EXTENDED REPORT

Radiation synovectomy with yttrium-90 for persisting arthritis has direct harmful effects on human cartilage that cannot be prevented by co-administration of glucocorticoids: an in vitro study

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Background: It was recently shown that radiation synovectomy with yttrium-90 (^{90}Y) and glucocorticoids is not superior to intra-articular glucocorticoids alone in the treatment of persistent gonarthrosis. In that study, it seemed that in patients treated by radiation synovectomy, progression of radiographic joint damage occurred.

Objective: To test in vitro the direct effects of radiation synovectomy with ^{90}Y on human cartilage.

Methods: Human cartilage tissue was exposed to ^{90}Y , glucocorticoids or the combination. 1:2000 to 1:20 dilutions of the clinical dose of 5 mCi/ml ^{90}Y and 20 mg/ml glucocorticoids were used. After a 4-day exposure and a subsequent 12-day recovery period, proteoglycan synthesis, proteoglycan release and proteoglycan content were measured. In addition, human synovial tissue was cultured for 4 days with ^{90}Y or glucocorticoids. Culture supernatants were analysed for cartilage-destructive activity.

Results: ^{90}Y , glucocorticoids and the combination inhibited proteoglycan synthesis considerably and dose dependently, an effect that sustained for at least 12 days. Proteoglycan release was transiently increased by ^{90}Y , an effect that was not changed by addition of glucocorticoids, which had no effect on its own. Proteoglycan content was eventually adversely affected by ^{90}Y , an effect hardly influenced by glucocorticoids. Neither ^{90}Y nor glucocorticoids changed the cartilage-destructive properties of synovial tissue.

Conclusions: ^{90}Y , but not glucocorticoids, has direct harmful effects on cartilage in vitro. Indirect beneficial effects of ^{90}Y via inhibition of cartilage-destructive properties of synovial tissue could not be shown. These observations may explain the possible radiographic joint damage on radiation synovectomy.

As persistent arthritis may induce damage to articular cartilage, eventually leading to functional loss and thereby disability, adequate treatment of persistent arthritis is essential. Radiation synovectomy (radiosynovectomy (RSO)) can be considered if arthritis persists despite intra-articular treatment with glucocorticoids and oral treatment with non-steroidal anti-inflammatory drugs or disease-modifying antirheumatic drugs. Some trials have suggested that RSO of the knee is more effective than chemical synovectomy,¹ surgical synovectomy² or an intra-articular glucocorticoid injection.¹ However, until recently, RSO with yttrium-90 (^{90}Y) was not proved to be superior to intra-articular glucocorticoids in the treatment of persistent arthritis.^{3–6} Recently, our group showed in a randomised clinical trial that RSO with ^{90}Y and glucocorticoids is not superior to glucocorticoids alone, both combined with clinical bed rest, in the treatment of persistent gonarthrosis.⁷

Administration of ^{90}Y is often directly followed by flushing the needle with glucocorticoids, to prevent leakage of ^{90}Y due to skin burn and needle tract burn, and to bridge the lag phase before onset of the clinical effect of RSO. This lag phase is assumed to last 3–6 months.⁸ The precise mode of action involved in RSO is unclear and has sparsely been investigated. ^{90}Y is assumed to be taken up from the articular cavity by phagocytosis of the colloidal particles by synovial lining cells and macrophages,⁹ which distribute it evenly over the synovial surface.¹⁰ Necrosis of the synovium is induced by local irradiation, followed by fibrosis and finally sclerosis.^{9 11–13}

Although RSO with or without coadministration of glucocorticoids¹⁴ is often applied in the treatment of persistent arthritis, little is known about its direct effects on articular cartilage of the treated joint. ^{90}Y has been reported to be harmful to the knee by induction of cartilage degeneration in the vicinity of the cruciate ligaments by local irradiation,^{3 11} which could predispose to premature osteoarthritis. This was attributed to the fact that ^{90}Y also penetrates articular cartilage, with mean penetration depth 2.8 mm and maximal 8.5 mm.¹⁵ These adverse effects led to reluctance in some clinics for application of RSO, because of dreaded treatment-induced harm to articular cartilage. Conversely, positive effects of ^{90}Y on cartilage are also described, mirrored by increased glycosaminoglycan (GAG) synthesis by normal cartilage after RSO compared with cartilage of the contralateral non-irradiated knee.¹⁶ Similarly, negative effects of glucocorticoids on cartilage have been reported, such as decreased cartilage matrix synthesis and increased chondrocyte apoptosis,¹⁷ as well as protective effects of glucocorticoids on cartilage of arthritic joints, with substantial inhibition of progression of radiographic joint damage in patients with rheumatoid arthritis.^{18–22} However, in the studies on patients with rheumatoid arthritis the cartilage effects might have been indirect, by diminishing synovial inflammation and thereby cartilage damage.

