The Safety and Efficacy of Different Dose Schedules of Hyaluronic Acid in the Treatment of Painful Osteoarthritis of the Knee with Joint Effusion

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Summary

Intra-articularly administered hyaluronic acid (HA) has been shown to be effective, in the treatment of knee osteoarthritis (OA). We carried out a double-blind randomised placebo- and arthrocentesis-controlled study to evaluate the efficacy of 3 different dose schedules of HA. One hundred patients with knee OA and at least 3cc of joint effusion were enrolled and randomly assigned to the 5 treatment groups.

Pain on movement and at rest, the Lequesne index, joint mobility, volume of joint effusion, intake of analgesic, and overall judgement of efficacy were evaluated at baseline and on Days 7, 14, 21, 28, 35, and 60. Recurrence was also evaluated up to six months. The evaluation of these parameters showed a significantly superior effect of 5 and 3 injections of HA in comparison with placebo, arthrocentesis and one injection of HA.

Long-term monitoring of the patients, over a period of six months, provided evidence of the value of repeated injections of HA in terms of maintenance of the results. Only few local adverse reactions, essentially transitory pain after injection, were reported. These reactions were equally distributed between the groups.

Introduction

Current medical therapies for OA of the knee are directed only towards pain relief and the reduction of secondary functional disability using symptom modifying drugs having an immediate effect, such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids, although their efficacy remains controversial[1].

Two new therapeutic approaches are currently being developed in OA:

- drugs having a delayed but long term efficacy able to reduce or avoid the use of any other treatment such as NSAIDs and intra-articular corticosteroids[2,3]. These drugs are currently termed SYSADOA or "symptomatic slow acting drugs in osteoarthritis"[29b].
- disease modifying agents ("chondroprotective" drugs) able to improve cartilage repair and/or delay breakdown (DMOAD)[29b].

Several experimental and clinical studies suggest that hyaluronic acid may belong to the first category, i.e. as an anti-osteoarthritis drug with a long term symptomatic effect. Hyaluronic acid is a natural biopolymer made up of repeating sequences of disaccharides (glucuronic acid and N-acetylglucosamine)[4]. Synthesised by synoviocytes, it is responsible for the viscoelastic properties of synovial fluid and plays a fundamental role in the maintenance of the trophic status of the cartilage[5-10]. In joint disease there is a reduction in the concentration and molecular weight of HA in synovial fluid due to the action of superoxide ions and decreased synthesis by synoviocytes[11,12]. This leads to a reduction in the viscosity of synovial fluid, its shock-absorbing and anti-oxidant capacities, and favours the appearance of abnormalities of the articular cartilage due to an inappropriate metabolic response of chondrocytes, and an increase in proteoglycans and collagen breakdown[13].

Hyalgan® (Fidia S.p.A., Italy) is a viscous solution of highly purified HA (10 mg/ml) of well defined molecular weight (500-730 kiloDaltons: Hyalectin® fraction) extracted from rooster combs. *In vitro* and *in vivo* experimental studies have provided clear evidence that HA neutralises superoxide ions[14], leads to reaggregation of proteoglycans, stimulates HA synthesis by synoviocytes, improves the rheological properties of synovial fluid[12], and reduces the degenerative pathological changes induced in experimental joint lesions[15,16,17]. These data have prompted the use of Hyalectin® in veterinary[18,19] and human joint disease.

Several clinical studies have been performed in patients with osteoarthritis of the knee, in comparison with placebo[20-23] or corticosteroids[24,25,26]. These have demonstrated the beneficial effects of 3-5 intra-articular injections of 20 mg/2 ml of Hyalgan®. The aim of this study was to evaluate the safety and efficacy of different dose schedules of HA in comparison with placebo and knee arthrocentesis.

TABLE 1
Treatment Schedule

		Day			
Group	**Baseline**	**7**	**14**	**21**	**28**
Placebo	A + P	P	P	P	P
Arthrocentesis	A	A	A	A	A
HA-1	A + HA	A	A	A	A
HA-3	A + HA	HA	HA	A	A
HA-5	A + HA	HA	HA	HA	HA

HA = Hyalgan® 20 mg/2 ml;
A = Arthrocentesis;
P = Placebo (2 ml buffered saline solution).

Patients and Methods

Male and female outpatients at least 40 years of age and fulfilling the criteria of the American College of Rheumatology for the diagnosis of osteoarthritis of the knee[27] were admitted to the study. The inclusion criteria were: a clinical history of painful knee osteoarthritis for over 6 months; the presence of knee effusion (> 3ml); pain on movement greater than 40 mm evaluated on a 100 mm visual analogue scale (VAS)[28].

