Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy

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Abstract

Objective—To determine the safety and efficacy of intra-articular injections of hyaluronan in the treatment of osteoarthritis of the knee.

Methods—A randomised double-blind placebo-controlled trial was carried out on 91 patients with radiologically confirmed osteoarthritis of the knee who were recruited from the outpatient clinics.

Results—It was found that weekly intra-articular injections of 20 mg of hyaluronan of $M_r = 750\,000$ (Hyalgan) in 2 ml of buffered saline performed no better than the inert vehicle alone over a five week period. The principal side effects of a transient increase in pain and swelling in the affected knee was observed in 47% of the treatment group compared with 22% of the placebo group. A few patients with radiologically mild disease treated with Hyalgan appeared to experience medium to long-term symptomatic improvement over matched placebo controls as judged by a delayed return to previous NSAID therapy or analgesia other than paracetamol. Patient numbers in the survival groups, however, were too small to be meaningful.

Conclusion—It is concluded that intra-articular administration of this preparation of 750 kD hyaluronan offers no significant benefit over placebo during a five week treatment period, but incurs a significantly higher morbidity, and therefore has no place in the routine treatment of osteoarthritis.

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Hyaluronan (hyaluronate, hyaluronic acid) is a linear repeating disaccharide, β -D-glucuronyl- β -D-N-acetylglucosamine, of high molecular weight which may range up to 10 megadaltons. Its physical properties vary discontinuously with its chain length.¹ Hyaluronan is secreted continuously into the joint space by elements of the synovium with some contribution by the chondrocyte.² It comprises the major macro-molecular species of the synovial fluid and is responsible for the unique visco-elastic properties of what is mainly a simple plasma dialysate.^{3–5}

Its clinical use was suggested by the finding that hyaluronan was reduced in concentration

and in chain length in the synovial fluids of arthritic patients.^{4,6} It was thought that the intra-articular administration of exogenous high-molecular-weight hyaluronan might restore the rheological environment of the joint ('visco-supplementation') thereby improving its load-transmitting function.

The first trials of intra-articular hyaluronan in human osteoarthritis were reported with mildly encouraging results by Helfet⁷ and by Peyron and Balazs⁸ in 1974. Several studies with various preparations of hyaluronan from different sources and of differing molecular weights have since been conducted.^{9–18} Although these variances in molecular weight and other methodological variations in trial design make direct comparisons difficult, there has been a broad consensus in the studies published that this treatment is well-tolerated and reduces the pain of osteoarthritis. Some of these studies indicated that symptomatic relief may be long lived, lasting six months or more.

Many of the published clinical studies suffered from small patient numbers (less than 50) or, in the case of the multi-centre studies, the inevitable difficulties of inter-observer variation. For this reason, we conducted a randomised double-blind placebo-controlled trial of weekly intra-articular hyaluronan of defined molecular weight (approx. $M_r = 750\,000$) in a number of patients recruited from a single centre sufficient to invest the study with the power to discriminate a clinically meaningful treatment efficacy.

Methods and materials

STUDY MEDICATION

Hyaluronan of approximately $M_r = 750\,000$ Daltons was supplied as Hyalgan, a stable and highly purified sodium salt of hyaluronan in phosphate buffered saline extracted from rooster combs, by Fidia SpA. Abamo Terme, Italy. Quality control analysis following purification confirmed the range of hyaluronan molecular weights in the samples used as 500 000–750 000 Daltons, and that no detectable residual protein remained from the original extraction.

PATIENT SELECTION

After Ethical Committee approval, 91 patients, 28 men and 63 women, were recruited with their fully informed consent from the rheumatology outpatient clinics of the Royal

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London Hospital. All had a clinical history and radiological evidence of osteoarthritis of the knee. All had pain at the time of recruitment in at least one knee of moderate or greater severity as defined by a minimum score of 30 mm or more on a 100 mm visual analogue scale (VAS) for pain evoked by at least one of five specified activities during the two week pre-study assessment period as outlined below. Patients with inflammatory joint disease, metabolic bone disease, anserine bursitis, or pain referred from other structures (for example, the ipsilateral hip or the lumbar spine) were excluded.

PATIENT STRATIFICATION

For the purposes of statistical analysis, the patients were stratified into two groups, I and II, on the basis of severity of radiological changes seen on radiographs taken before recruitment. Radiological evaluation was made using the criteria of Kellgren and Lawrence.¹⁹ Patients with grade I or grade II changes were assigned to Severity Group I; those with grade III or grade IV changes were assigned to Severity Group II. There were no patients with only grade I changes recruited to the trial. All except one patient had radiologically bilateral disease. The distribution of radiological grading within the Severity Groups is included in table 1.