Interestingly, in our recent trial on the clinical effect of ^{90}Y and glucocorticoids versus glucocorticoids alone, we found

Abbreviations: GAG, glycosaminoglycan; RSO, radiosynovectomy

Figure 1 Effect of glucocorticoid (GC), yttrium-90 (⁹⁰Y), the combination (⁹⁰Y+GC) and zirconium (Zr) on proteoglycan synthesis (A), proteoglycan release (B) and proteoglycan content (C) of human cartilage after a 4-day exposure. Values depict the percentage change compared with control cultures without additions, for 1:2000–1:20 dilutions of the clinically applied solutions. The 1:20 concentration represents the therapeutic concentrations at the moment of clinical intra-articular injection. **p* < 0.05; actual *p* values are given in the Results.

the progression of radiographic joint damage in 34% *v* 28% of the knees, respectively, with placement of knee prosthesis in 8% *v* 1%.⁷ In general, if progression of radiological damage was found, 61% of the knees were treated with ⁹⁰Y and glucocorticoids, and 39% with glucocorticoids alone. No improvement of the Steinbrocker radiological score was observed on RSO or glucocorticoid treatment.⁷

Owing to these conflicting data, indicating the possible harmful effects of RSO, in this study the direct effects of ⁹⁰Y with or without glucocorticoids on cartilage tissue were

tested in vitro. As these effects may be compensated for by the anti-inflammatory effects on synovial tissue during RSO, the effects on synovial tissue were studied as well.

MATERIALS AND METHODS

Cartilage tissue cultures

Macroscopically normal human articular cartilage tissue was obtained from the femoral condyles (*n* = 11) or humeral head (*n* = 14) within 24 h after death of the donor. Mean (standard deviation (SD)) age of the donors was 65 (13) years. Slices of full-thickness cartilage were cut aseptically from the underlying bone, and, within 1 h after dissection, aseptically cut into square pieces and weighed (range 5–15 mg).²³ The cartilage explants were cultured individually, at random, in 200 µl culture medium, in 96-well round-bottom microtitre plates. Culture medium consisted of Dulbecco's modified Eagle's medium supplemented with penicillin (100 IU/ml), streptomycin sulphate (100 µg/ml) and glutamin (2 mmol/l), ascorbic acid (85 µmol/l), and 10% heat-inactivated pooled human adult male AB⁺ serum.²³

Experimental set-up

Cartilage was cultured with ⁹⁰Y, glucocorticoids, the combination ⁹⁰Y and glucocorticoids, or zirconium (Zr, the final decay product of ⁹⁰Y, and not radioactive after a decay of at least 7 weeks; half life of ⁹⁰Y is 2.7 days). Culture medium without additions served as a control. To mimic the clinical application of RSO, we used the stock dose and volume of ⁹⁰Y and glucocorticoids identical to what is injected intra-articularly in clinical practice: 185 MBq (5 mCi) ⁹⁰Y (yttrium citrate, CIS Bio-international (Fifi, Yvette, France), in 1 ml) and 20 mg glucocorticoids (triamcinolone hexacetonide, Lederle (Heemstede, The Netherlands), in 1 ml). In clinical practice both are injected after aspiration of the knee joint, which is then expected to contain <20 ml of remaining synovial fluid. To each well of 200 µl culture medium, 10 µl of pure or diluted drug was added, leading to final dilutions of 1:20, or lower. Zr (radioactivity maximally 3.4 Bq) was added similarly. To the controls, 10 µl of culture medium was added.

After 4 days of culture in the presence of these additions, part of the cartilage explants were stored at -20°C for determination of proteoglycan synthesis, proteoglycan content and DNA content. Culture media were harvested and frozen for analyses of proteoglycan release.

As the effects after a 4-day exposure are direct effects, and in clinical practice ⁹⁰Y and glucocorticoids will be cleared from the joint rapidly, the (ir)reversibility of the effects on cartilage was also studied. These experiments were carried out only with the highest concentration (1:20), mimicking in vivo treatment. For this purpose, the remaining part of the explants were rinsed once and subsequently washed three times (45 min) in 1 ml culture medium without additions. Finally, samples were cultured for an additional 12 days. The culture medium was refreshed every 4 days during this recovery period. On day 16, cartilage explants and culture media of the last 4 days of culture were analysed. Analyses were carried out only after complete decay of ⁹⁰Y.