The following patients were excluded from the study: patients with generalised osteoarthritis; patients with secondary osteoarthritis of the knee; patients with a known or suspected joint infection; patients with a specific condition or poor general health status that would interfere with the functional assessments during the study; patients who had undergone arthrocentesis and/or intra-articular injection within the three months prior to the study; patients suffering from a very severe osteoarthritis of the knee, e.g. with a planned intra-medicinal product. Other concomitant treatments for osteoarthritis of the knee (besides paracetamol) - e.g. intra-articular corticosteroid, NSAIDs, analgesic, or physiotherapy - were not allowed for the duration of the study.

This was a 6-month prospective, single centre, randomised, double-blind, placebo- and arthrocentesis-controlled trial. The study was approved by the Ethical Review Board and all patients gave their informed consent to participate in the trial.

The study supplies (Hyalgan® 20 mg/2 ml or placebo 2 ml) were prepared in identical vials for intra-articular injection. Due to the lower viscosity of the placebo, clinical assessment was performed by a blind observer. The appearances of the solutions were identical and therefore gave no clue to the patients as to what they were receiving.

The patients were randomised to one of 5 treatment groups (Table 1). Intra-articular injections of Hyalgan®, or placebo, or arthrocentesis, were performed in an identical fashion at weekly intervals for 4 weeks.

At the first visit, knee effusion was aspirated to dryness and its volume recorded according to the inclusion criteria. At the following visits, arthrocentesis was performed only to verify the presence of an effusion, without aspiration except at Day 35 (one week after the last injection) and 2 months after the beginning of the study.

Clinical assessments for each patient were made by the same blind observer at weekly intervals during the first 5 weeks (Days 0, 7, 14, 21, 28, and 35) and then on Day 60, 4 weeks after the last injection and/or arthrocentesis. The following efficacy parameters were evaluated: severity of pain at rest and on movement evaluated by the patient using a 100 mm VAS[28]; range of motion evaluated by a goniometer in degrees of full flexion; Lequesne index of severity for osteoarthritis of the knee (ISOAK)[29]; daily paracetamol consumption; presence of joint effusion. In addition, global subjective assessments of treatment efficacy both by patients and observer were recorded at the final visit.

The duration of the effect was evaluated at the end of an additional 4-month follow up period on the basis of a global efficacy assessment by the investigator. According to the protocol, the follow up period involved only those patients whose efficacy assessment was judged to be: "fair", "good" or "very good" at the Day 60 visit. Those patients whose assessment was judged as "null" or "poor" were withdrawn from the study at this visit when a "negative" assessment was made by the investigator.

All adverse events reported by the patient and/or observed by the investigators were recorded. Complete haematology and biochemistry analyses were performed before the first injection (Day 0) and one week after the final injection (Day 35). The baseline data from the 5

TABLE 2
Description of the Patients at Baseline

Group	Placebo	Arthrocentesis	HA 1 injection	HA 3 injections	HA 5 injections
Number of patients	20	20	20	20	20
Sex: Female/Male	16 / 4	9 / 11	13 / 7	12 / 8	13 / 7
Age (years) M ± SD	60.0 ± 7.0	56.8 ± 7.5	61.3 ± 6.8	60.0 ± 7.1	60.6 ± 7.9
Weight (kg) M ± SD	69.9 ± 3.5	72.1 ± 6.5	73.6 ± 7.5	71.7 ± 4.5	70.5 ± 4.4
Height (cm) M ± SD	167.1 ± 3.7	169.2 ± 5.2	169.0 ± 4.9	167.5 ± 5.0	168.8 ± 4.3

groups were compared to assess their homogeneity (two-tailed tests at a 10% significance level).

The main efficacy analyses were performed 2 months after the beginning of treatment. An overall analysis of all the visits was also carried out. The comparison between groups was performed at a 5% significance level and pair-wise comparisons at 0.51% Sidak's protected significance level. Analysis of covariance was used to test continuous efficacy parameters. A repeated measurement model accounting for all the visits was also adjusted. When appropriate, time profiles were assessed using orthogonal polynomials. Model assumptions were checked and residuals were examined carefully. Ordinal parameters were analysed using Cochran-Mantel-Hanszel test, and dichotomous-measures were examined using Mantel-Hanszel Chi-squared test.

