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Intra-articular radioactive yttrium and triamcinolone hexacetonide: an inconclusive trial

ARTHRITIS AND RHEUMATISM COUNCIL MULTICENTRE RADIOSYNOVIORTHESIS TRIAL GROUP

SUMMARY A restricted sequential design multicentre controlled trial of yttrium-90 against triamcinolone intra-articularly was undertaken in patients with rheumatoid arthritis with knee involvement. The trial had to be discontinued because of dwindling recruitment over time. The reasons for this and other features contributing to an inconclusive outcome are noted. This experience lends little encouragement to the idea that yttrium-90 therapy is more or less advantageous than triamcinolone hexacetonide.

The results of a number of trials[1–4] had suggested that knee synovitis was improved more by yttrium-90 than by other substances, mainly steroid, injected intra-articularly. However, these reports were not very successful in influencing the therapeutic practices of many rheumatologists, and uncertainty was heightened by a study that revealed comparable arthroscopic improvement after either yttrium-90 or placebo.[5] There was a fairly widespread feeling that efforts ought to be made to resolve the question, and representations to this effect were transmitted to the Arthritis and Rheumatism Council (ARC). The ARC appointed an ad hoc group (Professor R. M. Acheson and Drs J. M. Gumpel, J. T. Scott and P. H. N. Wood) to make recommendations, and a multicentre controlled trial was suggested. Co-operation was solicited from interested rheumatologists, and the latter constituted the ARC Multicentre Radiosynoviorthesis Trial Group, which assumed responsibility for the trial thereafter.

Participants in the trial included the rheumatology departments at Addenbrooke's Hospital, Cambridge (Dr B. L. Hazleman), Canadian Red Cross Memorial Hospital, Taplow (Dr B. M. Ansell), Charing Cross Hospital, London (Dr J. T. Scott), Epsom District Hospital (Dr L. G. Darlington), Guy's Hospital, London (Dr R. Grahame), Heatherwood Hospital, Ascot (Dr S. P. Liyanage), Hope Hospital, Salford (Professor M. I. V. Jayson and Dr R. Hilton), Manchester Royal Infirmary (Dr P. J. L. Holt), Northwick Park Hospital, Harrow (Dr J. M. Gumpel), Nuffield Orthopaedic Centre, Oxford (Dr A. G. Mowat), Royal Berkshire and Battle Hospitals (Dr F. M. Andrews and Dr I. Meanock), Royal Cornwall Hospital, Truro (Dr A. K. Thould), Royal National Hospital for Rheumatic Diseases, Bath (Dr P. A. Bacon and Dr A. St J. Dixon), Royal Victoria Hospital, Belfast (Dr S. D. Roberts), St Peter's Hospital, Chertsey (Dr A. B. Myles), and St Vincent's Hospital, Dublin (Dr B. Bresnihan). Co-ordination of the trial and analysis of the results were undertaken by the ARC Epidemiology Research Unit, Manchester (E. M. Badley, J. Lee, O. V. Smith, P. H. N. Wood, and J. E. Zlosnik).

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Materials and methods

A restricted sequential design[6] with pairing at each centre was adopted to compare 5 mCi yttrium-90 silicate with 40 mg triamcinolone hexacetonide, administered intra-articularly to the knee in equal volumes by an 'injector'.

Assessments were to be carried out blind by a third party (an 'assessor') on entry to the trial and 3, 6, 12, and 24 months after treatment. Patients were entered into the trial if they were over 40 years of age and had 'definite' or 'classical' rheumatoid arthritis with persistent synovitis for at least six months in one or both knees and 'background' disease activity was minimal or had been steady during the six months preceding trial entry.

