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DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL AND SIX-YEAR OPEN FOLLOW-UP OF YTTRIUM-90 RADIOSYNOVECTOMY VERSUS TRIAMCINOLONE HEXACETONIDE IN PERSISTENT RHEUMATOID KNEE SYNOVITIS

E.N. GRANT[1], N. BELLAMY[2], K. FRYDAY-FIELD[2], T. DISNEY[2], A. DRIEDGER[3] and K. HOBBY[2]
[1]Department of Medicine, Dalhousie University, Halifax, Nova Scotia;
[2]Department of Medicine, University of Western Ontario, London, Ontario;
[3]Department of Nuclear Medicine, University of Western Ontario, London, Ontario, Canada

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Knee joints ($n=30$) from 22 adult rheumatoid arthritis (RA) patients who were previously randomized and subjected to a six-month double-blind controlled trial of yttrium-90 vs. triamcinolone hexacetonide with a six-year follow-up. In contrast to most previous studies, there was no co-administration of a steroid agent at the time the radiopharmaceutical was injected. One month after treatment the triamcinolone group had less pain ($p<0.05$), fewer effusions ($p<0.001$) and a better range of movement ($p<0.01$) than the yttrium group. Six months after treatment, the response in the triamcinolone group had partially regressed but was still superior to that of the yttrium group ($p<0.05$). At the six-year follow-up, half the yttrium-treated knees were found to have required treatment by intra-articular steroid, surgical synovectomy or total knee arthroplasty. The rates for therapeutic success were no different for yttrium-90 or triamcinolone. These results bring into question the reported efficacy of yttrium-90 and suggest that the benefit observed in clinical practice may be dependent upon the co-administration of a corticosteroid agent, and that the long-term benefits of yttrium may be relatively small.

Keywords: yttrium, triamcinolone, rheumatoid arthritis, synovectomy

INTRODUCTION

The effect of intra-articular radiocolloid on persistent knee effusions was first reported by Ansell et al. [1]. Since 1963, there have been numerous reports relating to radiation synovectomy [2–11]. The extent to which the observations can be usefully evaluated has been limited by a number of factors including the absence of control groups [2,6–9], unblinded observers [1,3,10–12], inclusion of patients with different types of musculoskeletal disease [5,9,12], and, in particular, the co-administration of intra-articular corticosteroid at the time of introduction of the radiopharmaceutical [4,6,8.9]. A number of studies have shown little, if any, benefits [13,14], and other authorities, including the Arthritis and Rheumatism Council Multicentre Radiosynoviorthesis Trial Group, have emphasized the uncertainties surrounding this area of musculoskeletal therapeutics [15,16]. To further evaluate the controversy, we have conducted a six-month double-blind randomized controlled trial of yttrium-90 vs.

triamcinolone hexacetonide with a six-year open follow-up in the treatment of persistent synovitis of the knee in patients with RA.

METHODS

Chronically effused knee joints ($n=32$), from 22 consenting adult RA patients attending Victoria Hospital, London, Ontario, were selected from subjects entered into the study which was approved by the University of Western Ontario Health Sciences Standing Committee on Human Research. To be eligible, patients were required to fulfil the following criteria: *inclusion* – ARA criteria for classic or definite RA [17], persistent knee effusion of at least 6 months duration, failure of prior intra-articular corticosteroid injection; *exclusion* – intra-articular steroid injection in preceding six months, intra-articular radiocolloid in preceding 12 months, introduction of a slow-acting anti-rheumatic drug within the preceding three months, women of child-bearing potential not using effective contraception.

Following clinical assessment of demographic and disease profiles, study knees were assessed for degree of instability, deformity, crepitus and effusion, ARA radiographic stage [18], and blood pool image. In addition, the following clinical assessment scales were used: knee pain at rest both in flexion and extension, and also while walking (5-point scale), joint line tenderness (4-point scale), range of movement (degrees), effusion (3-point scale) and patient overall assessment (3-point scale).

