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Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study

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Abstract

Objective. To compare the efficacy and safety of intra-articular injections of two different hyaluronan preparations and placebo in patients with knee osteoarthritis.

Methods. In a randomized, patient- and observer-blind, placebo-controlled and multicentre trial with parallel groups, 210 patients, aged 60 yr or above, with knee osteoarthritis were included in a per protocol analysis. The patients were treated with three injections, once weekly, of either native high-molecular-weight hyaluronan (Artzal®) or cross-linked hyaluronan (Synvisc®) or with placebo and were followed for 52 weeks. The primary efficacy measures were weight-bearing pain during study weeks 0–26 and the duration of clinical benefit measured with Kaplan–Meier survival analysis for weeks 0–52. The secondary outcome measures were resting and maximum pain, Lequesne index, WOMAC (Western Ontario and McMaster University Osteoarthritis Index) and SF-36 (Medical Outcomes Study Short Form Health Survey) scores.

Results. The intra-articular injections produced a significant reduction in weight-bearing pain, resting pain, maximum pain and Lequesne and WOMAC scores after 26 weeks. There were no significant differences in outcome between any of the three study groups during the first 26 weeks. In direct comparison against placebo for weeks 0–52, neither hyaluronan treatment (Artzal or Synvisc) showed a significantly longer duration of clinical benefit than placebo. However, when data for the two hyaluronan-treated groups were pooled, treatment with hyaluronan had a significantly longer duration of benefit compared with placebo ($P = 0.047$).

Conclusion. Patients with knee osteoarthritis who were treated by injection into the knee of either of two hyaluronan preparations or placebo showed clinical improvement during the first 26 weeks of treatment, though neither hyaluronan preparation gave a longer duration of clinical benefit than placebo. However, when data for the two hyaluronan treatments were pooled, there was a significantly longer duration of clinical benefit for hyaluronan treatment than for placebo.

KEY WORDS: Knee osteoarthritis, Intra-articular injections, Hyaluronan, Lequesne algofunctional index, WOMAC index, VAS measurements.

Osteoarthritis (OA) is the single most important cause of locomotor disability and is a major burden to the health-care system. The symptomatic treatment of OA focuses mainly on physical therapy, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of corticosteroids. However, the side-effects of NSAIDs [1] and intra-articular steroid injections have increased interest in alternative forms of treatment, such as hyaluronan [2, 3].

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Hyaluronan has been used as a pain reliever for patients with OA, particularly in the knee joint [4–16]. However, the efficacy of the treatment remains the subject of debate [17, 18]. Both native and cross-linked hyaluronans are being used for the treatment of human OA. Lower molecular weight preparations (e.g. Artzal®) generally range in molecular weight from 0.5 to 1 million, while the molecular weight of cross-linked preparations (e.g. Synvisc®), although difficult to estimate, is considerably higher. There is a lack of data and consensus on the relative importances of molecular weight and the concentration of hyaluronan for efficacy [19–22]. In general, previous trials have reported that

intra-articular hyaluronan is a safe and well-tolerated treatment. However, a recent report suggested that intra-articular treatment with cross-linked hyaluronan preparations was associated with a high rate of local reactions [23].

This is the first randomized, double-blind trial to compare the efficacy and safety of intra-articular injections of two different hyaluronan preparations and placebo injections in patients with knee OA.

Patients and methods

The inclusion criteria were: age at least 60 yr; Lequesne algofunctional [24] index of at least 10 points; weight-bearing pain of at least 40 mm on a 100-mm visual analogue scale at the time of inclusion; and a normal general physical examination. Further inclusion criteria were: dominant pain in one knee due to OA; and radiologically verified OA of grade I or II according to Ahlbäck [25] (grade I = loss of more than 50% of joint space, but less than 100%; grade II = complete loss of joint space; grade III = additional loss of bone substance; grade IV = major loss of bone substance and translation) estimated on the basis of an anteroposterior weight-bearing radiograph with a knee flexion angle of 10–15°. This corresponds to 50–100% obliteration of the joint space but no bone erosion. This radiographic examination was performed no more than 6 months prior to inclusion.