Adverse events and related information were compared among groups for severity and frequency. Descriptive statistics for clinical laboratory tests were tabulated. Any change from baseline for each laboratory parameter was tabulated and clinically significant abnormalities calculated. The analyses were performed by the Biometrics Department of FIDIA France using SAS software package (SAS Institute, Cary, NC, USA) run on a VAX 3100 Digital equipment.

Results

One hundred patients (37 males and 63 females) were included in the study, and randomised into 5 groups of 20 patients each. There were no protocol violations and no patients dropped out of the study between Day 0 and Day 60. The 5 groups did not differ significantly for demographic data (Table 2) and clinical parameters (Table 3) at baseline.

TABLE 3
Clinical Parameters of the OA at Baseline

Group	Placebo	Arthrocentesis	Hyalgan 1 injection	Hyalgan 3 injections	Hyalgan 5 injections
Evaluated knee Right/Left	13 / 17	15 / 5	15 / 5	12 / 8	15 / 5
Knee OA One compartment Two compartments	 2 18	 2 18	 0 20	 1 19	 0 20
Duration of OA (years) M ± SD	2.7 ± 1.4	2.1 ± 1.2	2.2 ± 1.3	2.3 ± 1.6	2.9 ± 1.3
Pain on movement (mm) M ± SD	64.4 ± 8.8	64.5 ± 10.9	61.7 ± 12.9	64.1 ± 12.6	63.3 ± 12.3
Spontaneous pain (mm) M ± SD	45.5 ± 10.2	43.2 ± 12.4	40.5 ± 11.7	44.7 ± 13.5	43.6 ± 10.7
ISOAK (total score) M ± SD	14.5 ± 3.0	14.3 ± 3.0	14.0 ± 3.8	14.9 ± 3.1	15.0 ± 2.5
Synovial effusion (ml) M ± SD	10.9 ± 5.8	13.1 ± 10.6	11.3 ± 8.0	13.6 ± 7.8	15.2 ± 7.2
Analgesics consumption No/Yes	18 / 2	16 / 4	16 / 4	17 / 3	17 / 3

TABLE 4
Evolution of Pain at Rest During the Study

	Day				
Group	Baseline	14	28	35	60
Placebo	45.6 ± 10.2	39.5 ± 12.8	37.6 ± 12.7	37.4 ± 13.7	39.9 ± 14.6
Arthrocentesis	43.3 ± 12.4	39.9 ± 14.7	39.9 ± 15.1	40.4 ± 14.7	43.2 ± 14.8
HA-1	40.5 ± 11.7	36.8 ± 11.7	34.3 ± 14.0	31.5 ± 14.0	34.1 ± 15.2
HA-3	44.7 ± 13.5	38.8 ± 14.3	33.3 ± 3.1	30.3 ± 14.5	33.0 ± 15.8
HA-5	43.6 ± 10.7	37.6 ± 11.7	32.0 ± 11.7	28.3 ± 11.6	29.3 ± 9.3

Pain at Rest [VAS (mm): mean ± SD]

Tables 4, 5 and 6 show the evolution of the main parameters for each treatment group between Day 0 and Day 60.

The improvement in all clinical parameters evaluated was significantly greater in groups treated with 3 or 5 intra-articular injections of Hyalgan®. Pain on movement (Table 5), which was high at inclusion (range 61.7 ± 12.9 to 64.5 ± 10.9) decreased in all groups but to a greater extent in the HA-3 and HA-5 groups ($p < 0.0051$). Pain at rest (Table 4) decreased in all groups with the exception of the group treated with arthrocentesis alone. On Day 35 the decreases were -8.2 mm in the placebo group, -2.9 mm in the arthrocentesis group, -9 mm in the HA-1 group, -14.4 mm in the HA-3 group, and -15.3 mm in the HA-5 group. At Day 60 these values were -5.7 mm in the placebo group, -0.1 mm in the arthrocentesis group, -6.4 mm in the HA-1 group, -11.7 mm in the HA-3 group, and -15.3 mm in the HA-5 group. There was a statistically significant

