rheumatic drugs (DMARDs) in the previous 3 months, 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). ^{153}SmPHYP and ^{90}Y can also be delivered to women using contraceptive drugs; however, we opted to exclude such patients due to the difficulty in monitoring contraceptive drug compliance. The following were the exclusion criteria: patients with collagen diseases other than RA, pregnant or breastfeeding women, intra-articular injection in the knee or other joint in the previous 3 months, prior knee surgery or skin lesion, suspected septic arthritis or ruptured popliteal cyst (knee), urinary incontinence, and any intervention in the knee in the previous 3 months. Written informed consent was obtained

from all subjects and the Ethics Committee approved the study. 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 using the Kellgren–Lawrence scale for secondary osteoarthritis [40]. After a 3-month follow-up period, the patients could have their DMARDs modified. The aim of this flexibility was to provide better clinical control of the disease and maximize patient adherence.

Intervention

The patients were allocated by simple randomization into three intervention groups using opaque-sealed envelopes: Y/TH Group—intra-articular injection with 5 mCi of Yttrium-90 plus 40 mg of triamcinolone hexacetonide, Sm/TH Group—intra-articular injection with 15 mCi of Samarium-153 particulate hydroxyapatite plus 40 mg of triamcinolone hexacetonide, and Control Group—intra-articular injection with 40 mg of triamcinolone hexacetonide alone. The 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 analog score (VAS) for pain was injected. Inclusion of the same patient in the study for a second time was permitted if the patient fulfilled the inclusion criteria after 3 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). ^{90}Y was imported by IPEN from Cis Bio Schering International (France). All procedures were done at the Nuclear Medicine Sector. Handling of the radioisotopes was in compliance with biosafety rules. Procedures were always performed in the same fluoroscopy room. Threaded syringes were connected to a three-way tap and 50×8-mm needles were used to avoid reflux of the injected medication.

Procedure

Each patient underwent fluoroscopy-guided IAI while lying comfortably on their backs. The knee was positioned at maximal extension with the needle entry point 2 cm from the upper lateral angle of the patella submitted to eversion. Lidocaine (3 ml, 2%) with no vasoconstrictor was injected into the joint. Three to five milliliters of non-ionic iodated contrast medium was also injected. Distribution in the intra-articular recesses of the knee was viewed continuously through fluoroscopy. The Y/TH group received 5 mCi of ^{90}Y diluted with 5 ml of 0.9% saline solution followed by 40 mg of TH. 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 little air was kept in the syringe avoiding 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 the group, remained at rest for 4 h in a wheelchair in the Nuclear Medicine Sector, and the knee was extended with the aid of a splint. So, the patients were then transported to their homes and they were made aware to remain at rest with splint on the infiltrated knee for 48 h.

Evaluation

Patients were assessed by a "blinded" physician at baseline (T0), 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), range of motion (ROM), morning stiffness, knee circumference (centimeters), Likert improvement scale (a lot of improvement, little improvement, unchanged, a little worse, much worse) according to the patient and evaluator, percentage of improvement, Lequesne index [41], calls to the physician, hospital visits, and adverse effects and events, use of non-steroidal anti-inflammatory drugs and oral corticosteroids; the Brazilian version of the Functional subscale of the Stanford Health Assessment Questionnaire (HAQ) [42] and Brazilian version of the SF-36 generic quality of life questionnaire [43] were applied at T1–T12 and T48.

The number of sodium diclofenac tablets and oral prednisone doses was counted at each evaluation and average daily doses for these drugs were recorded. Patients were considered withdrawals if they interrupted the follow-up in the first month of the study, had DMARDs altered, or experienced an interruption in their disease for a period of 2 weeks or more. During the 3-month follow-up period, 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, injections, and change in DMARDs according to need and activity of the disease.

Statistical analysis

Data are presented as mean±standard deviation. The significance level was set at $p<0.05$. Chi-square analysis was used to evaluate differences between categorical variables. Kruskal–Wallis test and one-way analysis of variance (ANOVA) were used for the analysis of numerical variables. ANOVA analysis was performed to compare numerical variables repeated over time. ANOVA with non-parametric repeated measurements was used in the analysis of ordinal data from the Likert scale. After ANOVA

analysis, Tukey multiple comparison test was performed for inter-group analysis and Bonferroni multiple comparison test to intra-group analysis.