The exclusion criteria were: bone attrition in either knee (Ahlbäck grade III–V); previous intra-articular fracture of the knee; rheumatoid arthritis or other inflammatory joint disease as defined by ACR criteria; intra-articular injections of steroids or hyaluronan or other invasive procedure (e.g. arthroscopy, arthrography, surgery) in the knee less than 6 months prior to inclusion; and known alcohol or drug abuse. Furthermore, patients were not included if they had a known allergy to any substance related to the study, including disinfectants and adhesives, clinically relevant haematological or known clinical chemistry values outside the reference values at the time of inclusion, or any disabling problem of the musculoskeletal system or other organ system which could interfere with the assessment of efficacy.

Study design

The study was a randomized, patient- and observer-blind, placebo-controlled, multicentre trial with parallel groups. The patients were given three intra-articular injections once a week (7 days apart) of Artzal 2.5 ml [1% hyaluronan (molecular weight $\sim 10^6$ Da); Astra Läkemedel, Södertälje, Sweden], Synvisc 2.0 ml [0.8% hyaluronan (molecular weight $\sim 7 \times 10^6$ Da); Roche, Stockholm, Sweden] or placebo [(phosphate-buffered saline solution), 3 ml solution in 5 ml ampoules; Astra Läkemedel]. Patients were randomized to the treatments and were given a patient number at study inclusion. The computer-generated randomization was balanced so that the treatment sequences occurred an equal number of times in each block.

The screening visit took place within 8 weeks prior to inclusion in the study. The first study period included follow-up examinations 1, 2, 3, 12, 20 and 26 weeks after the first injection. The second part of the study included follow-up examinations at weeks 39 and 52. The patients who required additional therapy due to symptoms of OA in the study knee during the course of the trial, and were therefore regarded as clinical failures, were also recalled at week 52 for a follow-up visit.

The preparations could be identified during handling because of their differing viscosity. The blind-observer technique was therefore used in order to maintain double-blind conditions. The investigator administered the injections and an independent examiner (not involved in the therapy) assessed the efficacy and safety for the same patient. In this way, neither the patient nor the examiner was aware of the nature of the treatment. The patient and physician (or nurse) who was responsible for the evaluation of the patient remained blinded throughout the entire study.

Washout and escape medication

To evaluate pain severity, analgesic and anti-inflammatory medications were discontinued prior to the start of treatment with the test drug. The washout period was 2 weeks for medications with a prolonged half-life or at least five times the half-life of the drug. During the washout period, the patients were allowed to use paracetamol (acetaminophen) if necessary (up to 4 g/day). Paracetamol (Alvedon®; Astra Läkemedal, Södertälje, Sweden), up to 8 × 500 mg = 4 g/day was allowed as rescue medication during the trial and could be used for pain anywhere. Additional analgesics that were considered necessary for the patient's well-being were allowed to be given at the discretion of the investigator. If the treatment dose was above the stipulated limit (4 g paracetamol/day) and if it was used for pain relief in the study knee, the patient was regarded as a clinical failure. Patients using concomitant analgesic treatment for other reasons were regarded as withdrawals. Recommendations for dose levels were made according to published guidelines [26]. The intake of analgesics was discontinued at least 12 h prior to the time of clinical assessment. The administration of all analgesic medication during weeks 0–26 was recorded on a diary card by the patient. The patient's change in the use of analgesics during the first 26 weeks of the study was evaluated by a blinded observer and classified on a scale with five levels: much more, more, unchanged, less, and much less.

Assessments

Baseline characteristics (weight, height, age, sex, study knee and Ahlbäck radiological grade) were recorded before the first injection. The patient rated the subjective status with regard to weight-bearing pain, resting pain and maximum pain of the knee using a 100-mm visual analogue scale (VAS). The examiner rated the index of severity of knee disease using the standardized Lequesne algofunctional index [24]. These parameters were recorded initially and at weeks 1, 2, 3, 12, 20, 26, 39

and 52. The WOMAC (Western Ontario and McMaster University Osteoarthritis Index) score [27, 28] was patient-administered and used initially and at weeks 12 and 26. Health-related quality of life was measured at baseline and week 26 using the SF-36 (Medical Outcomes Study Short Form Health Survey) score [29–31]. The blinded examiner recorded subjective and objective signs of inflammatory joint reactions according to a checklist. The patient made a global evaluation of the treatment at week 26 and any change in the intake of concurrent analgesic medication was evaluated by a blinded observer at the end of the study.

The primary efficacy parameters were weight-bearing pain during the first part of the study (weeks 0–26) and duration of clinical benefit measured using survival analysis during weeks 0–52.