STUDY DESIGN

Patients were seen weekly for seven weeks by the investigating physician and by the clinical metrologist, and monthly for five months thereafter. After a full assessment by the metrologist of pain at rest, on movement and on pressure applied directly on the patella with the knee extended (vertical pressure), and on the femoro-tibial joint lines (horizontal pressure), together with a detailed examination of the affected knee (taken as the most painful in the case of bilateral disease), the patient was instructed in the use of a standardised diary to record daily VAS scores of pain: 1) in the

morning; 2) in the evening; 3) on getting up from a chair; 4) on climbing stairs; 5) on an activity, which may include any of the above, nominated by the patient as being particularly painful to that individual.

These diaries were reviewed by the metrologist at each visit following the pain assessment procedure.

At the first visit (week 2), the patient was asked to discontinue any medication, including analgesics and NSAIDs, which she may have been taking for her arthritis. This also included any specific physical treatment, such as active physiotherapy or transcutaneous nerve stimulation (TNS), which she may have been receiving. Simple analgesia in the form of paracetamol was provided to all patients. Daily paracetamol consumption was recorded in the diaries throughout the study, as were any adverse events experienced by the patients. Consumption of NSAIDs or analgesics other than paracetamol were likewise recorded by patients in their diaries. Any such consumption during the treatment period was reported to the clinical monitor as a protocol violation. Diaries were collected, and new diaries issued, at each visit.

At the third visit (week 0), following a two week washout period, only patients meeting the above selection criteria entered a pre-assigned randomisation schedule which ensured that within each block of ten patients, equal numbers would receive treatment and placebo. A full medical history was taken from the patient. Before receiving an injection, the patient had a general physical examination by the investigating physician; blood was collected for extended haematological and biochemical profiles.

After randomisation, the patient's most severely affected knee was aspirated through a green (21 G) needle inserted into the patello-femoral space via the medial approach using an aseptic technique. Through the same needle, the patient received an intra-articular injection of either 20 mg Hyalgan in 2 ml of sterile buffered saline or 2 ml of the vehicle alone as for the randomisation schedule. Any effusion, if present, was aspirated to dryness before injection. Four subsequent aspirations and injections were administered in an identical fashion at weekly intervals.

Before aspiration and injection of the treated knee at each visit, the metrologist collected the diary data which were entered into the patient's individual case record book. Pain at rest (non-weight-bearing for 20 minutes) and on standardised active and passive movement was recorded as a 100 mm VAS score by the patient at each visit. With the patient's knee fully extended, patello-femoral tenderness was assessed by the metrologist using a standardised vertical pressure upon the patella with the patient again recording pain on a 100 mm VAS. Similarly, femoro-tibial tenderness was assessed by horizontal pressure on the joint line. The range of flexion of the treated knee was measured with a goniometer. The patient's estimates of duration of morning stiffness (in minutes) and of interference with

Table 1 Patient characteristics on entry to study

	Hyalgan		Placebo	
	Severity Group 1 <i>n</i> = 10	Severity Group 2 <i>n</i> = 25	Severity Group 1 <i>n</i> = 20	Severity Group 2 <i>n</i> = 26
Radiological grades				
I	0 (0%)		0 (0%)	
II	20 (100%)		20 (100%)	
III		17 (68%)		13 (50%)
IV		8 (32%)		13 (50%)
Age	63.9 (1.9)	72.1 (1.7)	60.0 (1.9)	67.0 (1.7)
Sex				
Female	10 (50%)	20 (80%)	15 (75%)	18 (69%)
Male	10 (50%)	5 (20%)	5 (25%)	8 (31%)
Bilateral disease	19 (95%)	25 (100%)	20 (100%)	26 (100%)
Effusion present in treated knee	6 (30%)	8 (32%)	3 (15%)	7 (27%)

Table 1 summarises the characteristics of age, sex, presence or absence of effusion and radiological disease severity of the 91 patients recruited to the trial. The randomisation procedure allocated 45 patients to the treatment (Hyalgan) group and 46 to the placebo group. After radiological stratification, there was no significant difference at the 5% level between the treatment and placebo groups. Seven patients, five in the Hyalgan group and two in the placebo group, withdrew during the five week treatment period leaving a final study population of 84.

acts of daily living on a 100 mm VAS were recorded, as was the weekly quantity of escape analgesia required.