Following enrolment, patients were randomized by one of the investigators (AD) not involved in the clinical care or assessment of study patients. In the case of patients receiving treatment to both knees, the first knee was randomized, the contralateral knee receiving the alternative agent. Patients were admitted to hospital for administration of the intra-articular agent. Technetium-labelled sulphur-colloid was then injected and the joint scintiscanned to ensure accurate localization of the needle within the synovial cavity. The therapeutic agent (either yttrium-90, 8 mCi; or triamcinolone hexacetonide, 20 mg) was injected by another investigator who had no knowledge of the contents of the injected material. Treated knees were then splinted for 48 h, after which the patient was discharged from hospital. Patients were reassessed at one, three and six months after injection and were finally assessed approximately six years after initial treatment. Since the trial was originally designed as a six-month follow-up, the randomization code was broken at six months. For ethical reasons, we elected to perform the long-term management and six-year follow-up of study patients on an open basis.

Statistical analysis was performed using SPSS-PC software. Descriptive statistics were calculated for all demographic and disease characteristics. Comparative analysis of response to treatment was performed using the Mann–Whitney U test. Categorical data for success vs. failure of treatment were analysed using Fisher's Exact test.

RESULTS

Due to technical reasons it was not possible to inject the knees of one patient scheduled for bilateral treatments. Of the 21 patients studied, nine received bilateral injections, seven triamcinolone only and five yttrium-90 only. This resulted in the

treatment of 16 knees with triamcinolone and 14 with yttrium-90. The demographic and disease characteristics of patients receiving injections in one or both knees are listed in Table 1. No significant differences were noted in radiographic staging, blood pool imaging, instability, deformity, crepitus or effusion in the two treatment groups (Table 2). No patients were withdrawn from the double-blind portion of the study due to adverse reactions either to intra-articular yttrium-90 or to intra-articular triamcinolone hexacetonide.

Table 1. Demographic and disease characteristics of patients receiving injections in one or both knees

	Yttrium-90 alone	*Triamcinolone alone*	*Bilateral injections*
Number of patients	5	7	9
Age	61.00	53.00	50.11
Sex (M/F)	2/3	3/4	6/3
Duration of illness (years)	15.80	8.00	9.78
Number seropositive	5	7	7
Number with nodules	2	2	2
2nd line drug	A = 2 D = 2	G = 1 D = 6	A = 2 D = 3
Number on prednisone	2	4	3
Haemoglobin	123.60	125.00	116.67
ESR	60.80	66.71	63.33
50 foot walk time (s)	20.60	17.00	18.22
Duration of AM stiffness	98.00	125.00	96.67
Number of active joints	22.20	15.14	17.22

A = antimalarial
D = D-penicillamine
G = gold

Double-blind phase

In the six months following intra-articular treatment, three patients (5 knees) were withdrawn from the study because the knees required surgical attention (total knee replacement). One patient was withdrawn one month after yttrium injection, and two other patients, who had both received bilateral injections, were also withdrawn. In the first bilateral case, the yttrium-treated knee and in the second bilateral case a triamcinolone-treated knee required surgical intervention. One triamcinolone patient failed to attend for one and three month assessments, but was reviewed at six months. The following modifications to treatment were made: modification of NSAID therapy (triamcinolone = 1), introduction to slow-acting anti-rheumatic drug therapy (triamcinolone = 4), increase in systemic corticosteroid dosage (yttrium-90 = 1, triamcinolone = 2), intra-articular steroid injection into a non-study joint (triamcinolone = 1, yttrium-90 = 4). No patient received any additional intra-articular steroid into the study knee during the double-blind trial.