The primary efficacy parameter for the duration and clinical benefit of the treatment during a period of 1 yr was time to clinical failure. Whenever the patient required additional treatment during the study, this was noted on the study report form and the patient was regarded as a clinical failure or withdrawal. Clinical failure was defined as the use of concurrent treatment for the study knee, i.e. analgesics (more than 4 g paracetamol/day), surgery or new injections. If the patient required more than the permitted treatment during the study for reasons unrelated to the study knee, he or she was withdrawn from the efficacy analysis from that date but was not regarded as a clinical failure.

Statistical methods

Fifty patients who could be evaluated were needed in the placebo group and 75 patients in each of the two active groups, to enable us to detect a difference of 15 mm in the decrease in weight-bearing pain from baseline between the placebo group and the two active treatment groups. This was based on a *t*-test with a probability level of 5%, assuming a standard deviation of 30 mm [16] in this particular subgroup of patients and a power of 80% to detect the 15 mm difference in VAS decrease. In addition, 75 patients who could be evaluated in each active group would yield a confidence interval of 10 mm if the standard deviation was 30 mm and there was no difference between the two active treatments.

A 'per protocol' (PP) analysis was performed for the outcome of primary and secondary variables. Patients were included in the analysis if they had received three injections, rated weight-bearing pain according to the VAS of 40 mm or above, and had a Lequesne algofunctional index of 10 points or above at baseline, without any major protocol violation. In addition, an intention-to-treat (ITT) analysis was performed to evaluate adverse events in patients who had received at least one injection and had adverse event data. Patients were excluded from all evaluations if no drug was used or if follow-up data were missing.

The PP analysis was used as the main analysis because a high drop-out rate at the end of the study was expected. This decision was taken before the study code had been broken.

No adjustments for multiple comparisons were made. In general, Wilcoxon's two-sample test was used for all continuous or ordinal data. In order to adjust for possible differences (regardless of whether they were significant), the changes from baseline values were used for the Lequesne index and VAS data. The χ^2 test (or Fisher's exact test when appropriate) was used for dichotomous data. The method of carrying the last value forward for each variable was used to prevent missing values at different time points. All the tests were two-sided and P values of less than 0.05 were regarded as significant. For spontaneously reported adverse symptoms (according to the WHO classification), the worst reported severity for each symptom was used and, if no severity was given, it was assumed to be mild. Wilcoxon's two-sample test was used for the severity (none, mild, moderate, severe) of each separate symptom in order to compare the treatment groups. The χ^2 test was used to compare the treatment groups both within system–organ classes (according to the WHO classification) and overall. For checklist adverse symptoms, i.e. pain, redness and swelling at the injection site, Wilcoxon's two-sample test was used.

To compare the time to clinical failure requiring renewed treatment from the start of the study until week 52, standard life methods, i.e. Kaplan–Meier survival function estimates, were used. Tests of equality over strata were performed with Wilcoxon's test.

Legal provisions

The study was conducted in accordance with the principles of good clinical practice and in accordance with the Declaration of Helsinki, and was approved by all the regional ethics committees for the participating centres and the Swedish regulatory authorities. The investigators obtained signed informed consent from all patients before enrolment.

Results

Patient characteristics

Of the 246 patients enrolled from the 19 centres, 242 were treated with the study drug (Table 1). One of the

Table 1. Numbers of patients participating in the analyses

	Artzal	Synvisc	Placebo
Randomized patients	92	88	66
Reason for exclusion from safety analysis			
Erroneously randomized; no data available	1	1	
No injections given		1	
No follow-up data	1		
Patients included in ITT analysis	90	86	66
Reason for exclusion from PP analysis			
Age <60 yr		1	
Rheumatoid arthritis		1	
VAS <40	10	5	3
Lequesne score <10	3	1	5
Lequesne score <10 and VAS <40 mm	1	1	1
Patients included in PP analysis	76	77	57

TABLE 2. Comparison of patient characteristics at baseline for treatment and placebo groups [mean (S.D.)]

