Abstract

Objective. Magnetic resonance techniques have recently been investigated as tools with which to monitor inflammatory joint disease. Our aim was to use a contrast-enhanced T1-weighted protocol to monitor the short-term changes in knee synovial lining volume in a double-blind, randomized, controlled trial of intra-articular samarium-153 particulate hydroxyapatite (Sm-153 PHYP).

Methods. Twenty-four out-patients with chronic knee synovitis, from a cohort who had been recruited to a long-term clinical efficacy trial, were recruited for this study. Patients received either intra-articular Sm-153 PHYP combined with 40 mg triamcinolone hexacetonide or 40 mg intra-articular triamcinolone hexacetonide alone. Synovial lining volumes were calculated from three-dimensional T1-weighted contrast-enhanced images made before and after contrast enhancement with thresholding and pixel counting, immediately before and 3 months after treatment.

Results. Paired pre- and post-treatment magnetic resonance data were obtained for 18/24 (75%) patients. There was no significant difference in mean pre-treatment synovial volume between the two treatment groups (139 vs 127 ml). A mean reduction in synovial lining volume was detected in the Sm-153 PHYP/steroid-treated group (139 to 110 ml, \(P = 0.07\)) and in the steroid-treated group (127 to 58 ml, \(P < 0.001\)). The reduction was significantly greater in the steroid-treated group (−61\% vs −23\%, \(P < 0.05\)).

Conclusions. Short-term changes in articular synovial lining in response to intra-articular treatment for chronic synovitis may be monitored by magnetic resonance imaging. After 3 months, a greater mean reduction in synovial lining volume had occurred in response to intra-articular steroid alone compared to combined Sm-153 PHYP/steroid injection.

Key words: Radiation synovectomy, Samarium-153 particulate hydroxyapatite, Quantitative magnetic resonance, Synovial lining.
in comparing the large number of (mainly non-randomized) radiation synovectomy efficacy studies has been in interpreting the variety of outcome measures used [11, 12]. Frequently, the measures have been clinically based examination indices: largely qualitative and derived subjectively. The development of objective techniques, such as quantitative MR, which are able to quantify outcome, may be helpful for evaluating existing and new treatments for synovitis.

Our aim was to measure changes in SLV in the short term by quantitative MR [7] in a sample of patients with chronic knee synovitis recruited to a double-blind, randomized, controlled trial comparing combined intra-articular Sm-153 PHYP and steroid injection with intra-articular steroid alone.

**Methods**

**Patients**

A sample of 24 sequential patients with chronic knee synovitis, who were recruited to a large double-blind, randomized, intra-articular glucocorticoid-controlled study of the long-term effects of Sm-153 PHYP, were then asked to join the MR study. Inclusion criteria for the whole study were: age 18 yr or older, chronic knee synovitis for at least 2 yr, and clinical indication for intra-articular therapy judged by knee pain and stiffness being the factor limiting mobility. Exclusion criteria were: Steinbrocker radiological grade III/IV [13] for rheumatoid arthritis (RA) patients or <2 mm tibiofemoral joint space scored on a weight-bearing anteroposterior knee radiograph (non-RA patients), any form of intra-articular therapy within the previous 3 months, and a change in type or dose of slow-acting anti-rheumatic drug (SAARD) within the previous 3 months. The study was approved by the UCL Hospitals Trust Ethical Committee and all patients signed a written informed consent.

**Treatment procedure**

Randomization codes were held by the radiopharmacist. Patients were given either 40 mg triamcinolone hexacetone (TH) alone or in combination with 555 MBq (13.2 mCi) Sm-153 PHYP as a single intra-articular injection, by an investigator blinded to the randomization code. The injection procedure has been described in detail [9]. In brief, joints were aspirated, then injected using a 21-gauge needle attached to a three-way tap attached to two syringes, one containing the treatment substance and the second, a saline flush. The system was fully flushed to ensure full delivery of the drug(s). To maintain blinding, the syringe containing the drug and the three-way tap were obscured by tape. Subsequently, patients were kept non-weight bearing with knees immobilized for 4 h using a semi-rigid splint. Injected radioactivity was calculated by subtraction of activity remaining in the injection apparatus after injection from prepared activity. Patients were reviewed clinically for unwanted effects related to the treatment prior to discharge and when they returned for the second MR study. Formal clinical review was not undertaken as part of this study. Long-term symptomatic response of the ‘parent’ patient cohort will be reported separately (manuscript in preparation).

