Double blind glucocorticoid controlled trial of samarium-153 particulate hydroxyapatite radiation synovectomy for chronic knee synovitis

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Abstract

Background—Samarium-153 particulate hydroxyapatite (Sm-153 PHYP) is a relatively new radiation synovectomy agent developed for the treatment of chronic synovitis. Although it has been shown that the levels of unwanted extra-articular radiation are lower after intra-articular injection of Sm-153 PHYP than yttrium-90 colloid, its clinical efficacy has not been rigorously studied.

Objectives—To establish whether Sm-153 PHYP radiation synovectomy results in a clinically useful benefit sustained at one year.

Methods—In a randomised double blind study, patients received either intra-articular 40 mg triamcinolone hexacetonide alone or 40 mg triamcinolone hexacetonide combined with Sm-153 PHYP in an outpatient clinic.

Results—Sixty patients (28 male, 32 female), median age 51 (18–75) with chronic knee synovitis were studied. Diagnoses included: rheumatoid arthritis (n=29); psoriatic arthritis (n=9); ankylosing spondylitis (n=3); reactive arthritis (n=2); undifferentiated seronegative oligoarthritis (n=13) and miscellaneous inflammatory conditions (n=4). More patients who received Sm-153 PHYP/triamcinolone hexacetonide sustained clinical benefit a year after treatment compared with patients who received corticosteroid alone (12 of 31 (39%) v 6 of 29 (21%), a difference of 18% more patients (95% CI -5% to 41%)) though the difference was not significant ($\chi^2=2.31$, $0.2 > p > 0.1$, $n=60$). Despite the variation in injected activity (median 563 MBq, range 218–840 MBq), there was no obvious relation between low levels of injected activity (<555 MBq) and relapse within 12 months of treatment ($\chi^2=2.61$, $0.2 > p > 0.1$, $n=31$).

Conclusions—There was no clear beneficial clinical effect of combined Sm-153 PHYP/triamcinolone hexacetonide injection over triamcinolone hexacetonide alone a year after treatment for chronic knee synovitis.

(Ann Rheum Dis 1999;58:554-558)

Radiation synovectomy is one of several local treatments for chronic synovitis, which include glucocorticoid injection, saline irrigation, chemical or surgical synovectomy. All procedures have potential disadvantages. For exam-

ple, patients may develop reduced range of movement after open synovectomy,¹ arthroscopic synovectomy is technically demanding and highly operator dependent,² chemical synovectomy can be a painful procedure and may cause cartilage damage,^{3,4} and, despite only a few published case reports,⁵⁻⁷ concerns remain about the incidence of malignancy after radiation synovectomy. The development of yttrium-90 (Y-90) colloids was primarily a response to the concerns about the high levels of extra-articular leakage of gold-198 (Au-198) after Au-198 colloid joint injection.^{8,9} However, both radiopharmaceuticals have been associated with extra-articular activity levels that correlate with chromosome damage manifest by an increase in specific chromosomal aberrations.¹⁰⁻¹² Leakage of radioactivity from a joint can be reduced by both immobilisation of the joint after the procedure and injection of glucocorticoid with the radiopharmaceutical.^{13,14} Randomised controlled trials comparing Y-90 colloids with placebo or other treatments have been limited and do not show clear evidence for their efficacy.¹⁵ A multicentre trial attempted to resolve this question by comparing Y-90 with triamcinolone hexacetonide but the target patient number was not reached because of problems with recruitment.¹⁶ Furthermore, published data show no difference in efficacy between radiation and surgical synovectomy,¹⁷ radiation and chemical synovectomy¹⁸ and chemical and surgical synovectomy.¹⁹

New radiopharmaceuticals would ideally be safe, implying an ability to be highly retained within joints, and efficacious when compared with alternative treatments. Samarium-153 particulate hydroxyapatite (Sm-153 PHYP) is stable and remains tightly bound in vivo.²⁰ Clinical trials confirm that extra-articular escape of Sm-153 PHYP compares favourably with Y-90 colloids as <1% of injected activity is detectable outside the knee.²¹ The extra-articular whole body radiation (unwanted) dose is approximately 3.8 mSv, which is no more than the estimated dose from an isotope bone scan (3.7–6 mSv).²² This dose is significantly lower than the dose estimated from Y-90 synovectomy and similar to the dose after intra-articular dysprosium-165 macroaggregates,²³ another radiopharmaceutical currently available. There is no evidence for an increase in chromosome-type damage after Sm-153 PHYP therapy.^{23a} There are additionally no local side effects or clinically observed unwanted effects from the injection of the

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Accepted for publication
4 May 1999

particulate hydroxyapatite (diameter range 5–45 µm) up to a year after injection.²⁴ Chemical and physical characteristics of Sm-153 PHYP are included in appendix 1.