	ITT analysis			PP analysis		
	Artzal	Synvisc	Placebo	Artzal	Synvisc	Placebo
Age (yr)	72 (7)	70 (7)	71 (6)	72 (7)	71 (7)	71 (6)
Sex (% female)	67	65	61	71	68	65
Weight (kg)	81 (13)	79 (13)	81 (16)	81 (13)	78 (13)	81 (16)
Height (cm)	169 (8)	169 (9)	170 (9)	168 (8)	169 (8)	170 (8)
Study knee (right %)	63	53	55	66	52	53
Ahlbäck grade I (%)	60	61	58	58	61	60
Ahlbäck grade II (%)	40	39	42	42	39	40

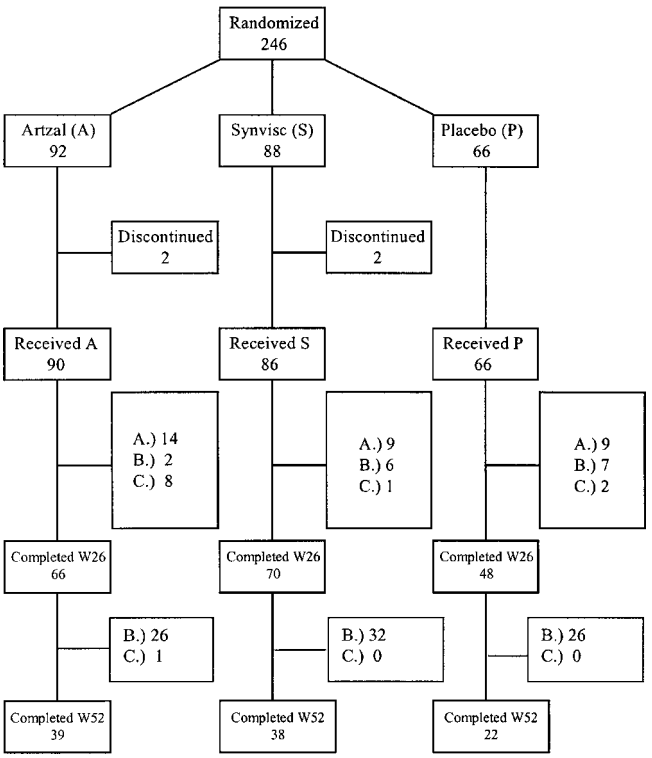

FIG. 1. Scheme showing participation of the patients in the study. (A) Deleted from PP analysis because of failure to comply with inclusion criteria. (B) Patient regarded as a clinical failure. (C) Patient regarded as a withdrawal. See text for definitions of clinical failure and withdrawal.

patients received one injection but was withdrawn from the study because he/she did not fulfil the inclusion criteria. This patient had no follow-up data and could consequently not be included in the ITT analysis. A total of 210 patients were included in the PP analysis; those who were excluded did not fulfil the inclusion criteria (Fig. 1). The patient's age, sex, weight and height and the classification of the radiologically verified OA [25] are shown in Table 2. All the patients included in the study were Caucasians. The majority of the patients were women (65% of ITT patients and 68% of PP patients) and most of them had Ahlbäck grade I OA (60% of ITT and PP patients). There were no significant differences between the treatment groups with respect to demographic and clinical characteristics at study entry.

TABLE 3. Comparisons at baseline between treatment and placebo groups of weight-bearing pain (VAS), resting pain (VAS), maximum pain (VAS), WOMAC score and Lequesne index score [PP analysis; mean (S.D.)]

Outcome measure	Artzal (n = 76)	Synvisc (n =77)	Placebo (n = 57)
VAS (mm)[a]			
Weight-bearing pain	64 (15)	63 (15)	65 (15)
Resting pain	33 (24)	33 (20)	33 (20)
Maximum pain	78 (12)	76 (15)	78 (15)
WOMAC[a]			
Total score	48.7 (13.3)	48.7 (11.4)	48.9 (12.9)
Pain	10.0 (3.0)	9.9 (2.6)	9.9 (2.4)
Physical function	34.5 (10.5)	34.4 (8.7)	34.8 (10.3)
Stiffness	4.1 (1.6)	4.3 (1.5)	4.3 (1.4)
Lequesne algofunctional index[a]			
Total score	13.9 (2.7)	13.4 (2.3)	13.6 (2.4)
ADL[b]	4.9 (1.0)	4.7 (0.9)	4.9 (0.9)
Maximum walking distance	3.1 (1.7)	2.8 (1.6)	2.8 (1.6)
Pain	5.9 (1.2)	5.9 (1.1)	6.0 (1.2)

Maximal scores were 24 for the Lequesne index and 68 for the WOMAC score.
[a]Higher scores represent worse pain, function and quality of life.
[b]Activities of daily living.

The mean value for weight-bearing pain was high for the patient population included in this study, as were the mean values for resting pain and maximum pain (Table 3). The high WOMAC and Lequesne scores confirmed that these were patients with significant knee pain and impairment. The treatment groups were comparable with respect to all these variables at study entry.