**MR methodology**

All patients were examined on a 1 T scanner (Siemens Magnetom 42SP) in a circularly polarized transmit and receive knee coil the week before and 3 months after treatment. The post-treatment MR study was timed to balance the chance of observing an optimal, though, as far as was practicable, clinically relevant (prolonged) effect of both intra-articular glucocorticoid and the particulate radiopharmaceutical on the synovitis. This was based on previous experience with Sm-153 PHYP [9, 10] and from experience derived from the use of the only other available particulate radiopharmaceutical, dysprosium-165 ferrie hydroxide macro-aggregates (Dy-165 FHMA) (S. Shortkrof, personal communication).

Scanning details and image analysis methods are described in detail elsewhere [7]. In brief, the knee was stabilized with foam padding and the foot stabilized with sandbags. A long i.v. line with a 21-gauge butterfly needle was inserted in the forearm before the procedure. The evaluation of SLV was made from three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo (MP RAGE) sequences [14] (TR 10 ms; TE 4 ms; TI 500 ms; FA 40°; FOV 210 mm; Ma 256 × 256; slice thickness 2 mm; Nex 1; Taeq 9 min) made before and after i.v. injection of 0.1 mmol/kg dimeglumine gadopentetate (Gd-DTPA) [Magnevist®, Schering Healthcare]. Scan datasets were transferred to a Sun SPARC 2 WorkStation and analysed by an investigator blind to treatment randomization (GC).

Pre- and post-enhancement images were subtracted using in-house software and, using XDISPIM (UCL, London), enhancing, non-vascular structures were manually segmented in each sagittal slice. Sagittal images were preferred to axial images for analysis because, in our experience, the synovial lining image was easier to interpret, could be more simply segmented, and could in many slices be segmented in a single region of interest. It was reasoned that total image analysis time and errors inherent in manual segmentation of an image would, therefore, be minimized. Total pixel area above the optimum preset threshold of the signal intensity on the post- minus pre-enhancement subtraction images [7] was calculated and total voxel volume derived as a measure of the volume of enhancing synovial tissue.

**Statistical analysis**

Baseline SLVs were distributed approximately continuously. The significance of the difference in mean pre-treatment SLV in the two treatment groups and the difference between mean per cent change in SLV in the two groups after treatment was compared by two-tailed Student’s t-test. The paired t-test was used to test the significance of the mean change in SLV within each group after treatment.
The Pearson correlation coefficient ($R_p$) was calculated to examine the relationship between pre-treatment SLVs and the per cent change in SLV after treatment, both overall and within each treatment group. The Spearman rank correlation coefficient ($R_s$) was calculated to examine the relationship between injected activity of Sm-153 PHYP and change in SLV in the combined-treatment group. For correlation, significance was tested ($\alpha = 0.05$) using one-way analysis of variance (ANOVA).

Results

Twenty-four patients were recruited to the MR study. Four patients subsequently withdrew: two after the initial MR and two between treatment and the second MR. Poor contrast enhancement and movement artefact resulted in image degradation in a further two patient studies which precluded paired image analysis. Therefore, pre- and post-treatment MR data were available for 18/24 (75%) patients. Clinical details of these 18 patients are shown in Table 1. Diagnoses were: RA ($n = 7$) diagnosed according to ARA criteria [15]; juvenile chronic arthritis ($n = 1$); seronegative spondylarthritides—consisting of patients with a characteristic inflammatory arthropathy clearly associated with psoriasis ($n = 3$) and patients with a proven characteristic infection prior to the onset of chronic oligoarticular arthritis ($n = 1$; in this case, sexually acquired reactive arthritis); and finally patients who were rheumatoid factor seronegative with oligo- or monoarticular inflammatory arthritis in whom the diagnosis had not been satisfactorily characterized any further ($n = 6$). There was no significant difference in mean baseline SLV in the two treatment groups (Table 2); however, there was a trend towards a larger mean SLV in patients treated with Sm-153 PHYP/TH. Mean injected Sm-153 activity was 490 MBq (13.2 mCi) with a range of 300–725 MBq (8.1–19.6 mCi).