Results

After three withdrawals, the final sample of the present study was made up of 87 knees (81 patients). Six patients participated in the study twice and were randomized twice (once for each knee). The second randomization was for the contralateral knee and occurred at least 3 months after the intervention on the first knee. The data displayed in the tables refer to the number of knees rather than the number of patients. There were no statistically significant differences between groups regarding baseline (T0) variables (Table 1).

The radiological assessment was performed using the Kellgren–Lawrence scale [40], and no differences were found between groups. Six patients were absent from the T32 evaluation (two from the Sm/TH group, one from the Y group, and three from the TH group). Two patients were absent from the T48 evaluation (one from the Y group and one from the TH group). In these cases, the data from the previous evaluation were repeated for the statistical analysis.

There was a statistically significant difference between groups regarding the VAS for pain variable, favoring the Y/TH group (p=0.022; Table 2). No significant differences between groups were found for the other variables throughout the study (Table 2). The Y/TH group had statistically lower VAS for pain scores in comparison to the Sm/TH group at T1 (p=0.025) and in comparison to the TH group at T48 (p=0.026; Table 3 and Fig. 1).

In the intra-group analysis, there was a statistically significant improvement at all evaluation times in relation to T0 (baseline) for VAS for pain, morning stiffness, swelling, and ROM and from T4 to T48 for knee circumference in all three groups (Table 2). There were no statistically significant differences between groups for the following variables: Likert scale of improvement according to patient and evaluator, percentage of improvement (Table 4), Lequesne index [41] and HAQ [42] (Table 3), SF-36 questionnaire [43], use of non-steroidal anti-

Table 1 Characteristics of sample at baseline

Time points (weeks)	Sm/TH group[a] (n=29)	Y/TH group[b] (n=28)	TH group[c] (n=30)	p
Age, years (mean±SD)	53.5±5.7	54.2±7.1	52.4±8.8	0.646[a]
Gender (women/men)	28:1	25:3	25:5	0.249[b]
Race (white/non-white)	24:5	20:8	22:8	0.560[b]
Disease duration, years	9.0±7.1	9.3±6.9	7.3±5.6	0.448[a]
FR+	19	14	13	0.218[b]
Functional class I/II/III	3:14:12	1:12:15	1:14:15	0.706[b]
DMARDs	28	24	28	0.304[b]
Methotrexate	26	24	26	0.896[b]
Chloroquine diphosphate	6	4	4	0.708[b]
Sulfasalazine	1	2	3	0.610[b]
Leflunomide	5	2	4	0.513[b]
Infliximab	0	1	1	0.598[b]
Time since past knee injection (months) (mean±SD)	14±10	18±22.7	15.3±9.4	0.673[c]
Fibromyalgia	7	8	8	0.930[b]
Kellgren–Lawrence Classification				0.582[b]
Grade 0	2	2	1	0.819[b]
Grade 1	6	3	10	0.143[b]
Grade 2	10	11	9	0.905[b]
Grade 3	9	11	10	0.905[b]
Grade 4	2	1	0	0.564[b]

SD standard deviation, *Sm/TH group* ^{153}SmPHYP+TH, *Y/TH group* Yttrium-90+TH, *TH group* triamcinolone hexacetonide