Efficacy measures

All data presented below are PP data. An additional ITT analysis was done; there were no significant differences from the results presented in the PP analysis.

During the first 26 weeks, weight-bearing pain (VAS) was defined as the primary efficacy measure and resting pain (VAS), maximum pain (VAS) in the knee, Lequesne index and WOMAC were defined as the secondary efficacy measures. During the second part of the study (weeks 27–52), time to clinical failure was the main criterion. In addition, VAS data for pain and Lequesne index data were collected at weeks 39 and 52.

TABLE 4. Change from baseline in weight-bearing pain in the knee (rated on a 100-mm VAS scale) at 26 weeks in PP patients [mean (S.D.); last valid value was carried forward]

Week	Artzal	Synvisc	Placebo
1	−5 (16)	−7 (17)	−7 (22)
2	−12 (21)	−16 (21)	−11 (25)
3	−20 (23)	−18 (24)	−21 (28)
12	−22 (26)	−22 (29)	−19 (32)
20	−21 (26)	−27 (29)	−19 (29)
26	−16 (31)	−20 (31)	−21 (31)

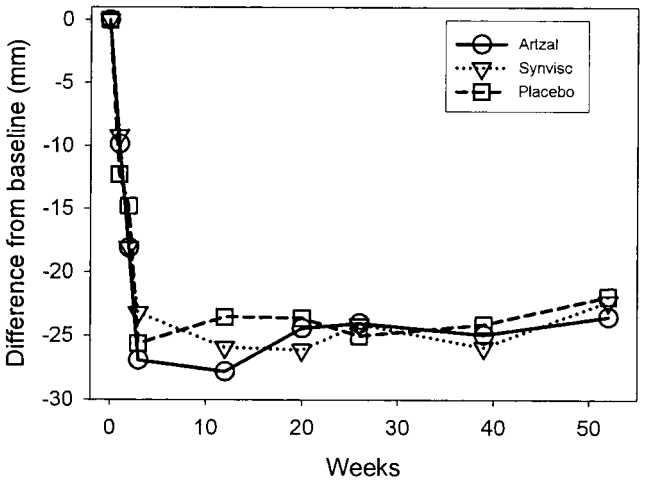

FIG. 2. Maximum pain for the three study groups shown as difference from baseline value.

Weight-bearing pain was reduced in all the study groups at 3 weeks compared with baseline (Table 4). The mean reduction of approximately 20 mm was consistent for all groups throughout the first 26 weeks ($P < 0.001$). There were no statistical differences (pairwise comparisons between treatments and times of evaluation) between the three groups during this period. A similar pattern was observed for resting pain (data not shown) and maximum pain (Fig. 2). The mean reduction after 3 weeks was approximately 14 mm for resting pain ($P < 0.001$) and 25 mm ($P < 0.001$) for maximum pain and was consistent during the first 26 weeks.

After 20 and 26 weeks, all three groups had an improved Lequesne algofunctional index compared with baseline, with a considerable reduction of approximately 4.5 points ($P < 0.001$) (Table 5); there were no statistical differences between the active treatment and placebo groups during the first 26 weeks. Treatment with intra-articular injections also improved knee pain and function as assessed by the WOMAC instrument in all three groups, again with no significant differences between the active treatments and placebo (Table 6). All the treatment groups were similar to one another at baseline and improved between weeks 0 and 26, as monitored by the SF-36 dimensions Physical Functioning, Role Physical, Bodily Pain, General Health and Vitality. For the dimensions of Social Functioning, Role Emotional and of Mental Health, the Synvisc and the placebo groups improved whereas the Artzal group deteriorated during the same period.

TABLE 5. Change from baseline in Lequesne index during 26 weeks in PP patients [mean (S.D.); last valid value was carried forward]

Week	Artzal	Synvisc	Placebo
20	−4.2 (3.7)	−4.9 (3.6)	−5.1 (4.4)
26	−3.9 (4.6)	−4.4 (4.1)	−4.7 (4.4)

The differences between treatment groups are not statistically significant.