On the eighth visit (week 5), one week after the final injection, the affected knee was aspirated only. Blood was again taken for analysis identical to the pretreatment samples. Global subjective assessments of treatment efficacy by both patient and metrologist were recorded.

Following this period, all patients were reviewed at one, three and five months post treatment. As in the treatment phase, pain at rest, on movement and on vertical and horizontal pressure was assessed by the metrologist using the patient's VAS scores, as was interference with daily life. The range of flexion of the knee was recorded. A global assessment of the state of the knee relative to previous visits was made by both patient and metrologist. The knee was aspirated if a clinically evident effusion was present.

Any adverse event experienced by the patient was reported to the 'blinded' metrologist and recorded by the 'unblinded' clinical investigator. All adverse events were then reported to the principal investigator who made any final decision to withdraw the patient. All patients were offered the opportunity to withdraw from the study at each visit throughout the treatment and follow up periods. Alternative analgesia or anti-inflammatory treatment was permitted during the follow up but not during the treatment period.

Throughout the study, all patient assessments (apart from the general physical examination at the third visit) were made by the metrologist who was 'blind' to the treatment received. As the physician drawing up and administering the injections could distinguish treatment from placebo by its greatly increased viscosity, he had played no part in patient assessment at any time. The appearances of the solutions were identical, however, and therefore gave no clue to the patient as to which she was receiving.

DATA HANDLING AND STATISTICAL METHODS

All data from the case record forms were scrutinised by an independent clinical monitor operating to the standards of Good Clinical Practice. Statistical analysis of the data was performed using the TABULATE, GLM and FREQ programmes of the SAS statistics and data management system (PC Version 6.04) on an IBM-compatible personal computer.

All tests of the null hypothesis were two-tailed with confidence intervals set at the 95% level.

At the outset of the trial, it was calculated that a sample size of 100 patients, 50 receiving Hyalgan and 50 receiving placebo, would be expected to invest the study with 90% power to detect a mean treatment difference of 13.1 mm in VAS scores. Time did not permit us to recruit the target figure. However, it was felt that the final study population was adequate to detect a clinically meaningful treatment difference if one existed.

Comparison of treatment versus placebo in terms of VAS scores and use of escape analgesia were made using the analysis of covariance to take into account differences in patients' pretreatment disease severity. In each analysis, the baseline (third visit) observation was used as a covariate. Diary VAS data were averaged for each parameter over the weekly intervals between visits. If for any reason less than four scores were recorded by the patient for any parameter in any week, that week's data were omitted from the subsequent analyses of that parameter.

Comparison of the metrologist's and the patients' global assessment of treatment efficacy was made using the Chi-square test in 2×4 contingency tables.

Shift tables were prepared for each of the haematological and biochemical parameters measured pre-and post-treatment. Adverse events were also tabulated and summarised by severity and by relationship to treatment.

A survival analysis of the follow up concomitant medication data was undertaken to compare the rate of return to previous NSAID therapy, or analgesia other than paracetamol alone, in both severity strata of the Hyalgan and placebo groups. Survival rates were estimated by the Kaplan-Meier method, and survival distributions were compared with the Mantel-Haenszel test.

Results

Ninety one patients (28 men and 63 women) entered the study at week three. Forty five patients (15 men and 30 women) were allocated to the treatment group and received Hyalgan; 46 patients (13 men and 33 women) received saline placebo.

Seven patients were withdrawn from the study during the treatment period. Five, all on Hyalgan, withdrew of their own volition because they were unable to tolerate the injections. Two patients, both on placebo, were withdrawn by the investigating physician because their synovial fluid analyses suggested a diagnosis other than osteoarthritis: gout in one case and an unidentified crystal arthritis in the other. The final study population therefore numbered 84.

Twenty eight patients, 13 on Hyalgan and 15 on placebo, were lost to the study in the five month follow up period due to non attendance. Analysis of the follow up phase has therefore been carried out separately from the treatment phase.

Analyses of the diary data revealed that both the Hyalgan and placebo groups improved in their mean VAS scores for all five parameters measured over the five week treatment period. There was, however, no statistically significant difference in the behaviour of the two groups at any point during that period. The patient diary mean VAS scores for the start (week 0) and the end (week 5) of the treatment period are summarised in table 2.