[a] One-way ANOVA

[b] Pearson's chi-square

[c] Kruskal–Wallis test

Table 2 Assessment of clinical parameters

Evaluations (weeks)	Sm/TH group (n=29) Mean±SD	Y/TH group (n=28) Mean±SD	TH group (n=30) Mean±SD	Inter-group p
VAS for pain (0–10 cm)				0.022[a]
T0	6.7 (1.7)	7.1 (1.5)	6.6 (1.6)	
T1	3.2 (2.6)*	1.7 (2.0)*	2.2 (2.0)*	
T4	2.8 (2.8)*	1.8 (2.2)*	2.0 (2.5)*	
T12	2.3 (2.2)*	1.9 (2.5)*	2.8 (2.8)*	
T32	3.3 (2.9)*	2.8 (3.1)*	4.0 (3.1)*	
T48	3.8 (3.1)*	2.5 (2.4)*	4.4 (2.8)*	
VAS for swelling (0–10 cm)				0.887[a]
T0	4.2 (2.0)	4.1 (1.5)	3.9 (1.9)	
T1	1.3 (1.9)*	1.0 (1.2)*	1.1 (1.4)*	
T4	1.0 (1.3)*	1.0 (1.3)*	0.9 (1.4)*	
T12	0.9 (1.2)*	0.7 (1.1)*	0.7 (1.1)*	
T32	1.3 (1.5)*	1.4 (1.8)*	1.1 (1.6)*	
T48	1.4 (1.5)*	1.5 (1.8)*	2.9 (7.2)*	
Morning Stiffness				0.108[a]
T0	13.6 (14.4)	41.7 (60.5)	50.4 (80.7)	
T1	3.0 (7.5)*	1.8 (5.3)*	2.2 (11.0)*	
T4	4.5 (9.9)*	6.1 (13.2)*	5.2 (13.8)*	
T12	6.6 (13.5)*	4.3 (11.3)*	1.8 (5.8)*	
T32	8.0 (16.2)*	10.3 (14.8)*	23.8 (60.1)*	
T48	13.3 (38.5)*	7.8 (13.5)*	19.9 (37.9)*	
ROM				0.167[a]
T0	105.8 (23.6)	106.2 (16.8)	112.5 (14.3)	
T1	115.2 (25.0)*	114.2 (16.6)*	121.3 (10.7)*	
T4	116.4 (24.2)*	113.8 (17.9)*	122.8 (10.2)*	
T12	115.8 (22.5)*	115.2 (18.6)*	122.8 (11.3)*	
T32	114.9 (23.3)*	110.6 (19.9)*	120.2 (13.6)*	
T48	111.2 (25.4)*	112.7 (20.1)*	121.2 (12.8)*	
Knee circumference				0.721[a]
T0	41.2 (4.4)	41.5 (4.7)	40.8 (3.4)	
T1	40.9 (5.3)	41.0 (4.6)	40.1 (4.0)	
T4	40.6 (4.7)*	40.8 (4.9)*	40.0 (3.6)*	
T12	40.7 (4.6)*	40.9 (5.0)*	40.2 (3.8)*	
T32	40.5 (4.3)*	41.0 (5.0)*	40.0 (4.0)*	
T48	40.9 (4.2)*	40.9 (4.6)*	39.8 (4.0)*	

Sm/TH group ^{153}SmPHYP+TH, *Y/TH group* Yttrium-90+TH, *TH group* triamcinolone hexacetonide, *VAS* visual analog scale, *SD* standard deviation

*$p<0.001$ (intra-group p in relation to T0), Bonferroni multiple comparison test

[a] ANOVA for repeated measurements

inflammatory drugs and oral corticosteroids (Table 4), calls to the physician, and hospital visits. Only one patient (in the TH Group) went to the hospital for pain in the knee under study, but this occurred at T48.

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. Among the adverse effects (Table 5), pain (five) and post-injection flare (four) were the most frequent, accounting for 5.7% and 4.6% of the cases, respectively. Post-injection flare did not persist to the second evaluation (T1). The Sm/TH group experienced more adverse effects when assessing the total value (p=0.042), more common at T1 (p=0.046). The Y/TH had more adverse effects at T12 (p=0.013). Two patients had hypochromia at the needle entry point, observed at 2 and 3 months, respectively. One of these patients had knee valgus and the second had a high body

Table 3 Lequesne index and HAQ

Evaluations (weeks)	Sm/TH group (n=29) Mean±SD	Y/TH group (n=28) Mean±SD	TH group (n=30) Mean±SD	Inter-group p
Lequesne index (±SD)				0.787[a]
T0	16.4 (3.0)	17.0 (3.4)	16.9 (3.4)	
T1	12.2 (3.6)*	11.6 (3.0)*	11.0 (4.7)*	
T4	12.0 (4.0)*	11.7 (4.3)*	11.4 (5.6)*	
T12	12.0 (3.9)*	12.0 (4.0)*	11.8 (4.3)*	
T32	12.3 (4.1)*	13.6 (5.0)*	12.8 (5.2)*	
T48	13.0 (4.2)*	14.3 (4.0)*	12.8 (4.7)*	
	HAQ			0.339[a]
T0	1.4 (0.4)	1.6 (0.5)	1.6 (0.5)	
T1	1.1 (0.6)*	1.2 (0.5)*	1.1 (0.5)*	
T4	1.2 (0.6)*	1.3 (0.5)*	1.2 (0.6)*	
T12	1.2 (0.5)*	1.4 (0.4)*	1. 2 (0.7)*	
T48	1.2 (0.6)*	1.4 (0.5)*	1.2 (0.6)*	

Sm/TH group [153] SmPHYP+TH, *Y/TH group* Yttrium-90+TH, *TH group* triamcinolone hexacetonide

*p<0.001 (intra-group p in relation to T0), Bonferroni multiple comparison test

[a] ANOVA for repeated measurements

mass index; both were classified as Grade III on the Kellgren–Lawrence scale [40].