TABLE 6. Mean change in WOMAC score from baseline and the factors of pain, physical function and stiffness at 12 and 26 weeks for PP patients (last valid value was carried forward)

	Artzal	Synvisc	Placebo
WOMAC score			
12 weeks	−14.0	−17.0	−18.2
26 weeks	−11.3	−16.8	−16.8
Pain			
12 weeks	−3.5	−4.0	−3.9
26 weeks	−3.1	−3.6	−3.8
Physical function			
12 weeks	−9.3	−11.4	−12.6
26 weeks	−7.3	−11.7	−11.1
Stiffness			
12 weeks	−1.2	−1.6	−1.4
26 weeks	−0.9	−1.4	−1.6

The differences between treatment groups are not statistically significant.

The patient's global assessment of the overall response to treatment was evaluated at week 26 and assessed with an eight-point ordinal scale. No difference was found between the treatment and placebo groups. Of the PP patients treated with either Artzal or Synvisc, 64% reported that they were much improved, improved or somewhat improved during the first 26 weeks. The corresponding value for those treated with placebo was 62%. The patient's change in the use of analgesics during the first 26 weeks was classified on five levels (Table 7). The demand for analgesics was generally low and there were no major changes or significant differences between the groups at 26 weeks. Of the active treatment and placebo groups, 16 and 21% respectively were classified as using less or much less analgesics. On the other hand, 3% of the patients who were receiving active treatment used much less analgesics, but none of the placebo-treated patients recorded a consumption level that was much less. More or much more analgesics were used by 12% of the patients in all the groups during the 26-week period.

Kaplan–Meier failure–time curves were used to show the cumulative probability of patients not requiring additional treatment for their study knee during the 52 weeks (Fig. 3). Because the first part of the study (weeks 0–26) gave no indication of any significant differences between the two active hyaluronan treatment drugs (Artzal and Synvisc, hereafter referred to collectively

TABLE 7. Patients' use of paracetamol and supplementary analgesia during the study

	No. patients using paracetamol/ total no. of patients (%)	No. of patients using supplementary analgesia in addition to paracetamol	Change in use of analgesics in first 26 weeks (% of patients in PP analysis; $n = 210$)				
			Much more	More	Unchanged	Less	Much less
Artzal	42/90 (47%)	8	1	11	71	13	4
Synvisc	41/86 (48%)	5	1	10	71	16	1
Placebo	38/56 (58%)	6	2	10	67	21	0

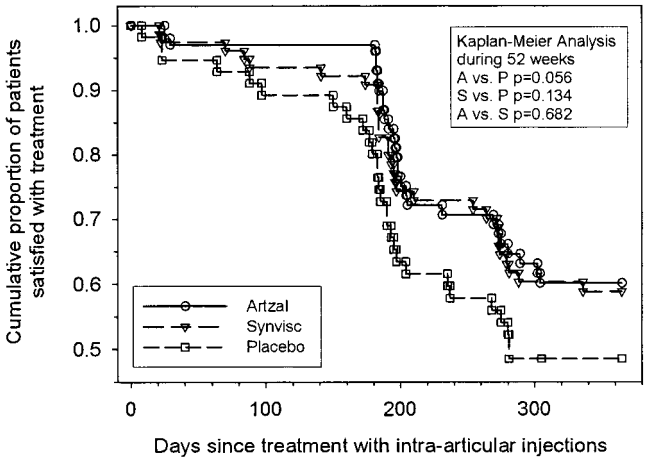

FIG. 3. Kaplan–Meier curves showing cumulative probability failure–time curves of the patients' need for additional treatment (other than maximum 4 g paracetamol/day) according to number of days since treatment with intra-articular injections and treatment group (A, Artzal; S, Synvisc; P, placebo). The percentage of patients who required additional treatment is shown on the *y*-axis. At the end of the study (after 52 weeks), 39 patients receiving Artzal, 38 receiving Synvisc and 22 receiving placebo were classified as survivors, i.e. they did not require any treatment that was not allowed in the protocol.

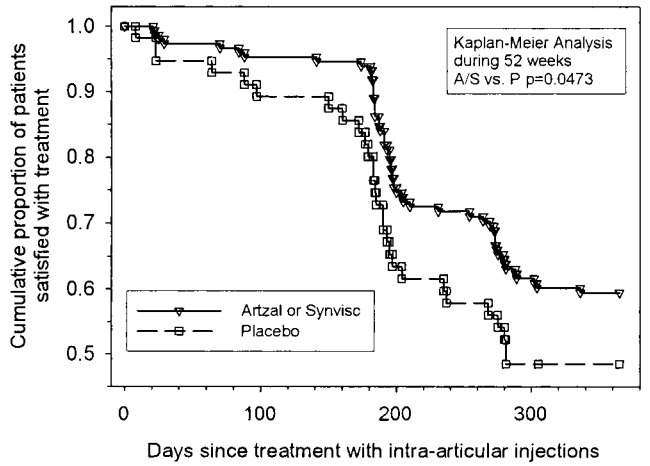

FIG. 4. Kaplan–Meier curves showing cumulative probability failure–time curves of patients' need for additional treatment (other than maximum 4 g paracetamol/day) according to number of days since treatment with intra-articular injections and treatment groups (HA, placebo). The percentage of patients who required additional treatment is shown on the *y*-axis.