The aim of this study was to compare symptomatic outcome in a cohort of patients with chronic knee synovitis at one year after treatment with either Sm-153 PHYP combined with triamcinolone hexacetonide (TH) or TH injection alone. The study was conducted according to a double blind, randomised controlled, intention to treat design.

Methods

PATIENTS

Patients were referred from rheumatology departments in the Greater London region. Patients were recruited if they were age 18 or over, had had synovitis of the knee for at least two years, which, on clinical review, was causing pain and/or stiffness that limited their mobility. Current medication, including oral glucocorticoids, was recorded. Exclusion criteria were: pregnant or breast feeding women; patients who had had either a change in their slow acting anti-rheumatic drugs (SAARDs) or their dose, or any intra-articular therapy in the study knee in the previous three months; less than 2 mm in either tibiofemoral joint space measured with a ruler on weightbearing radiographs. Informed written consent was obtained. Ethical approval was obtained from the University College London Medical School Clinical Investigations Panel.

PROCEDURE

Patients were randomised by the radiopharmacist to receive approximately 555 MBq (15mCi) Sm-153 PHYP with 40 mg TH or TH alone. The procedure was performed by an investigator, blinded to the randomisation, in an outpatient setting in the Institute of Nuclear Medicine. All women of childbearing age had to have a negative pregnancy test before proceeding with the study injection. The knee was drained using a 21 gauge needle. The injection apparatus, which was covered by tape, consisted of a three way tap attached to a small syringe containing Sm-153 PHYP/TH or TH in a 3–5 ml volume. The drug was injected and the syringe and three way tap flushed three times by drawing in a total of 5 ml of saline from a reservoir attached to the side port of the three way tap. After withdrawing the needle, the knee was passively flexed twice to augment intra-articular distribution of injected drugs and injection apparatus returned to radiopharmacy for activity analysis.²¹ The knee was splinted in a semi-rigid splint for four hours after the procedure. Transport home was provided and the patients advised to rest at home for the subsequent 24 hours.

PRIMARY CLINICAL OUTCOME

A simple measure of outcome, termed symptom score (0, 1 or 2), was chosen as primary outcome to reflect chronic knee synovitis symptom severity and consequent functional impairment. The scores were: 2 = knee pain and/or stiffness limiting mobility; 1 = knee pain

Table 1 Clinical details at baseline

Clinical details	Sm-153 PHYP/TH (n=31)	TH alone (n=29)
Mean age (SD)	46 (14)	51 (14)
Age range	24–72	17–75
Male/female	15/16	13/16
Diagnosis		
Rheumatoid arthritis	13	16
Psoriatic arthritis	3	6
Ankylosing spondylitis	1	2
Reactive arthritis	2	0
Undifferentiated*	10	3
Other†	2	2
Number of previous knee joint corticosteroid injections (range)	4 (1–15)	4 (2–20)
Median number of months since last knee joint corticosteroid injection (range)	5 (3–24)	6 (3–36)
Median number of years of disease duration (range)	8 (2–32)	8 (2–30)
Number of patients taking		
SAARDs	17	18
NSAIDs	27	20

*Undifferentiated rheumatoid factor seronegative oligoarthritis.
†Polyarteritis nodosa (1); juvenile chronic arthritis (1); sarcoid (1); Sjögren's syndrome (1).

and/or stiffness not affecting mobility; 0 = no pain or stiffness. The scores were recorded during the clinical review at baseline and at 3, 6, 9 and 12 months after treatment by an investigator blinded to the randomisation code. According to entry criteria, therefore, all patients scored 2 at entry to the study.

CLINICAL REVIEW

At baseline clinical and follow up clinical review (3, 6, 9 and 12 months) the following measures were also recorded: joint tenderness and swelling using a modified Ritchie score²⁵; knee circumference²⁶; range of movement (degrees); full blood count (FBC); erythrocyte sedimentation rate (ESR). Patients were unblinded from the study if they had relapsed at any follow up visit or after 12 months. Criteria for relapse were: a symptom score of 2 (thus reflecting the need for further intervention) or having received intra-articular glucocorticoid into the study knee from the patient's rheumatologist in the period between reviews (thus implying a symptom score of 2 in the interim). Changes in systemic treatment, including dose alteration, were recorded at each visit but not considered to indicate relapse. Patients who had relapsed in under 12 months and had not received Sm-153 PHYP were offered it on an open basis.