Table 2. Comparison of target knee status in yttrium-90 and triamcinolone groups prior to treatment

	Yttrium-90	*Triamcinolone*	*Probability* ($p \leq 0.05$)
Number of knees	14	16	
Radiographic staging	I = 3,II = 3,III = 8	I = 3,II = 6,III = 7	NS
Blood pool imaging	1.80	1.71	NS
No. with any instability	10	12	NS
No. with deformities	7	6	NS
No. with crepitus (palpable, none had bone-on-bone)	14	13	NS
No. with large effusions	5	11	NS

Table 3. Double-blind study. Comparison of outcome measures

		Baseline	*1 month*	*3 months*	*6 months*
Pain at rest	T	1.31	1.00*	1.14	1.43
	Y	1.43	1.54	1.18	1.45
Pain at rest	T	1.81	1.07**	1.36	1.43
	Y	1.93	1.92	1.73	1.55
Pain walking	T	2.50	1.07**	1.64	1.86
	Y	2.93	1.85	2.09	2.45
Joint line tenderness	T	2.31	1.33**	1.54**	1.57
	Y	2.00	2.15	2.27	1.91
Range of movement	T	108.5	124.7**	121.9**	122.4*
	Y	106.6	106.9	103.6	107.9
Knee effusions	T	16/16	5/15**	5/13*	6/14
	Y	14/14	13/13	10/11	9/11
Change in status:					
Improvement	T	-	14/14*	10/14	5/14
	Y	-	6/12	3/11	3/11
Worsened	T	-	0/14	2/14	4/14
	Y	-	2/12	3/11	3/11

T = triamcinolone; Y = yttrium-90
*$p \leq 0.05$
**$p \leq 0.01$

No statistically significant differences were noted in outcome measures at baseline (Table 3). One month after injection, the triamcinolone group showed a statistically superior response to the yttrium-90 in pain at rest in flexion, pain at rest in extension, pain on walking, joint line tenderness, range of movement, knee effusion, and change in clinical status (Table 3). By three months after injection, a statistically superior response persisted in the triamcinolone group for joint line tenderness, range of movement and knee effusion. Six months following injection, a statistically superior response was observed in the triamcinolone group for range of movement (Table 3).

Six year open follow-up

Of the 19 patients (25 knees) who completed the double-blind study, 18 were contacted. Eight of these were re-examined and the remainder were interviewed by telephone. The status of the one patient who could not be contacted was verified from the hospital record. Because of the small residual sample sizes for outcome measures, we have not performed a statistical analysis of six-year versus six-month status. Instead, we have compared the proportion of patients in the two groups experiencing success (i.e. no need for further local therapy) vs. failure (i.e. need for further local therapy with intra-articular corticosteroids, medical or surgical synovectomy or total joint arthroplasty). Of the 16 triamcinolone knees originally treated, four were subsequently re-injected with corticosteroids, two were injected with yttrium-90, one underwent surgical synovectomy and five underwent total knee arthroplasty at some point in the six years. Some triamcinolone patients received more than one local intervention over that time. Of the 14 yttrium-90 knees, three required further intra-articular steroid injection, one underwent surgical synovectomy and four required total knee arthroplasty. Some yttrium-90 patients received more than one local intervention over the six years. No significant differences between these two patient groups were noted in the proportion experiencing therapeutic success vs. failure ($p > 0.05$).

DISCUSSION

Yttrium-90 and other radiopharmaceuticals have been used in the treatment of chronic rheumatoid synovitis for over 25 years. The efficacy and toxicity of these agents have been widely studied and the relationship of toxicity to both colloidal particle size and type of radiation has been considered [18,19]. It has been suggested that these latter two properties determine the extent of tissue penetration. Yttrium-90 has been favoured in many recent trials, because it emits exclusively beta rays, and yet its soft-tissue penetration appears to be sufficient to confer advantage over other agents. However, acute knee rupture has been observed [20] and several investigators have reported chromosomal damage [4,21–24]. The clinical importance of the latter observation remains unresolved. In clinical practice, concomitant administration of intra-articular corticosteroid has been a standard protocol used to provide prophylaxis against local irritation (i.e. yttrium-induced synovitis or so-called radiation synovitis) and to reduce the risk of needle-track-related tissue necrosis. This technique has been incorporated in many therapeutic trials making it difficult to isolate and understand

the role of yttrium-90 in the response observed in such studies [4,6,8,9]. Much support for the efficacy of yttrium-90 has come from studies with uncontrolled designs [2,3,6–9,11]. Furthermore, trials using uncontrolled and non-blind designs consistently show a response to yttrium-90 superior to that seen in controlled and blind studies, suggesting that the apparent response may be related to factors such as placebo effect, natural variation in disease course, and patient and physician bias in evaluating the treatment effect. The studies by Bridgman et al. [13] and Yates et al. [14], which appear adequate in study design, respectively show either no benefit or benefit of questionable clinical importance.