TABLE 5
Evolution of Pain on Movement During the Study

	Day				
Group	**Baseline**	**14**	**28**	**35**	**60**
Placebo	64.4 ± 8.8	57.2 ± 12.0	56.0 ± 11.6	56.4 ± 13.5	59.8 ± 14.5
Arthrocentesis	64.5 ± 10.9	58.5 ± 13.3	58.7 ± 14.4	59.7 ± 14.9	63.2 ± 13.7
HA-1	61.8 ± 12.9	57.5 ± 13.7	53.7 ± 16.8	51.8 ± 19.1	53.4 ± 20.4
HA-3	64.2 ± 12.6	58.1 ± 14.7	49.8 ± 13.3	46.0 ± 16.5	47.8 ± 17.7
HA-5	63.3 ± 12.3	55.0 ± 12.7	46.0 ± 14.0	41.8 ± 14.4	42.1 ± 12.5

Pain on Movement [VAS (mm): mean ± SD]

TABLE 6
Evolution of the ISOAK During the Study

	Day				
Group	**Baseline**	**14**	**28**	**35**	**60**
Placebo	14.5 ± 3.1	13.8 ± 3.5	13.3 ± 3.3	13.4 ± 3.4	13.9 ± 3.5
Arthrocentesis	14.3 ± 3.1	13.6 ± 3.3	13.7 ± 3.7	14.1 ± 3.5	14.4 ± 3.2
HA-1	14.1 ± 2.9	13.5 ± 3.8	12.8 ± 4.5	12.3 ± 4.8	12.7 ± 5.1
HA-3	14.9 ± 3.1	13.9 ± 3.2	12.4 ± 3.5	11.6 ± 3.7	12.0 ± 4.3
HA-5	15.1 ± 2.5	13.8 ± 2.8	12.3 ± 2.9	11.5 ± 3.0	11.6 ± 2.6

ISOAK Score [mean ± SD]

difference between the HA groups treated with 3 and 5 injections and the other groups ($p < 0.0051$). The maximal improvement observed on Day 35 was maintained up to the end of the study (Day 60) in these two groups. Functional capacity, assessed using the ISOAK scale (Table 6), improved only in the groups treated with Hyalgan® (HA-1: -1.4; HA-3: -2.9; HA-5: -3.5 at Day 60 follow up visit). This improvement observed from Day 28 onwards, was significantly greater in the HA-3 and HA-5 groups compared to the HA-1 group ($p < 0.0051$ at Day 60).

The range of flexion improved in the HA-3 and HA-5 treated groups only, with a statistically significant difference ($p < 0.0051$) when compared with the other groups. Similar results were obtained for joint effusion between Day 0 and Day 60 (data not shown). At baseline, very few patients (less than 15%) took paracetamol tablets and there was no change over time.

When asked for a global assessment of treatment efficacy at the end of the first study period, significantly more patients in the Hyalgan®-treated groups, (HA-1, HA-3 and HA-5), gave a positive judgement. The investigator's global assessment was similar. The results are shown in Table 7 which summarises the results of the comparison between groups made at the Day 60 follow up visit. When the HA-3 and HA-5 groups were compared with the arthrocentesis and placebo groups, there were significant differences in favour of these HA groups for all the parameters.

TABLE 7
Group Comparison at Day 60

Parameter	**HA-5 vs HA-3**	**HA-5 vs HA-1**	**HA-5 vs AR**	**HA-5 vs PL**	**HA-3 vs HA-1**	**HA-3 vs AR**	**HA-3 vs PL**	**HA-1 vs AR**	**HA-1 vs PL**	**AR vs PL**
Pain on movement	NS	*	*	*	*	*	*	NS	NS	NS
Pain at rest	NS	*	*	*	NS	*	NS	*	NS	NS
ISOAK Score	NS	*	*	*	*	*	*	NS	NS	NS
Knee flexion	NS	*	*	*	NS	*	*	NS	NS	NS
Joint effusion	NS	*	*	*	*	*	*	NS	NS	NS
Investigator judgement	NS	*	*	*	NS	*	*	NS	NS	NS
Patient judgement	NS	0.008	*	*	NS	*	*	*	NS	NS

Comparison of means two by two (* < 0.0051; NS > 0.0051)

FIGURE 1

Duration of treatment effect evaluated on the basis of the positive efficacy judgement expressed at each control visit by the investigator. The values in brackets indicate the cumulative number of drop-outs at each control visit