Table 2 Symptom scores at intervals up to a year after treatment

Time after treatment (months)	Symptom score* in number (%) patients treated with Sm-153 PHYP + TH (n=31)		Symptom score* in number (%) patients treated with TH alone (n=29)	
	Score 0/1	Score 2	Score 0/1	Score 2
3	21 (68)	10 (32)	19 (66)	10 (34)
6	16 (52)	15 (48)	11 (38)	18 (62)
9	13 (42)	18 (58)	7 (24)	22 (76)
12	12 (39)	19 (61)	6 (21)	23 (79)

*Symptom scores: 2 = knee pain and/or stiffness limiting mobility; 1 = knee pain and/or stiffness not affecting mobility; 0 = no knee pain or stiffness.

Table 3 Clinical and laboratory measures before treatment (baseline) and at three monthly intervals after treatment with either Sm-153 PHYP + TH or TH alone

Clinical or laboratory measure (mean (SD))		Baseline	3 months	6 months	9 months	12 months
Knee flexion range (°)	Sm-153 PHYP +TH	112 (16) n=31	126 (17) n=29	128 (17) n=18	131 (16) n=13	133 (16) n=10
	TH	113 (15) n=29	121 (25) n=28	129 (15) n=19	126 (15) n=10	135 (15) n=7
Knee circumference (cm)	Sm-153 PHYP +TH	41 (4) n=31	41 (4) n=29	40 (4) n=18	39 (3) n=13	41 (4) n=10
	TH	41 (4) n=29	39 (4) n=22	38 (3) n=19	39 (4) n=10	38 (2) n=7
Swollen joint count (scored out of 34)	Sm-153 PHYP +TH	4 (3) n=31	3 (3) n=29	3 (3) n=18	4 (5) n=13	3 (3) n=10
	TH	4 (4) n=28	0 (0.5) n=28	4 (4) n=19	3 (2) n=10	3 (3) n=7
Ritchie score (pain score out of 34)	Sm-153 PHYP +TH	6 (7) n=31	5 (7) n=29	4 (4) n=18	6 (10) n=13	4 (3) n=10
	TH	6 (6) n=29	3 (4) n=28	5 (7) n=19	2 (2) n=10	2 (2) n=7
Haemoglobin (g/dl)	Sm-153 PHYP +TH	13.0 (14) n=27	13.2 (15) n=25	13.1 (14) n=15	12.9 (14) n=10	13.9 (15) n=5
	TH	12.4 (15) n=22	12.3 (16) n=25	12.1 (5) n=14	12.7 (12) n=6	12.2 (5) n=7
Platelets ($\times 10^9/\text{mm}^3$)	Sm-153 PHYP +TH	293 (73) n=27	315 (90) n=25	309 (85) n=15	282 (74) n=10	261 (75) n=5
	TH	339 (96) n=22	361 (148) n=25	390 (195) n=14	350 (184) n=6	347 (74) n=7
ESR (mm 1st h)	Sm-153 PHYP +TH	32 (27) n=27	37 (32) n=25	32 (28) n=14	33 (27) n=10	18 (18) n=7
	TH	47 (34) n=22	44 (32) n=25	52 (36) n=14	38 (40) n=5	56 (32) n=7

n = the number of patients for whom data were available at that time.

STATISTICAL METHODS

The number of patients who had relapsed in each group was compared at 12 months after treatment using χ^2 (2×2) test. A sample size of 60 was estimated to be necessary to allow detection of a 30% difference in relapse (score 2) between the two groups with 95% confidence. This difference in relapse rate was taken to denote a clinically useful benefit. The relation between injected Sm-153 activity and relapse at 12 months and was also examined using a χ^2 test.

Results

Sixty five patients were recruited. Three patients withdrew before treatment. Injection of one patient was aborted as intra-articular needle access could not be confidently confirmed and a further patient withdrew three months after treatment because of difficulty attending follow up and deteriorating cardiovascular health. Sixty patients were included in the final analysis (28 men, 32 women). Table 1 shows the baseline characteristics.

Of the patients who received Sm-153 PHYP/TH, 19 of 31 (61%) had relapsed within 12 months whereas 23 of 29 (79%) of those treated with TH alone had relapsed (table 2). The difference was not significant ($\chi^2 = 2.31$, $0.2 > p > 0.1$, $n=60$). However, more patients had sustained a benefit (symptom score 0 or 1) from combined treatment compared with triamcinolone hexacetonide alone at a year (18% more patients, 95% CI -5% to 41%) and consistently at three monthly intervals up to a year after treatment (table 2). Table 3 shows baseline and follow up clinical and laboratory indices in the two treatment groups. There appeared to be an improvement in knee flexion from baseline measurements in both groups. There were no obvious trends in the other clinical parameters over time during the study. Subgroup clinical

symptom score analysis according to diagnosis was not undertaken; however, there was no obvious difference in the response to treatment between different diagnostic groups. Of the undifferentiated seronegative oligoarthritis patients two of three in the TH alone group had relapsed at one year, compared with 7 of 10 in the Sm-153 PHYP/TH group.