as HA treatment), patients treated with either of these drugs were regarded as one group and were tested against the placebo group by Kaplan–Meier analysis (Fig. 4). The cumulative percentage of patients still satisfied with the initial treatment after 1 yr, estimated from Kaplan–Meier curves, was 60% in the Artzal group, 59% in the Synvisc group—or 60% in the group receiving active treatment—compared with 49% in the placebo group. In direct comparison against placebo, neither HA treatment (Artzal or Synvisc) showed a significantly longer duration of clinical benefit than placebo. However, when data for the two HA groups were pooled, treatment with hyaluronan had a significantly longer duration of benefit compared with placebo ($P = 0.047$).

VAS pain and Lequesne index were measured after 39 and 52 weeks. There were no significant differences between the treatment groups in any of the parameters at any of these times (Fig. 2). Because about 45% of the patients were withdrawn from the second part of the study, these data are not conclusive and have not been analysed further.

Adverse events and concomitant medication

A total of 314 adverse events were reported in 132 patients. Because the study population was elderly, many concomitant diseases occurred during the course of the study and were registered as adverse events without any causal relationship with the treatment given (Table 8). A total of 55% of the patients reported at least one adverse event. No differences were found between treatment groups. In the primary adverse event report made by the investigators, all adverse events but five were judged to be unrelated to study treatment. After further investigations and an evaluation by the independent safety committee (appointed before the start of this study) of these five adverse event reports, the events were all judged to be causally related to the underlying disease and not to the study drug. Thirty serious adverse advents were reported. We cannot tell from our data if any of these serious adverse events resulted from the use of concomitant analgesics. Nineteen patients (eight receiving Artzal, five receiving Synvisc, six receiving placebo) received concomitant analgesic medication not allowed in the protocol. However, the last date for efficacy analysis was adjusted to the first day of additional treatment, and these patients were considered as clinical failures if the

TABLE 8. Overview of adverse events reported in the study for patients included in the ITT safety analysis

	Artzal	Synvisc	Placebo
No. of patients included in the safety analysis	90	86	66
No. of serious adverse events	12	8	11
No. of adverse events	146	90	78
Treatment discontinued due to adverse events	2	1	2
Total number of adverse events reported primarily as probably or possibly related to the product	2[a]	1[a]	2[a]
Patients reporting adverse events (%)	61	51	50

[a]In the primary adverse event report made by the investigators, all adverse events but five were judged as unrelated to study treatment. After further investigations and an evaluation by the Safety Committee of these five adverse event reports, all events were judged to be causally related to the underlying disease and not to the study drug.

treatment was given for the study knee; otherwise they were classed as withdrawals.

Discussion

A principal finding in this prospective, randomized, blind and placebo-controlled study was the lack of a significant difference in clinical efficacy between the two hyaluronan preparations evaluated, Artzal and Synvisc. Furthermore, these preparations did not differ from placebo injections, as assessed by patient-administered outcome instruments. However, treatment with hyaluronan had a significantly longer duration of clinical efficacy compared with placebo in the analysis performed at 52 weeks.

The pain-relieving mechanism of intra-articular injections of hyaluronan is unknown. It has been suggested that the injections may stimulate the synthesis of endogenous hyaluronan [19, 20] or act as a scavenger, reducing the amount of inflammatory degradation products in the joint [32, 33]. Furthermore, the viscoelastic and anti-inflammatory functions of the synovial fluid may be improved by the treatment [32, 33]. Several different hyaluronan preparations are currently being used for intra-articular injections, but our understanding of the role of either molecular size or concentration for the efficacy of the treatment is incomplete [19–21]. The present investigation is the first double-blind, placebo-controlled study which compares the efficacy and safety of high-molecular-weight and cross-linked hyaluronan preparations.