Ideal subjects had a stable knee with some chance of improvement—that is, surgical synovectomy rather than arthroplasty would otherwise have been the orthopaedic treatment of choice. Patients with large calf or leaking popliteal cysts were excluded, as were those in whom disease-modifying drugs had been started or discontinued in the previous six months. Previous intra-articular injections were not a contraindication provided response had been

minimal or decreasing, so that repeated injections would otherwise have been necessary. Entrants to the trial gave informed consent and were randomised after stratification according to whether there was unilateral or bilateral knee involvement, and whether non-steroidal anti-inflammatory agents were being given alone or in combination with disease-modifying drugs (including steroids).

Attention was paid to assessment procedures,[7] and the technique for making duplicate measurements of leg circumference 1 cm above the patella was specified in advance; conventions for recording ranges of motion were also agreed. Other attributes assessed are indicated in Table 1. Radiographs of hands, feet, and affected knees were taken on entry to the trial, and the latter were repeated after 6, 12, and 24 months. The size of the suprapatellar pouch was assessed on standard lateral radiographs exposed for soft tissue. Rheumatoid factor status was established, and the haemoglobin level and erythrocyte sedimentation rate (ESR) were estimated at trial entry and after six months; alternative acute-phase reactants could be substituted for the ESR. Lack of improvement after six months was regarded as treatment failure, and intra-articular steroid could be used within the period only in exceptional circumstances and then not within six weeks prior to the six month assessment.

The trial began early in 1980. There were 40 recruitments and 6 withdrawals in that year, 25 entries and 11 losses in 1981, and 3 entries and 5 losses in the first 6 months of 1982. It was then decided to discontinue the trial because of dwindling recruitment and increasing withdrawal. Analysable data were available from 20 matched pairs, 12 of which were contributed by patients in whom both knees were entered into the study, and 14 pairs were on disease-modifying therapy. The results are summarised in Table 1.

Results and discussion

Although the overall outcome of the trial was inconclusive, participants considered that a number of comments were worth reporting so that the experience could be brought before a wider audience. These comments related to various aspects of the trial.

OBJECTIVES

The intention had been to observe a very specific effect, reduction of synovitis, in an accessible joint. However, difficulty in determining synovial thickening objectively led to what was probably an over-ambitious decision to assess a range of related variables. The initial enthusiasm of investigators then became overtaxed by the time taken in registering the data, and this contributed to incomplete recording of information.

LOGISTICS

Difficulty in arranging meetings which all investigators could attend prevented reconciliation of contrasting views on the scope of the trial and contributed to its complexity. This had a knock-on effect in regard to other colleagues involved at co-operating centres.

Injection of yttrium-90 necessitated a four-day admission to hospital or, failing that, immobilisation of the limb in plaster-of-Paris. Factors such as availability of beds gave rise to difficulties in scheduling injections, thus disrupting programmes of care and acting as a deterrent to recruitment.

Implementation of new EEC regulations ultimately precluded the use of isotopes at some hospitals. The necessity to make alternative arrangements at another centre interrupted treatment programmes and served as a deterrent to sustained participation by some investigators.

Table 1 *Responses at six months in paired trials of intra-articular radioactive yttrium*

*Response variable**	*Advantage in response*		*Tied responses*†		
	^{90}Y	*TCH*§	*Total*	*Successes*	*Failures*
Generalised morning stiffness‡	2	1	5	0	5
Knee stiff or painful: in morning	2	3	14	6	8
after sitting down	3	3	13	3	10
Pain-free walking distance‡	2	2	2	1	1
Range of motion (total flexion-fixed flexion)	1	5	13	10	3
Synovial thickening—before aspiration	4	5	10	2	8

* Volume of fluid aspirated and synovial thickening after aspiration not included because of a large number of missing observations. There were eight unilateral pairs, and 20 pairs altogether. Totals less than these are due to missing observations.
† Both members of pair either successes or failures.
‡ Only patients with unilateral involvement of knee included.
§ TCH=triamcinolone hexacetonide.