Determination of proteoglycan turnover Proteoglycan synthesis

As a measure of proteoglycan synthesis, the rate of sulphate incorporation into GAGs was determined during the last 4 h of the 4-day and 16-day culture period, using ³⁵SO₄²⁻ as a tracer, as has been described previously.^{24, 25} Briefly, Na₂³⁵SO₄²⁻ was added; after 4 h, the tissue samples were rinsed and digested with papain. GAGs were precipitated by addition of cetylpyridinium chloride. The amount of ³⁵SO₄²⁻ incorporated was measured by liquid scintillation

analysis and normalised to the specific activity of the pulse medium.

Proteoglycan release

As a measure of proteoglycan release, the medium of the 4-day culture period and of the last 4 days of the recovery period were analysed for GAG content, using Alcian Blue (Sigma, Zwijndrecht, The Netherlands) for precipitation and staining of GAGs.²⁶ GAG release was quantified photometrically by the change in absorbance at 620 nm. Chondroitin sulphate (Sigma, C4383) was used as a reference.

Proteoglycan content

The amount of GAGs in cartilage was determined as a measure of the proteoglycan content of the cartilage explants. In the papain digest GAGs were precipitated and stained with Alcian Blue as described earlier.

DNA content

The DNA content of cartilage was determined as a measure of its cellularity by use of the fluorescent dye Hoechst 33258 (Sigma) as described previously.²⁷ Calf thymus DNA (Sigma) was used as reference.

Synovial tissue cultures

The effects of RSO are directed against synovial inflammation. These effects may indirectly have an effect on cartilage that may dominate the direct effects of RSO on cartilage. For this reason, human synovial tissue (50–100 mg samples, triplicates, retrieved from the suprapatellar pouch of the knee of donors after death without known history of joint disorder) was cultured for 4 days in culture medium and under conditions as described above. ⁹⁰Y, glucocorticoids or the combination in concentrations as described above were added. Interferon γ (300 U/ml) and lipopolysaccharide (40 μ g/ml) were added simultaneously to all cultures including controls to stimulate the proinflammatory activities of the tissue, mimicking inflammation.

Culture supernatants were analysed for cartilage-destructive properties by adding them to healthy cartilage (10% vol/vol) for 4 days, after which proteoglycan synthesis and proteoglycan release were determined as described earlier.

Statistical analysis

Owing to focal differences in composition and bioactivity of cartilage and synovial tissue, the results of 10 cartilage and 3 synovial tissue samples per parameter per donor, obtained randomly and handled individually, were averaged and taken as a representative value for cartilage of that donor. All parameters for each experiment were expressed as percentage of the untreated controls (0%).

For cartilage experiments, cartilage of at least five different donors was used. For synovial tissue experiments, at least three donors were used. Mean values of the different experiments (standard error of mean) are shown. Differences between treatments were analysed for statistical significance using Wilcoxon or Mann–Whitney U test, where appropriate. For all analyses, values of $p < 0.05$ were considered significant.

RESULTS

Direct effects of ⁹⁰Y, glucocorticoids and the combination on cartilage

As shown in fig 1A, a 4-day exposure of cartilage to ⁹⁰Y inhibited proteoglycan synthesis dose dependently and significantly (at the highest concentration: 56% inhibition, $p < 0.018$). Surprisingly, this adverse effect was also observed when cartilage was exposed to glucocorticoids (at the highest concentration: 34% inhibition, $p < 0.018$). The combination of

both displayed a similar dose-dependent inhibition of proteoglycan synthesis (72% inhibition, $p < 0.043$), which was a stronger inhibitory effect than that of the individual components (compared with glucocorticoids: $p < 0.003$, compared with ⁹⁰Y: $p < 0.030$). Zr did not influence proteoglycan synthesis.

As shown in fig 1B, ⁹⁰Y induced an increase in proteoglycan release at the highest (clinically relevant) concentration (206%, $p < 0.018$). Glucocorticoids did not display such an adverse effect on cartilage proteoglycan release and did not change the adverse effects of ⁹⁰Y (⁹⁰Y and glucocorticoids: 172% inhibition at the highest concentration, $p < 0.043$). The adverse effect of ⁹⁰Y and glucocorticoids was not significantly different from that of ⁹⁰Y alone ($p < 0.53$). Again, Zr was inert.