Events (22) that were not correlated to the procedure performed included: trembling (one), diarrhea (one), dysuria (one), paresthesia (one), nausea (one), spinning dizziness (one), tachycardia (two), conjunctivitis (one), VAS (two), acute sinusitis (two), cholecystectomy (one), tracheobronchitis (two), weight gain (two), fracture (two), skin lesions on lower limbs (one), and hysterectomy (one). After the 3-month period, 48 patients (55.17% of patients; 15 from the Sm/TH group, 15 from the Y/TH group, and 18 from the TH group; p=0.450, Pearson's chi-square test) modified their DMARDs due to a worsening of the global activity of the disease. After 3 months, two patients from the Sm/TH group, two from the Y/TH group, and two from the TH group (p=1.00, Fisher's exact test) required a further injection with TH in the same knee due to aggravation of the arthritis.

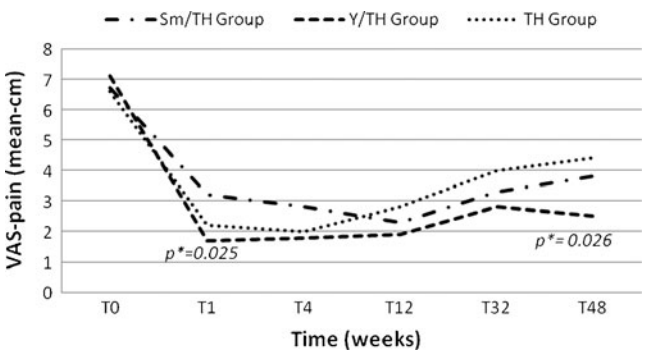

Fig. 1 Inter-group comparison of mean VAS for pain values (centimeter) in knee; *Sm/TH group* [153]SmPHYP+TH, *Y/TH group* Yttrium-90+TH, *TH group* triamcinolone hexacetonide; (Sm/TH versus Y/TH) *p= 0.025* (T1); (Y/TH versus TH) *p= 0.026* (T48); Tukey multiple comparison test

Discussion

The present study analyzed the therapeutic response of synovectomy by a widely used radioisotope (^{90}Y) and a recently studied radiopharmaceutical (^{153}SmPHYP). Despite the widespread use of ^{90}Y in clinical practice, there is as yet no consensus on its superiority over IAI with GC. Of the six randomized controlled studies comparing ^{90}Y to IAI with GC [27, 30, 32, 48–50], only three found ^{90}Y to be superior to IAI with GC [27, 49, 50], whether with triamcinolone [27, 50] or with methylprednisolone acetate [49]. Jahangier et al. [48] compared the clinical efficacy and safety of RS with IAI ^{90}Y plus GCs with IAI placebo ^{90}Y plus GCs and concluded that ^{90}Y plus GCs was not superior to IA with GCs. In the study, ^{90}Y efficacy seems to be equivalent to the placebo.

^{153}SmPHYP has recently been studied for RS. However, randomized controlled studies with this drug have had the limitation of not using a homogeneous sample of patients with RA [37] or of assessing the treatment response only using magnetic resonance [44]. The only randomized controlled study on ^{153}SmPHYP involving a homogeneous sample of only patients with RA and using assessment tools for joint inflammation, function, and quality of life was carried out by Dos Santos et al. (2009) [38], who found no difference between ^{153}SmPHYP+TH and TH alone.

Table 4 Use of sodium diclofenac (tablets) and oral prednisone (doses) and percentage of improvement