Median injected activity of Sm-153 was 563 MBq (range 218–840 MBq), which represented between 35–95% of prepared activity. Low levels of injected activity occurred resulting from particulate hydroxyapatite getting caught in the needle hub during the injection procedure. Injected activity did not appear to be related to operator experience. There was no obvious association between injected activity (<555 MBq or >555 MBq) and relapse within a year of treatment ($\chi^2 = 2.61$, $0.2 > p > 0.1$, $n=31$).

Discussion

In this group of patients with various diagnoses, there appeared to be no significant additional clinical effect from injecting both Sm-153 PHYP combined with 40 mg TH compared with injecting 40 mg TH alone for knee synovitis. However, the data show that consistently fewer patients relapsed (or more sustained benefit) after combined treatment notably after a year (18% of patients) but also at each interim analysis (see table 2). This suggests that there is likely to be a therapeutic effect from Sm-153 PHYP though perhaps smaller than anticipated. The failure to demonstrate a significant effect compared with injected corticosteroid may have been a consequence of the power of the study.

A number of features in this study are worthy of discussion: the use of Sm-153 PHYP as a radiopharmaceutical, the variability of injected intra-articular activity of Sm-153 PHYP and

the inclusion of several different diagnostic groups.

The safety of Sm-153 PHYP is supported by the low levels of unwanted extra-articular escape of activity from the joint²¹ and the absence of any increase in chromosomal aberrations after treatment with this radiopharmaceutical.^{23a} Sm-153 PHYP has been shown to be stable in vitro, the labelling procedure is efficient and reproducible and its half life allows time for transportation.²⁰ No local side effects have been observed though almost 100 patients have been treated. Although Sm-153 PHYP has a relatively short maximum tissue penetration compared with other radioisotopes used for synovectomy of the knee (3.1 mm compared with 10 mm for Y-90), it is distributed throughout the synovial lining,^{20, 27} suggesting that deeper layers of the synovial subintima will be irradiated.

It has been evident from previous data that the Sm-153 PHYP sediments within the syringe,²¹ and although in our protocol the injection apparatus was flushed thoroughly in an attempt to reduce sedimentation, the injected activity was variable. Injected activity did not improve with increasing operator experience. By reducing the mean size and size range of particles, the potential for sedimentation of hydroxyapatite particles has now been reduced (James Brodack, personal communication). However, there was no clear relation between injected activity and relapse, suggesting against a major dose response effect and in keeping with the findings from an open study of clinical outcome.²⁴ To explore a dose response relation further, information could have been obtained from post-injection imaging, as previously described,²¹ and findings compared with clinical outcome. However, the methodology was optimised to maintain "blinding" of both operator and patient and any attempts at imaging could have undermined this. We would recommend that any further investigations of Sm-153 PHYP, possibly in smaller joints, should include evaluation of a relation between injected activity and outcome.

Predicted recruitment rates and considerations of statistical power required pooling of diagnostic groups; however, could the variation in underlying disease have influenced the outcome? Probably not, as the range of diagnoses, historical features of the disease and treatment was broadly comparable in the two treatment groups (table 1), and there were no substantial differences in the clinical and laboratory indices of disease at baseline (table 2). We would, therefore, conclude that there is no clear variation in response between diagnostic groups.

In summary, our data suggest that in this group of patients with various diagnoses there is no sustained therapeutic effect from combining Sm-153 PHYP radiation synovectomy with injection with 40 mg TH for knee synovitis compared with injecting 40 mg TH alone. However, our data do not suggest against a therapeutic effect from Sm-153 PHYP. Given its favourable physical and radiobiological properties, further studies with Sm-153 PHYP

will be worthwhile; however, it will be important to consider carefully whether less of a difference, in clinical outcome between Sm-153 PHYP and injected long acting corticosteroid, than we have considered here, should be regarded as clinically useful in the context of balancing relative risk:benefit and cost effectiveness of the two treatments.

Appendix 1

Physical and biological data of Sm-153 and particulate hydroxyapatite

Physical characteristics of Sm-153 (All data from Raddecay, Grove engineering Inc, 1987); half life 46.3 hours; mean β decay range = 0.081–0.263 MeV; most abundant β energies (% total) = 0.199 MeV (34%), 0.224 MeV (44%), 0.263 MeV (21%); β penetration in soft tissue = 3.1 mm (maximum)/0.7 mm (x_{90}); most abundant γ energies (% total) = 0.041 MeV (17%), 0.042 MeV (31%), 0.103 MeV (28%). *Particulate hydroxyapatite (PHYP) size range* = 5–45 μ m diameter. x_{90} is the therapeutic range (mm) of β decay and is defined as the depth in synovium by which 90% of the dose from β particles, present at the surface of the tissue, has been absorbed.²⁸

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