Although analysis of the VAS scores for pain at rest and for pain on both active and passive movement of each group assessed at each visit

Table 2 Patients mean (SD) diary VAS scores at start (week 0) and end (week 5) of a 5 week treatment period

	Hyalgan		Placebo	
	Severity Group 1 n = 18	Severity Group 2 n = 22	Severity Group 1 n = 19	Severity Group 2 n = 25
Pain in the morning				
week 0	62.2 (6.3)	58.5 (6.4)	63.6 (5.5)	65.7 (5.2)
week 5	44.5 (7.3)	49.4 (7.5)	51.3 (6.7)	58.8 (6.3)
Pain in the evening				
week 0	69.6 (4.5)	68.3 (4.7)	68.0 (4.7)	73.3 (3.9)
week 5	45.5 (6.7)	60.2 (6.4)	54.2 (6.2)	60.8 (5.1)
Pain on climbing stairs				
week 0	67.8 (6.7)	72.4 (4.3)	71.7 (4.4)	80.0 (3.2)
week 5	56.9 (7.9)	63.9 (5.8)	55.0 (5.9)	73.1 (4.4)
Pain on rising from chair				
week 0	71.2 (5.8)	66.0 (4.4)	65.9 (5.0)	72.7 (3.7)
week 5	48.5 (7.2)	62.8 (5.7)	54.7 (6.3)	65.2 (4.9)
Pain on nominated activity				
week 0	71.0 (5.4)	71.6 (4.5)	67.2 (4.4)	74.3 (3.6)
week 5	48.6 (6.6)	60.9 (6.5)	53.9 (5.6)	63.0 (5.1)

Table 2 summarises the patients' diary data for the week before the start (that is, the first injection at week 0) and the week before the finish (that is, the week following the last injection at week 4) of the five week treatment period. Although all patient groups improved, there was no significant difference at the 5% level of the behaviour of the treatment and placebo groups at any point during that period.

Table 3 Patients mean (SD) visit assessment VAS scores at start (week 0) and end (week 5) of a 5 week treatment period

	Hyalgan		Placebo	
	Severity Group 1 n = 18	Severity Group 2 n = 22	Severity Group 1 n = 19	Severity Group 2 n = 25
Pain at rest				
week 0	20.8 (5.5)	25.2 (5.8)	30.3 (6.9)	38.9 (6.3)
week 5	17.7 (5.6)	25.3 (6.5)	31.3 (7.2)	24.0 (6.0)
Pain on active movement				
week 0	43.7 (7.8)	48.5 (5.5)	53.0 (7.2)	49.3 (6.2)
week 5	28.1 (7.6)	39.8 (7.3)	38.8 (6.5)	31.3 (6.1)
Pain on passive movement				
week 0	44.8 (8.0)	41.1 (5.3)	42.2 (6.6)	44.8 (6.3)
week 5	27.3 (7.5)	37.7 (7.5)	33.8 (6.4)	34.9 (5.8)
Pain on horizontal pressure				
week 0	51.5 (8.0)	43.7 (6.1)	38.4 (6.4)	44.3 (6.6)
week 5	25.8 (6.5)	34.5 (7.2)	34.7 (7.0)	29.3 (6.5)
Pain on vertical pressure				
week 0	42.4 (8.0)	44.8 (6.6)	46.2 (8.0)	47.2 (5.9)
week 5	22.6 (6.1)	32.9 (6.9)	39.2 (7.1)	28.7 (6.1)

Table 3 summarises the patients' visit assessment data for the week before the start (that is, the first injection at week 0) and the week before the finish (that is, the week following the last injection at week 4) of the five week treatment period. Although all patient groups improved, there was no significant difference at the 5% level in the behaviour of the treatment and placebo groups at any point during that period.

Table 4 Weekly consumption of oral escape analgesia (paracetamol 500 mg tablets/week) at start (week 0) and end (week 5) of a 5 week treatment period

	Hyalgan		Placebo	
	Severity Group 1 n = 18	Severity Group 2 n = 22	Severity Group 1 n = 19	Severity Group 2 n = 25
1st quartile				
week 0	8	12	5.5	15
week 5	1	14	0	14
Median				
week 0	26.5	28	18	25.5
week 5	23.5	25	18	34
3rd quartile				
week 0	34	44	36	42
week 5	36	34	38	41