Joint aspiration and injection were completed uneventfully in each case. There were no local side-effects observed immediately after the procedure or reported after the treatment. Within the study period, no patient discontinued or changed the dose of their SAARD.

There was a non-significant reduction in mean SLV in the Sm-153 PHYP/TH-treated group (139 to 110 ml, $P = 0.07$), but a significant reduction in mean SLV in the TH-treated group (127 to 58 ml, $P < 0.001$) by 3 months after treatment. The size of the reduction was significantly greater in patients treated with TH alone ($−0.61\% \text{ vs } −23\%, P < 0.05$) (Table 2). An example of paired pre- and post-treatment subtraction MR images is shown in Fig. 1. The maximum reduction of SLV achieved was similar in both groups ($−95\%$), but in the combined-treatment group there were 5/9 patients in whom the SLV changed <15% after treatment.

There was a weak non-significant correlation between baseline SLV and per cent reduction in SLV overall ($R_p = −0.3, P = 0.14, n = 18$) in the Sm-153 PHYP/TH-treated group ($R_p = −0.2, P = 0.60, n = 9$) and in the TH-treated group ($R_p = −0.5, P = 0.14, n = 9$). There was no clear relationship between the injected activity of Sm-153 PHYP and change in SLV ($R_s = −0.3, P = 0.50, n = 9$).

Discussion

Quantitative MR has been used as a tool to monitor changes in SLV in patients treated with various intra-articular therapies: glucocorticoid [5–7], osmic acid [3] and yttrium-90 (Y-90) colloid synovectomy [6]. Change in SLV measured by contrast-enhanced MR is likely to represent a change in cell-infiltrated, vascularized subin-

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Sm-153 PHYP + triamcinolone hexacetonide (n = 9)</th>
<th>Triamcinolone hexacetonide alone (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± s.d.) age (yr)</td>
<td>46 (± 14)</td>
<td>47 (± 15)</td>
</tr>
<tr>
<td>Age range</td>
<td>27–62</td>
<td>18–67</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>7/2</td>
<td>3/6</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Juvenile chronic arthritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Seronegative spondylarthritides</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sexually acquired reactive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Seronegative other</td>
<td>2$^a$</td>
<td>4$^b$</td>
</tr>
<tr>
<td>Median disease duration (range) (yr)</td>
<td>6 (3–24)</td>
<td>8 (2–25)</td>
</tr>
<tr>
<td>Median (range) number of months since last knee joint steroid injection</td>
<td>5 (3–24)</td>
<td>4 (3–18)</td>
</tr>
<tr>
<td>Patients taking non-steroidal anti-inflammatory drugs</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Patients taking SAARDs</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

$^a$Undifferentiated seronegative oligoarthritides (2).

$^b$Undifferentiated seronegative oligoarthritides (2); monoarthritis associated with polyartitis nodosa; and monoarthritis associated with ulcerative colitis.

<table>
<thead>
<tr>
<th>Sm-153 PHYP + triamcinolone hexacetonide-treated group (n = 9)</th>
<th>Triamcinolone hexacetonide-treated group (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± s.d.) baseline SLV (ml)</td>
<td>139 (± 56)</td>
</tr>
<tr>
<td>Mean (± s.d.) post-treatment SLV (ml)</td>
<td>110 (± 68)</td>
</tr>
<tr>
<td>Mean (± s.d.) reduction in SLV (%)</td>
<td>$−23$ (± 34)</td>
</tr>
<tr>
<td>Median (range) change in SLV</td>
<td>$−13%$</td>
</tr>
</tbody>
</table>

SLV, synovial lining volume.