In a previous study by Lohmander *et al.* [16], a subgroup analysis suggested that patients aged 60 yr or above with a baseline Lequesne index above 10 and radiographically verified OA of the knee (Ahlbäck grade I–II) showed significant benefit from intra-articular treatment with Artzal. Patients with these characteristics were therefore investigated further in the present study. In comparison with previous studies [10, 11, 13, 16], it appears that the patients treated with hyaluronan in the present study obtained approximately the same pain relief as those in the previous studies. However, the placebo group in the present study showed a more long-term beneficial response than expected from the results of previous studies with a similar design [10, 11, 13, 16]. The placebo response curve in this study followed the response curves for the active substances throughout the follow-up period. This indicates that these patients, who were well matched at baseline with the patients in the active groups, experienced a marked long-term beneficial effect from the intra-articular placebo injections. There is a possibility that the relatively high amount of paracetamol allowed (4 g/day) gave the placebo patients significant pain relief. However, our data do not support this as the intake of analgesic during the first 26 weeks of the study was evaluated by a blinded observer and classified on five levels (much more, more, unchanged, less, much less) and it was not possible to detect any changes above the stipulated limit in the placebo group. Hence, one limitation of the study is the lack of information with respect to actual paracetamol use. Our observation is in line with the well-recognized significant placebo response in patients with OA after either aspiration of the knee or injection with non-active drug [9–17, 21, 22, 34, 35].

One possible reason for the different placebo response in the present study compared with our previous studies with a similar controlled, double-blind design [13, 16] is a difference in the patient population studied. In the present study, we recruited a community-based out-patient population cared for by family doctors, general practitioners and orthopaedic surgeons mainly in private practice. In contrast, our previous studies focused on hospital-based out-patient care and recruitment. Another possible reason is the statistical method chosen for analysis of the outcome of this study. Results were analysed by the PP method using the last valid value carried forward, and there was a high dropout rate during the second half of this 1-yr study. Consequently, it was difficult to detect differences during the second part of the study as many of the values originated from patients who dropped out, thereby reducing the sensitivity of changes as only the centremost of the values are real. Finally, it is of note that several studies have failed to show a significant benefit from hyaluronan treatment in patients with OA of the knee, compared with placebo injections [13, 36]. A further study failed to show benefit of hyaluronan over placebo injection in an ITT analysis [35].

After we had completed the present study, results of a comparison between two different preparations of hyaluronan were published, suggesting a greater pain-relieving effect of a higher-molecular-weight hyaluronan than that of a lower-molecular-weight hyaluronan [37]. However, this study lacked a saline injection control group. Further analysis of the complete data set of this trial failed to show benefit of the higher-molecular-weight preparation over any of the other two comparator hyaluronan preparations or a denatured hyaluronan preparation [38].

During weeks 26–52, significantly more patients in the placebo group, compared with the groups treated with hyaluronan, dropped out due to clinical failure, i.e. they required additional treatment for their knee OA. At 49 weeks after the last injection, 49% of the patients remained in the placebo group compared with 60% in the active groups ($P = 0.047$). Kaplan–Meier survival analysis was conducted at 52 weeks. In direct comparison against placebo, neither HA treatment (Artzal, Synvisc) showed a significantly longer duration of clinical benefit than placebo. However, when data for the two HA groups were pooled, treatment with hyaluronan had a significantly longer duration of benefit compared with placebo ($P = 0.047$).

Treatment with intra-articular hyaluronan injections, as performed in the present study, was shown to be a safe form of treatment. During the follow-up period of 52 weeks, no serious adverse reactions due to the treatment (either active or placebo) were registered. Thus, we could not verify the finding of Puttick *et al.* [23] that intra-articular injection of high-molecular-weight hyaluronan (Synvisc) was associated with frequent local inflammatory reactions. Treatment with hyaluronan appears to be well tolerated and no serious adverse events related to any of the treatments were registered.

On the basis of this prospective, randomized, double-blind and placebo-controlled study of patients with knee OA, we conclude that three intra-articular injections at intervals of 1 week produced a pronounced reduction in weight-bearing pain, resting pain, maximum pain, Lequesne index and WOMAC score during a period of 26 weeks. However, no differences were shown between hyaluronan treatment and placebo during the first 26 weeks of the study. Furthermore, no difference in pain relief was demonstrated between the two hyaluronan preparations studied here. However, in the study period between 27 and 52 weeks, significantly more patients in the placebo group than in the hyaluronan groups dropped out (requiring further treatment) because of knee pain.

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Appendix

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