In contrast, in our study, a double-blind randomized controlled parallel design showed triamcinolone to be superior to yttrium-90 on all outcome measures at one month, although this response deteriorated with the passage of time [18]. Thus, by three months, triamcinolone was superior on three measures and at six months on only one measure. Since there was no significant difference between the knees at baseline, the difference in response to triamcinolone compared with yttrium-90 cannot be explained by start time differences. The induction response interval, favouring triamcinolone at one month, was in accordance with the known induction response profile of corticosteroid drugs. However, the superiority of triamcinolone was in part due to the poor response (at all times) to yttrium-90, and in part due to the positive response to triamcinolone. This differential response is particularly impressive when the small sample size in this study is considered along with the selection of patients on the basis of their having failed to achieve a sustained response to prior intra-articular steroid therapy. Although yttrium-90 was administered without concomitant intra-articular corticosteroids, no patient reported symptoms suggestive of immediate or delayed post-injection radiation synovitis. Furthermore, no patient developed the complication of needle-track necrosis. Thus, the significant difference between treatments cannot be explained by a worsening in knee status directly attributable to the known side-effects of yttrium-90 injection. We have no reason to doubt the potency of our radiocolloid as it was administered on the day of preparation. Furthermore, our study was of sufficient duration to have detected the three to six month induction–response lag to radiocolloid reported by other researchers.

Some patients were withdrawn from the double-blind study and underwent total knee arthroplasty, or had this procedure performed during the six-year follow-up. This was probably due to the inclusion of some patients having advanced radiographic changes. However, no patients with ARA functional grade 4 disease were entered in the trial. Although the numbers were small, there was no difference between the two groups with respect to withdrawal from treatment in either phase of the study for total knee arthroplasty.

We have carefully examined the two treatment groups for possible sources of bias which could explain the superiority of triamcinolone over yttrium-90. We noted that, while the yttrium-90 group were older and had had their condition longer, this was not associated with more severe knee disease. Furthermore, measures of disease activity did not differ between the two treatment groups at baseline. Finally, during the course of the study, four of seven triamcinolone patients required alteration in second-line agents because of generalized increase in disease activity. While this had a potential modulating effect on the disease status, we found: (1) improvement in knee status to be most marked before modification of second-line therapy; (2) the rate of

improvement in the treated knee was diminishing at the time when a response to modification of second-line therapy would have been expected to favourably affect knee status. As a result, we believe that changing second-line agents did not explain the between-group difference we observed.

An increasing number of radiopharmaceuticals have been used for medical synovectomy. These have included gold-198 [1,5], yttrium-90 [2,3,6,11,13,14], rhenium-186 [25], ^{32}P colloid chromic phosphate [9,26], erbium-169 [27,28] and dysprosium-165 [10]. Of these, yttrium-90 is in common use, despite controversy about its efficacy.

Although we have studied a relatively small number of patients, we have found triamcinolone to have a statistically significant and clinically important superiority over yttrium-90. This result was achieved, despite a small sample size, in a group of patients who had previously failed to experience a long-term response to intra-articular corticosteroid therapy. This might have been expected to introduce a response bias favouring the yttrium-90 group, but little response was achieved with yttrium-90 given alone rather than with the intra-articular corticosteroid commonly co-administered in routine practice and reported used in several radiation synovectomy studies. We conclude that the co-administration of intra-articular corticosteroid contributes to the response observed following yttrium-90 synovectomy for a variable time. We remain concerned about the clinical efficacy of yttrium-90 synovectomy and to directly address this issue it would be necessary to conduct a double-blind randomized controlled trial of intra-articular yttrium-90 alone versus intra-articular yttrium-90 together with triamcinolone hexacetonide. Patients who should be excluded would be those with advanced radiographic changes, since they are likely to be less responsive to this form of therapy and may require surgical intervention before completion of long-term studies.

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