$^a$Significance calculated using two-tailed Student’s t-test.
timal synovial tissue mass [16], although other aspects of joint tissue such as subintimal fibrosis [17] may influence measurements. Measurements of tissue volume, however, may be approximate as results may be affected by the timing of the i.v. contrast injection and post-contrast-enhanced T1-weighted sequence, by partial volume effects and by movement artefact if the joint is not kept still between sequences [2, 6, 7]. Nevertheless, previous analyses have shown that, from errors associated with the technique, SLV changes in excess of 15% are likely to be significant [7] and thus the mean reduction in SLV from both combined Sm-153 PHYP/TH treatment and TH alone is significant 3 months after treatment. The size of the reduction in SLV and the number of patients who achieved a >15% reduction in SLV was greater in the TH-treated compared to the combined-treatment group. The efficacy in both groups could be explained on account of the effects of intra-articular steroid alone. It is possible that Sm-153 PHYP may have initially aggravated the synovitis either through a mild pro-inflammatory effect of the particulate hydroxyapatite [18] or perhaps as a result of the initial ‘therapeutic’ effect of the radiation causing tissue necrosis, fibrin deposition and synovial lining thickening, similar to that observed following joint injection of Y-90 colloid [19–21]. Thus, these effects may have led to a more variable but overall lesser effect of combined Sm-153 PHYP and TH injection in reducing SLV in the short term. It is interesting to note that co-injection of Y-90 colloid and glucocorticoid leads to a wide variation in MR-quantified SLV with no significant change in median SLV after 12 weeks [6]. These results might also be consistent with the arthroscopic finding that Y-90 colloid may initially increase synovial thickening [21] before resulting in an improvement. It should also be noted that in the combined-treatment group more patients were taking both non-steroidal anti-inflammatory drugs (NSAIDs) and SAARDs, suggesting a greater extent and/or severity of polyarticular synovitis (Table 1), and that baseline mean SLV was greater than in the combined-treatment group (Table 2), both factors recognized to be associated with poorer outcome from radiation synovectomy [12]. These data were obtained despite randomization and may have contributed to bias. There was no significant correlation between pre-treatment SLV and per cent reduction in SLV overall or in either group. There are too few data in each group to allow a rigorous analysis of this relationship; however, subgroup analysis suggested that there was a greater strength of this relationship in the TH-only-treated group than in the combined-treatment group. Larger studies would be needed to explore this relationship further.

There was no clear relationship between injected Sm-153 PHYP activity and change in SLV. In view of the absence of any detailed Sm-153 dosimetry studies, we had aimed to inject ~555 MBq (15 mCi) Sm-153. This activity was estimated to give a dose to synovium roughly equivalent to the dose given by 185 MBq (5 mCi) of yttrium-90 (Y-90) [9], a dose associated with a clinical response in the long term [22]. Mean injected Sm-153 activity was 490 MBq (13.2 mCi). The minimum injected was 300 MBq (8.1 mCi) and the maximum 725 MBq (19.6 mCi). The variation in dose
occurred as a result of particles becoming lodged in the three-way tap and needle hub during administration. Almost certainly, the technique could be completed more efficiently without the masking tape occluding the injection apparatus as particles could be identified and flushed through the needle. Ultimately, the lack of a dose–response relationship here or in our previous study [10] suggests that there are factors more important than injected activity in influencing outcome, although there may be a ‘threshold’ value of injected activity below which a response does not occur at all, or for any given SLV.

In summary, we have applied a quantitative MR technique to measure the 3 month change in knee SLV in a randomized controlled trial of intra-articular Sm-153 PHYP. Overall, a mean reduction in SLV occurred in patients treated with both Sm-153 PHYP/TH and in patients treated with TH alone, although only in the steroid-treated group was the mean reduction significant. The difference in SLV reduction between the two groups was significant, suggesting that TH injected alone for chronic knee synovitis reduces synovial bulk more effectively in the short term than combined Sm-153 PHYP and TH.

References