Proteoglycan content was adversely and dose dependently affected as well (fig 1C). The combination of ⁹⁰Y and glucocorticoids displayed the clearest adverse effects (16% decrease at the highest concentration, $p < 0.035$, one sided). Similar effects were found for ⁹⁰Y (8% decrease, $p < 0.044$, one sided). Glucocorticoids (–2%, $p < 0.25$) and Zr did not induce significant changes in proteoglycan content. The adverse effect of ⁹⁰Y and glucocorticoids was not significantly different from that of ⁹⁰Y alone ($p < 0.639$).

We found no significant change in cellularity of cartilage (DNA content) for either of the additions in both concentrations (data not shown).

Prolonged direct effects on cartilage

As shown in fig 2A, the decrease in proteoglycan synthesis as induced during the 4-day exposure period was sustained for at least 12 days. No significant difference was found between the effects observed directly after exposure and after a subsequent recovery period.

For proteoglycan release this was different. The adverse effects of ⁹⁰Y alone and in combination with glucocorticoids vanished after a 12-day recovery period (fig 2B).

Proteoglycan content was slightly more variable. The effects of glucocorticoids alone or those of Zr on proteoglycan content after 12 days of recovery were comparable with the effects immediately after exposure. However, the effect of ⁹⁰Y alone was tripled (–8% at day 4, and –24% after recovery, $p < 0.073$), whereas the effect of the combination ⁹⁰Y and glucocorticoids was halved (–16% at day 4 and –8% after recovery, $p < 0.221$).

DNA content was not influenced (data not shown).

Indirect effects via synovial tissue on cartilage

When supernatants of the control synovial tissue cultures (stimulated with lipopolysaccharide and interferon γ) were added to healthy cartilage in a 10% vol/vol concentration, as expected, proteoglycan synthesis decreased significantly (approximately 50% and 70% for the control cultures of the glucocorticoid and ⁹⁰Y experiments, respectively, $p < 0.002$ for both; fig 3A). Proteoglycan release, as expected, increased significantly (about 25% and 50% for the control cultures of the glucocorticoids and ⁹⁰Y experiments, respectively, $p < 0.038$ and < 0.009 , respectively; fig 3B). Interestingly, the addition of either ⁹⁰Y or glucocorticoids did not change the cartilage-destructive properties of stimulated synovial tissue. Proteoglycan synthesis remained inhibited (not different from the control of the culture condition; fig 3A), whereas proteoglycan release remained enhanced (not different from the control of the culture condition; fig 3B).

DISCUSSION

Although RSO with ⁹⁰Y is being applied and has been for decades throughout the world,^{14–28} relatively little is known about the direct effects of ⁹⁰Y on articular cartilage of the

Figure 2 Effect of glucocorticoid (GC), yttrium-90 (^{90}Y), the combination (^{90}Y +GC) and zirconium (Zr) on proteoglycan synthesis (A), proteoglycan release (B) and proteoglycan content (C) by human cartilage after a 4-day exposure (open bars) and a 12-day recovery period (at day 4+12; black bars). Values depict the percentage change compared with control cultures without additions, for a 1:20 dilution of the clinically applied solutions representing the therapeutic concentrations at the moment of intra-articular injection. *Significant difference compared with controls, $p < 0.05$; #statistical differences between 4-day effects and effects after a 12-day recovery period, $p < 0.05$. Actual p values are given in the Results.

treated joint. In general, destruction of the inflamed synovial membrane after RSO is attributed to local irradiation by the ^{90}Y colloidal particles.^{9-29,30} These particles are phagocytosed by synovial cells within 24 h after RSO,²⁹ and become distributed in the joint in the shape of the synovial tissue.³¹ RSO may result in coagulation necrosis of the superficial layer of synovial tissue within 2 weeks after ^{90}Y treatment, as has been shown both in animal models^{9-11,13} and in humans.³² However, radiation emitted by the radioactive colloidal particles may affect not only the synovial tissue but also the cartilage, as ^{90}Y has a mean penetration depth of 2.8 mm in cartilage. Irradiation of cartilage may result in chondrocyte

Figure 3 Indirect effects of glucocorticoid (GC) and yttrium-90 (^{90}Y) via synovial tissue on cartilage proteoglycan synthesis (A) and proteoglycan release (B). Values depict the percentage change compared with cartilage cultures without additions (0%) for culture supernatants from untreated synovial tissue (0) and 1:2000–1:20 dilutions of the clinically applied solution. The 1:20 concentration represents the therapeutic concentration at the moment of clinical intra-articular injection. Asterisks indicate significant difference compared with untreated cartilage, $p < 0.05$. Actual p values are given in the Results.

damage and thereby impaired extracellular matrix turnover, leading to cartilage degeneration.