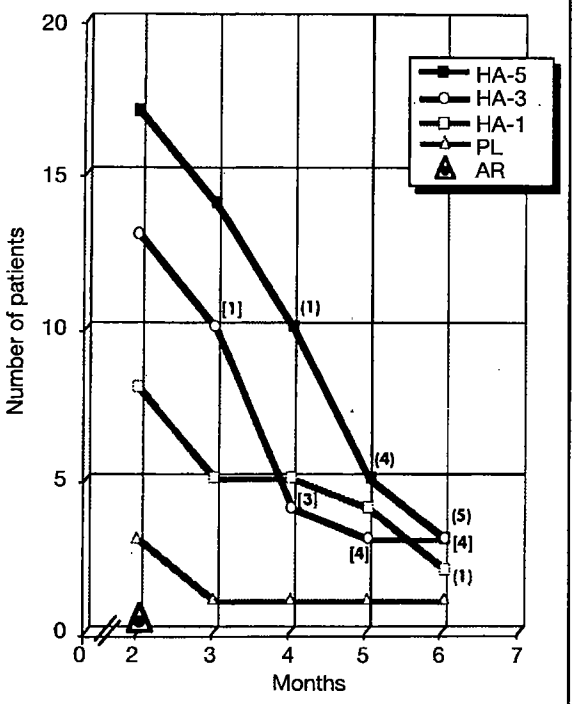

Figure 1 shows the number of patients for whom a "positive" efficacy judgement was expressed by the investigator at each follow up visit from the 2nd to the 6th month. This parameter was used for the duration of the evaluation for therapeutic effect.

It can be seen that 4 months after the beginning of treatment the efficacy judgement was still positive in 10 (50%) of the patients in the HA-5 group. At this time, 4 patients in the HA-3 group, 5 patients in the HA-1 group, and 1 patient in the placebo group, were still in the study. None of the patients in the arthrocentesis group entered the long term phase. The sudden decrease in the number of patients with "positive" efficacy judgement in the HA-5 group and in the HA-3 group after the 4th month, is heavily influenced by the high number of patients lost to follow up. The results at 5 and 6 months are therefore less reliable.

No severe adverse experiences were reported during the study. Only 4 patients complained of minor local adverse events; 1 patient from the arthrocentesis group reported a mild transient increase of pain after each puncture; 1 patient from the HA-1 group reported mild transient local pain after the first injection; 1 patient each from the HA-3 and HA-5 groups reported a moderate increase of pain and local swelling after the first injection. There were no relevant changes in any of the laboratory parameters at the end of the treatment period.

Discussion

A number of studies have demonstrated mid to long term symptomatic efficacy of Hyalgan® in the treatment of knee osteoarthritis. The aim of this study was to evaluate the safety and efficacy of 3 different dose regimen of Hyalgan® (1, 3 and 5 injections) in comparison with arthrocentesis and placebo in the treatment of knee osteoarthritis.

Primary endpoints for the first phase of the study were pain symptoms and the interference of the disease with activities of daily living (ISOAK scale) at 2 months after the beginning of treatment. Analysis of efficacy at two months, mainly on the basis of decrease in pain at rest and on movement, and of the Lequesne index of severity for osteoarthritis of the knee, showed a significant improvement of patients receiving 3 or 5 injections of Hyalgan® in comparison with patients in the other groups. Similar results were obtained for the other criteria such as, range of flexion, joint effusion, and global assessment by the patients and the blind observer.

There were no statistically significant differences in the behaviour of the HA-3 and HA-5 groups. However, there was a global trend in favour of the 5 injection group, and the improvements seemed to be longer lasting with this dose regimen. This was confirmed with the ISOAK scale which evaluates both pain and activities of daily living.

As far as the second phase of the study, the long term follow up period, is concerned the main evaluation criterion was the investigator's overall assessment of the therapeutic effect. The results of this phase confirmed that the effects of the arthrocentesis and the placebo are short lived. In fact, most of the patients in these groups did not even enter the long term phase and the remaining were soon withdrawn because of a "negative" efficacy judgement. In the HA-treated groups the duration of the therapeutic effect in the first four months seemed to be dose-dependent, the longest lasting effects being found in the HA-5 group. Unfortunately, the high drop out rate in the last two months of the study did not allow any definite conclusion for this period.

No severe adverse events were reported during the study, confirming the safety of intra-articular HA injection. The results of this trial confirm that a dose regimen of 3-5 intra-articular injections of Hyalgan® at a rate of 1 injection per week is effective and well tolerated in the treatment of osteoarthritis of the knee. The maximal therapeutic response was found after the third injection. This persisted throughout the second month and relapsed only after the third to fourth month of follow up.

Acknowledgement

We are indebted to Dr GB Guillou and Dr E Maheu for their helpful assistance in preparing this paper, and to JM Grouin for the statistical analysis.

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