Table 4 summarises the distribution of permitted oral escape analgesia consumption within each of the Severity Groups. Due to wide inter-patient variation of paracetamol consumption, these data are expressed as the median [rather than mean (SD)] and quartile ranges of numbers of 500 mg paracetamol tablets taken during the week before the start (that is, the first injection at week 0) and the week before the finish (that is, the week following the last injection at week 4) of the five week treatment period. Although there was a modest reduction in the median number of tablets taken by both severity groups of the Hyalgan cohort, and an increase in the median figure for Severity Group II of the placebo cohort, non-parametric comparison (Wilcoxon signed rank test) revealed no significant difference between the treatment groups at the 5% level.

showed an apparent improvement in the Hyalgan group at week 2, there was no statistical difference in the behaviour of the two groups at any other time point in the five week treatment period. Analysis of the VAS scores for patello-femoral and femoro-tibial joint tenderness, and of the duration of morning stiffness and interference with activities of daily living, also showed some early improvement over placebo in the Hyalgan group which reached its maximum at week 2, that is, after two intra-articular treatments. This was not sustained over subsequent weeks, however, and there was no significant difference in the behaviour of the two groups over the whole of the five week treatment period. The patient visit mean VAS scores for the start (week 0) and the end (week 5) of the treatment period are summarised in table 3.

There was no significant change either in the range of flexion of the treated knee or in the number of paracetamol tablets taken as escape analgesia in either group over the treatment period. The distributions of weekly paracetamol consumption within each of the Severity Groups at the beginning (week 0) and end (week 5) of the treatment period are summarised in table 4.

The only adverse event attributable to treatment was a transient increase in pain and/or swelling in the treated knee; this usually lasted less than four days. Such local adverse events occurred in 21 (47%) of the 45 Hyalgan treated patients, and in 10 (22%) of those who received placebo. In the Hyalgan group, five of those affected (24%) described this effect as mild; 14 (67%) described it as moderate, and two (9%) as severe. In the placebo group, one affected patient (10%) described the effect as mild; eight (80%) described it as moderate, and one (10%) as severe. There were no significant changes in any patient of any parameter of the full blood counts and biochemical profiles carried out at the beginning and at the end of the treatment period.

When asked for a global assessment of their progress at the end of treatment, 57.5% of the 40 patients treated with Hyalgan remaining in the trial said they felt better. This was mirrored by 61.5% of the remaining 44 members of the placebo group who also reported improvement. There was therefore no significant treatment difference. The clinical metrologist's global assessments likewise detected no significant treatment difference between the Hyalgan and placebo groups.

During the five-month follow up period, 28 patients (13 treated with Hyalgan and 15 receiving placebo) failed to continue attending the clinic. These patients were deemed therefore to have withdrawn from the study of their own volition. A separate analysis was carried out on the data of those patients who continued to the end of the follow up study.

Comparison of the rates of return to NSAID therapy, or analgesia other than paracetamol alone, in the surviving Hyalgan versus placebo cohorts of Severity Group I (fig) showed that the delay in seeking further treatment was

Figure 1 The figure represents a survival function analysis of those patients with radiologically judged early or mild disease (Severity Group I; $n = 28$) showing that the rate of return to previously prescribed or other NSAIDs, or analgesia other than paracetamol, is significantly slower ($p < 0.01$) in the Hyalgan treated cohort ($n = 14$). A similar analysis of the Severity Group II (moderate to severe; $n = 28$) cohorts showed no significant difference between the patients receiving Hyalgan ($n = 13$) and placebo ($n = 15$). Survival rates were estimated by the Kaplan-Meier method, and survival distributions were compared with the Mantel-Haenszel test.

significantly extended ($p \leq 0.01$) in the Hyalgan treated group. Similar analysis of the Severity Group II cohorts showed no statistically significant difference in the behaviour of the Hyalgan and placebo groups.

No statistically significant difference in pain assessment by the metrologist, range of knee flexion, patient's assessment of disease interference with activities of daily life, and global assessments by patient and metrologist was found between the Hyalgan and placebo groups in either severity group.

Discussion

Dieppe *et al* recently commented upon the dearth of published research on therapeutic modalities in the treatment of OA other than cross comparisons of different NSAIDs.²⁰ They suggest that much of this work, averaging about twenty trials per year appearing in previous reports since 1985, is predicated on the questionable assumption that NSAIDs are specifically appropriate to the management of OA in the first place. Some support for this view comes from an American study which found no significant difference in patient outcome in a three way trial comparing high (anti-inflammatory) and low (analgesic) doses of the NSAID ibuprofen with paracetamol alone.²¹ Another study from the same centre found a significant symptomatic improvement in patients who simply received monthly supportive telephone calls from trained but

non-medical personnel with no other change to their treatment.²² These papers highlight the need to evaluate alternatives to NSAIDs.