This study was conducted in view of this concern regarding the possible deleterious effects of RSO, which is to our knowledge the first study describing the direct in vitro effects of RSO on human articular cartilage. It was found that ^{90}Y in a concentration as used clinically during RSO had a sustained direct adverse effect on the proteoglycan turnover of cartilage. Proteoglycan synthesis was inhibited even after prolonged recovery. Although the enhanced proteoglycan release was recovered, proteoglycan content progressively decreased. The addition of glucocorticoids to ^{90}Y , as often carried out clinically during RSO, could hardly prevent these deleterious direct effects of ^{90}Y on cartilage, although the prolonged effects on proteoglycan content were less adverse when the combination was used. Glucocorticoids alone did not influence cartilage integrity (proteoglycan content), although proteoglycan synthesis was decreased. Zr, the non-radioactive decay product of ^{90}Y , was not found to affect proteoglycan parameters, indicating no effect of the non-radioactive colloids on cartilage.

These data corroborate the results of previous in vivo studies using rabbits and dogs. Treatment of the rabbit knee with ^{90}Y showed an increased cellular proliferation of the superficial tangential cells of cartilage with small foci of degeneration in the vicinity of the cruciate ligaments, 16 weeks after RSO.¹¹ This damage of cartilage was attributed to accumulation of ^{90}Y in the folds of the cruciate ligaments,

or by the thinness of cartilage around the cruciate ligaments.¹¹ Exposure of normal canine knees to 4 mCi ⁹⁰Y led to inhibition of GAG synthesis 24 h after RSO to 37% of the control level of non-irradiated cartilage and to 28% after 5 days, as illustrated by suppressed ³⁵S uptake by chondrocytes on autoradiography.³³ Moreover, 4 and 8 h after exposure to ⁹⁰Y, the cartilage GAG concentration was only 66% and 54%, respectively, of that before treatment, whereas the corresponding values for control, non-irradiated cartilage were 90% and 87%.³³

In patients with rheumatoid arthritis, 8 and 12 weeks after RSO of the knee with 5 mCi ⁹⁰Y, both cellular and extracellular matrix damage were found in cartilage biopsy specimens.³⁴ The chondrocytes underwent a diffuse vesicular-shaped transformation 8 weeks after RSO and included large quantities of intracellular particles containing Zr, proving that ⁹⁰Y did not selectively enter the synovial cells, as had been previously supposed,²⁹ but entered the chondrocytes as well.³⁴ In the matrix, the collagen fibres displayed irregular arrangement, innumerable ruptures and loss of the characteristic sub-banding, with complete disintegration of the fibres in a few places.³⁴ Using electron microscopy, we found that the surface of cartilage was not only coarse but also greatly split with many crevices.³⁴

On the other hand, in an animal study with healthy dogs, 4–13 weeks after 2–4 mCi ⁹⁰Y injection in the knee, GAG synthesis in cartilage cultures from irradiated knees was found to be increased, compared with cultures of the contralateral knee.¹⁶ Morphological abnormalities were not observed in articular cartilage from the irradiated knee, nor did the water content or concentrations of uronic acid or DNA in cartilage from the irradiated knees differ from that in the contralateral knee.¹⁶ This increased GAG synthesis was consistent with a cartilage anabolic response continuing for more than 5 weeks after RSO. However, it should be kept in mind that also in osteoarthritic cartilage, proteoglycan synthesis is increased in an attempt to repair cartilage; however, this attempt is ineffective.²⁷

The observed deleterious direct effects of ⁹⁰Y on cartilage during RSO, even in the presence of glucocorticoids, might be shadowed by the anti-inflammatory properties of ⁹⁰Y on synovial inflammation. However, our in vitro study could not support this idea. Supernatants of short-term cultures of stimulated synovial tissue were, as expected,³⁵ harmful to cartilage. But neither ⁹⁰Y nor glucocorticoids could prevent these harmful effects. Reasonably, the combination of both would not have changed the harmful effects of synovial tissue culture supernatants on cartilage either. We realise that in vivo more pathways are involved than can be mimicked in vitro, such as proliferative activities in time, antigen stimulation and recruitment of inflammatory cells, including polymorphonuclear cells, which may all be of major importance in the final outcome of RSO as a treatment of persisting arthritis. Nevertheless, our results could not take away the initial premise from our clinical trial that RSO with ⁹⁰Y is harmful to cartilage and thereby might lead to a further increase in joint damage rather than preventing joint damage, despite the expected anti-inflammatory effects on synovial tissue. Although these are short-term in vitro data, results urge for more detailed evaluation of cartilage changes on RSO as a treatment of persistent arthritis. As long as its safety in this respect cannot be proved, we suggest being reluctant with RSO in general practice.

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