Even with the modest scope proposed for this trial the burden of administration and co-ordination (registering patients; dispatching assessment forms, treatment allocations, and reminders; checking data sheets and chasing missing data) occupied more than one person-day per week at the height of the trial, and visits of encouragement to participating centres were not possible.

RECRUITMENT

Intuitive clinical experience led to overestimation of the likelihood of encountering eligible cases, presumably because of failure to appreciate that many cases treated similarly in the past might have been part of a backlog that had been largely exhausted. This may also have contributed to entry of a number of cases which, on review, were seen to be unsuitable for recruitment, because initial radiographs suggested that arthroplasty would have been more appropriate—an impression borne out by withdrawal of some patients when referred for this procedure. With hindsight it was a defect of the trial design that automatic independent review of radiographs shortly after entry was not required. Recruitment of more investigators could have overcome some of these difficulties.

In addition the investigators formed the strong impression that suitable patients were being seen less frequently than formerly. This accorded with a reduction in the rate at which surgical synovectomy was being undertaken, and the participants were inclined to attribute the change to increasing use of disease-modifying drugs.

WITHDRAWAL OF PATIENTS

Some participants found difficulty in sustaining co-operation over a one-year study period, both by themselves and by the patient when the latter was clincally little or no better. Some withdrawals were occasioned by breaking the code when the 'injector' inadvertantly inserted the injection allocation in a patient's dossier, so that subsequent assessments were not blind.

TRIAL DESIGN

In the absence of a single criterion by which to judge outcome, attempts to derive the stopping rule based on a combination of different assessments were frustrated by missing data. Unfortunately the observations with the greatest specificity (notably the volume of fluid aspirated) were also commonly the least often recorded. In the face of these difficulties a non-sequential design would have been preferable.

Non-homogeneous matching—i.e., both within and between patients, by including bilateral or unilateral involvement—could affect the power of any tests to detect a significant difference unless the strata were analysed separately (which small numbers precluded) and variation in the groups was pooled correctly.

The trial had been designed on the basis of work by Menkes[8] which suggested an improvement rate of 70% with yttrium-90 and 40% with triamcinolone, whence it was computed that a maximum of 135 pairs would have been required to yield a 95% confidence of detecting a difference at the 5% significance level. Other workers[9 10] have reported results broadly in accord with Menkes', but experience in this trial suggests that previous studies may lead to overoptimistic estimates in that yttrium-90 appears to have been credited with being more beneficial that we were able to observe.

The trial design included the option for treatment failures to be dealt with on a cross-over basis by then giving these patients the alternative therapy. Unfortunately this was never done; if it had been, the yield of data would have been increased.

OUTCOME

For what they are worth, the data in Table 1 do not lend support to the view that yttrium-90 is more or less advantageous than triamcinolone hexacetonide. Only a minority of comparisons led to responses that were not tied, and in most of these the benefit appeared to be with triamcinolone. Range of motion emerged as the only attribute to show benefit in the tied responses, an observation that scarcely supports the suspicion that a large number of 'irremediable' knees might have been included inappropriately in the trial.

CONCLUSIONS

Without being self-congratulatory the investigators regard this work as a worthy attempt by a group of enthusiasts. Nevertheless the overall tenor of the experience does not incline them to invest further effort in studying the efficacy of yttrium-90 by controlled investigation in relatively unselected patients. However, heterogeneity in response by patients has been demonstrated recently,[11] and further work might be worthwhile if attention could be concentrated on those who appear to be more likely to respond.

One way in which the trial design might have differed from clinical practice concerns ambiguity over eligibility for entry according to previous intra-articular injections. Triamcinolone may or may have not been equated with 'steroid' in this context, but, had only previous triamcinolone failures been recruited, the number of triamcinolone 'successes' might have been fewer.

The participants are indebted to the Arthritis and Rheumatism Council for initiating this study and supporting the staff who carried out the analyses.

References

1 Bridgman J F, Bruckner F, Eisen V, Tucker A, Bleehen N M. Irradiation of the synovium in the treatment of rheumatoid arthritis. *Q J Med* 1973; **42:** 357–67.