Evaluations (weeks)	Sm/TH group (n=29) Mean±SD	Y/TH group (n=28) Mean±SD	TH group (n=30) Mean±SD	Inter-group p
NSAIDS tablets/day (Mean±SD)				0.535[a]
T0	0.8 (1.1)	0.6 (1.0)	0.8 (1.0)	
T1	0.8 (0.9)	0.7 (0.9)	0.5 (0.6)	
T4	0.9 (0.9)	0.5 (0.7)	0.7 (1.0)	
T12	0.9 (1.0)	0.7 (1.0)	1.0 (1.1)	
T32	0.8 (1.0)	0.7 (1.0)	0.5 (0.8)	
T48	0.8 (1.0)	0.7 (1.0)	0.5 (0.8)	
Prednisone milligrams/day (Mean±SD)				0.641[a]
T0	5.9 (6.0)	6.1 (5.5)	6.7 (5.9)	
T1	6.7 (7.1)	6.0 (6.2)	5.4 (4.7)	
T4	5.8 (6.0)	6.4 (7.0)	5.5 (4.5)	
T12	6.3 (6.1)	7.4 (7.0)	5.5 (4.2)	
T32	6.4 (6.8)	5.4 (5.4)	4.2 (3.7)	
T48	4.9 (6.3)	5.4 (5.7)	3.3 (3.5)	
Percentage of improvement		(Mean±SD)		0.203[a]
T1	76.13 (22.5)	80.0 (17.9)	77.6 (20.3)	
T4	72.5 (29.2)	83.4 (17.9)	79.7 (28.2)	
T12	77.0 (24.4)	83.0 (19.8)	77.3 (23.6)	
T32	72.4 (27.2)	75.4 (27.3)	65.7 (32.7)	
T48	57.6 (29.5) *	75.0 (25.6) *	61.1 (35.6) *	

Sm/TH group ^{153}SmPHYP+TH, *Y/TH group* Yttrium-90+TH, *TH group* triamcinolone hexacetonide

*p<0.001 (intra-group p in relation to T0), Bonferroni multiple comparison test

[a] ANOVA for repeated measurements

In the present study, the difference in mean VAS for pain scores was 1.5 between the Sm/TH and Y/TH at T1 and 1.9 between the Y/TH and TH groups at T48. Despite the statistically significant difference between groups for the variable, the result with the greatest clinical relevance was between the Y/TH and TH groups; nonetheless, the difference in mean pain scores between these groups was less than 2.

Studies by O'Duffy et al. [37, 44] and Dos Santos et al. [39] demonstrated the effect of radioisotope synovectomy may be only attributed to the concomitant use of GC [48]. Theories can be posed to explain the lack of effectiveness of the radioisotopes used in the present study. ^{153}SmPHYP has a maximal penetration of 3.1 mm and may not have been effective for synovectomy in the knee, which is a large joint. The dose may have been too small for use on this

Table 5 Distribution of the types of adverse effects between groups

	Sm/TH group (n=29)	Y/TH group (n=28)	TH group (n=30)
Pain	1	1	3
Post-injection flare	1	2	1
Hypertensive peak	1	1	1
Chills	1	–	–
Hot flare	1	–	–
Urticaria	2	–	–
Rash on face	1	–	–
Sweating	1	–	–
Uncontrolled DM	1	1	–
Increased instability	2	–	–
Pruritus	2	3	–
Cutaneous depigmentation		2	–
TOTAL	14	10	5 *(p*< 0.05)*

*p=0.012, Chi-square

joint. However, there are no trials with higher doses of ^{153}SmPHYP to suggest this theory. Trials with larger doses of ^{90}Y (up to 8 mCi) are needed to determine whether ^{90}Y offers greater effectiveness. A larger sample size or longer follow-up could also have an effect on the statistical difference between groups for other variables. In the present study, TH was used at a dose of 40 mg. However, it is not known whether larger doses could achieve better results and perhaps be as effective as RS.

According to Kolarz and Thumb [45], actinic damage following RS occurs at a low frequency of two cases of necrosis in every 11,000 procedures, but the true number may be higher and undocumented [46]. There are no risk factors established in the literature for the appearance of actinic damage. However, it is suggested that joints with a reduction in the articular interline may contribute to the appearance of such lesions [47]. In the present study, the two patients who exhibited hypochromia were classified as Grade III on the Kellgren–Lawrence scale [40]. The valgus and obesity in these patients may also have contributed toward reflux of the radioisotope through the orifice of the needle.

The present study confirms that there is no indication for ^{153}SmPHYP at a dose of 15 mCi for radioisotope synovectomy in the knees of patients with RA. For the pain parameter alone, RS with ^{90}Y associated to TH proved superior to RS with ^{153}SmPHYP associated to TH at T1 and to synovectomy with TH at T48. Moreover, RS with ^{153}SmPHYP associated to TH caused more adverse effects. However, further controlled, randomized, double-blind trials comparing RS to IAI with TH are needed. Trials with larger doses of TH, the use of ^{153}SmPHYP on medium-sized joints, a longer follow-up period, a greater number of patients, and the inclusion of patients with lower grade classifications on the Kellgren–Lawrence scale [40] could help determine the actual cost–benefit of radioisotopic synovectomy in patients with rheumatoid arthritis.

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Disclosures None

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