Despite nearly twenty years of clinical use in other countries, there have been no single centre double-blinded placebo-controlled trials of intra-articular hyaluronan in the treatment of osteoarthritis reported in the UK. We have conducted such a trial of weekly intra-articular injections of hyaluronan of $M_r = 750\,000$ Daltons, 20 mg in 2 ml buffered saline (Hyalgan), over five weeks with five month follow up in the treatment of osteoarthritis of the knee.

Sixteen outcome parameters were evaluated: patient's diary VAS scores for: 1) pain in the morning, 2) pain in the evening, 3) pain on getting up from a chair, 4) pain on climbing stairs, 5) pain on a nominated activity, clinic assessment VAS scores for 6) pain at rest, 7) pain on standardised active movement, 8) pain on standardised passive movement, 9) pain on applied vertical pressure, 10) pain on applied horizontal pressure, 11) interference with daily living, and 12) range of flexion, 13) duration of morning stiffness, 14) patient's global assessment of state of the knee relative to previous visits, 15) metrologist's global assessment of state of the knee relative to previous visits, and 16) use of escape analgesia.

In terms of patients' daily subjective assessment of pain recorded as VAS scores in home diaries, both the Hyalgan and the placebo groups improved over the five-week period. The improvements were demonstrated by a reduction of adjusted weekly mean pain scores averaging between 10% and 15% by the end of treatment. The behaviour of the two groups was identical, however, and no statistically significant difference could be detected between them at any time point. This pattern of a measurable, though not clinically striking, placebo effect almost exactly matched by treatment was also seen in the more formal assessments by the metrologist of pain, joint tenderness and function and interference with activities of daily living at the clinic visits.

That Hyalgan performed no better than saline in the treatment phase of the study where both groups improved suggests two possible explanations: 1) that saline injection is itself a therapeutic manoeuvre at least as efficacious as Hyalgan, or 2) that a placebo effect was operating quite independent of the injections sufficient to skew the results of both groups swamping any difference between the two. If the former is true, then Hyalgan offers no advantage over saline. If the latter is the case, and a number of authors have commented on the 'personal attention factor' in trials treating chronic painful conditions, any difference between Hyalgan and saline would be so small as to be clinically insignificant.

In the five month follow up period, no statistically significant difference was found in the pain and functional parameters assessed with one exception. The return to previous NSAID therapy, or alternative analgesia other than paracetamol alone, was significantly delayed in the Hyalgan treated patients of

Severity Group I. No such difference was seen in Severity Group II. This implies that Hyalgan may be having a long-term effect upon either the natural history of some patients' disease, or some patients' perception of pain arising from their disease. Unfortunately, the number of patients surviving failure events was too small to permit any meaningful sub-group analyses which might identify cohorts with pretreatment characteristics, for example, the presence or absence of an effusion, predictive of this outcome.

It is not immediately obvious how Hyalgan might have any such long-acting effect in the absence of any demonstrable effect in the short term. Hyaluronan, however, is far from an inert space-filler or static scaffolding for other extracellular matrix molecules. Whether hyaluronan molecules of Hyalgan defined molecular weight (M_r = ca 750 000 Daltons) engage in any interactions with elements, either molecular or cellular, concerned with the pathogenesis of osteoarthritis is as yet a matter of speculation. Nevertheless, the failure-event survival in the follow up phase of cohort of patients treated with Hyalgan with early or mild disease suggests the possibility of a long-acting biological effect.

The study revealed one other apparent biological effect. The principle adverse effect of a transient increase in pain and/or swelling at the injection site occurred more than twice as often with Hyalgan than with saline. This suggests that Hyalgan, or one of its metabolites, may act either as a primary irritant or as an inflammatory mediator in some patients. The mechanism by which this may occur is under investigation in our laboratory.^{23, 24}

In summary, we have shown that weekly intra-articular injections of 20 mg of hyaluronan of M_r = 750 000 (Hyalgan) in 2 ml of buffered saline performed no better than the inert vehicle alone over a five week period in the treatment of osteoarthritis of the knee in 91 patients recruited from our outpatient clinics. There was, however, a considerable morbidity attached to the injection of Hyalgan over and above that of injection of the vehicle. Despite a possible medium to long term symptomatic improvement in some patients with radiologically judged early or mild disease which may justify further clinical studies, we conclude that the intra-articular administration of this preparation of hyaluronan has as yet no place in routine clinical practice with regard to the treatment of osteoarthritis.

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