2 Delbarre F, Le Go A, Menkes C J, Aignan M. Preuve par étude statistique 'en double aveugle', de l'effet thérapeutique d'un colloïde charge d'yttrium radioactif (^{90}Y) dans l'arthrite rhumatoïde du genou. *CR Acad Sci (Paris)* 1974; **279:** 1051–4.

3 Gumpel J M, Roles N C. A controlled trial of intra-articular radiocolloids versus surgical synovectomy in persistent synovitis. *Lancet* 1975; **i:** 488–9.

4 Menkes C J, Le Go A, Verrier P, Delbarre F. A controlled trial of intra-articular yttriym-90, osmic acid and triamcinolone hexacetonide in rheumatoid arthritis. *Abstracts XIV Int Congr Rheumatol*, San Francisco, 1977; 614.

5 Yates D B, Scott J T, Ramsey N. Double-blind trial of yttrium-90 for chronic inflammatory synovitis of the knee. *Ann Rheum Dis* 1977; **36:** 481.

6 Armitage P. *Sequential medical trials*. Oxford: Blackwell, 1975.

7 Kirwan J R, Byron M A, Winfield J, Altman D G, Gumpel J M. Circumferential measurements in the assessment of synovitis of the knee. *Rheumatol Rehabil* 1979; **18:** 78–84.

8 Menkes C J. Is there a place for chemical and radiation synovectomy in rheumatic diseases? *Rheumatol Rehabil* 1979; **18:** 65–77.

9 Szanto E. Long term follow-up of ^{90}yttrium treated knee joint arthritis. *Scan J Rheumatol* 1977; **6:** 209–12.

10 Sheppeard H, Alden A, Ward D J. Osmic acid vs yttrium-90 in rheumatoid synovitis of the knee. *Scand J Rheumatol* 1981; **10:** 234–6.

11 Kyle V, Hazleman B L, Wraight E P. Yttrium-90 therapy and ^{99m}Tc pertechnetate knee uptake measurements in the management of rheumatoid arthritis. *Ann Rheum Dis* 1983; **42:** 132–7.

Book review

Radiological Investigations in Rheumatology. Clinics in Rheumatic Diseases. Vol. 9, No. 2. Eds. D. Forrester and J. C. Brown. Pp. 488. £11·75. Saunders: Philadelphia. 1983.

The old *x*-ray departments, which lasted from Roentgen in 1895 until when I knew them in the 1930s, began to take on scientific airs and became departments of radiology about 1940, with special interventionist procedures such as Jacques Forestier's introduction of iodised oil, and then other contrast media such as the barium meal. Now, however, a new revolution has started, based as always on new techniques, and this issue of 'Clinics in Rheumatic Diseases' successfully outlines the New Way – the department of imaging or imagery or imagology.

In a few instances these departments could be called departments of imaginary concepts or departments of the imagination, since statements or assertions are sometimes made without reliable anatomical, pathological, surgical, or other means of confirmation. In general, however, the new techniques of scintigraphy, computerised scanning, nuclear magnetic resonance, and ultrasound, or even thermography, greatly improve our verification procedures, since they can be tested against each other as well as against the ultimate morphological anatomical standards.

This current assessment, edited by that well known team Brown and Forrester, engagingly starts with their own photogenic images and begins with a conservative statement on 'The plain film,' which 'remains the cornerstone in the diagnosis of arthritis'. There are usually four cornerstones in the average building, the others being occupied in this special respect by clinical assessment, laboratory tests, and follow-up. The last is the best, and even the pathological verdict depends on that.

Technetium and gallium imaging, sonography, and computed tomography, as well as nuclear magnetic resonance, are reviewed pithily. All in all, this is a timely and welcome publication. The reproduction of various images is better than most, and certainly better than in certain current rheumatological journals.

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