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Efficacy and Safety of Intraarticular Hylan or Hyaluronic Acids for Osteoarthritis of the Knee

A Randomized Controlled Trial

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Objective. **To compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee.**

Methods. **This was a multicenter, patient-blind, randomized controlled trial in 660 patients with symptomatic knee OA. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight cross-linked hylan, a non–cross-linked medium molecular weight HA of avian origin, or a non–cross-linked low molecular weight HA of bacterial origin. The primary outcome measure was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 6 months. Secondary outcome measures included local adverse events (effusions or flares) in injected knees. During months 7–12, patients were offered a second cycle of viscosupplementation.**

Results. **Pain relief was similar in all 3 groups. The difference in changes between baseline and 6 months between hylan and the combined HAs was 0.1 on the WOMAC pain score (95% confidence interval [95% CI] −0.2, 0.3). No relevant differences were observed in any of the secondary efficacy outcomes, and stratified analyses provided no evidence for differences in effects across different patient groups. There was a trend toward more local adverse events in the hylan group than in the HA groups during the first cycle (difference 2.2% [95% CI −2.4, 6.7]), and this trend became more pronounced during the second cycle (difference 6.4% [95% CI 0.6, 12.2]).**

Conclusion. **We found no evidence for a difference in efficacy between hylan and HAs. In view of its higher costs and potential for more local adverse events, we see no rationale for the continued use of hylan in patients with knee OA.**

In patients with osteoarthritis (OA), synovial hyaluronic acid (HA) is depolymerized and cleared at higher rates than in normal individuals, resulting in a

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decrease of molecular weight and concentration (1). To improve biomechanical function, different HAs were developed for intraarticular injection (1). Injected HA is cleared from the joint in less than 1 day (2), but the benefits of a single treatment cycle are claimed to last for several months (3,4). To explain this prolonged action, different mechanisms have been discussed, including the stimulation of de novo synovial synthesis of HAs (5,6), suppression of cartilage matrix degradation (7), and suppression of inflammatory responses to interleukin-1 (8,9). To increase viscosity and decrease clearance from the joint, HAs were modified to form hylans, chemically cross-linked molecules with average molecular weights as high as 23×10^6 daltons and intraarticular half-lives of 1.5–9 days (2). This was suggested to increase both the benefits and the risks of viscosupplementation. Higher viscosity and longer intraarticular half-life of hylans may increase long-term efficacy in terms of duration and intensity of pain relief (10,11). Meta-analyses found more pronounced pain reduction in sham-controlled trials of hylans than in trials of HAs (12–14). Conversely, case reports suggested that injection of hylans may lead to flares, typically defined as hot, painful, swollen knees occurring within 48 hours of injection (15,16). A nonrandomized study by Brown et al (17) found hylans to be associated with a considerably higher rate of flares compared with conventional HAs.

Until recently, 3 viscosupplementation preparations were available in Switzerland, differing in terms of their origin, structure, molecular weight, and costs. These included a cross-linked high molecular weight hylan, a non–cross-linked medium molecular weight HA of avian origin, and a non–cross-linked low molecular weight HA of bacterial origin. To evaluate these preparations, a trial program on viscosupplementation was initiated by the Swiss government's Department of Home Affairs. The First Swiss Viscosupplementation Trial (SVISCOT-1) was a multicenter, patient-blind, randomized controlled trial designed to determine the comparative efficacy and safety of these preparations in patients with knee OA. Members of the SVISCOT-1 steering group and recruiting physicians are listed in Appendix A.

PATIENTS AND METHODS

Patients. Overall, 165 centers in Switzerland participated, including private practices, general hospitals, and tertiary care centers. Men and nonpregnant women with radiographically confirmed knee OA (Kellgren/Lawrence grade ≥ 2 [18]) who were symptomatic for at least 6 months and reported pain on most days for the previous 3 months were eligible. Patients had an American College of Rheumatology functional class rating of II to IV (19) and had not responded sufficiently to, or could not tolerate, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) taken regularly in adequate dosages. Patients were excluded if they had inflammatory joint disease, chondrocalcinosis (evidence from radiographs or synovial fluid analysis), infection in or around the study knee, relevant skin disease in the area of the injection site, a history of allergy or intolerance to experimental preparations, or previous replacement surgery in the study knee, or if they were currently receiving anticoagulant therapy or had received previous viscosupplementation treatment within 6 months.

The trial was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the relevant research ethics committees. Written informed consent was obtained from each patient.

Interventions. Patients were randomly allocated to receive 1 cycle of 3 intraarticular injections of 2 ml per treated knee of 1 of the following 3 preparations: 1) a high molecular weight cross-linked hylan derived from rooster combs (Synvisc; Genzyme, Cambridge, MA), 2) a non–cross-linked medium molecular weight HA derived from rooster combs (avian HA) (Orthovisc; Anika Therapeutics, Woburn, MA), or 3) a non–cross-linked low molecular weight HA obtained through bacterial fermentation (bacterial HA) (Ostenil; TRB Chemedica, Geneva, Switzerland). Injections were administered at weekly intervals. The decision about whether bilateral knee OA required injections in both knees and the designation of the study knee remained at the discretion of the treating physician. One cycle per knee was allowed during the first 6 months of the trial. Intraarticular corticosteroid injections concurrent with the injection of viscosupplementation preparations were not permitted. Injections were performed according to the guidelines of the Swiss Association of Rheumatologists (20).

Randomization. Computer-generated random numbers in blocks of 21 were used for the allocation sequence. Randomization was stratified by disease severity at baseline (standardized Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] [21] pain score [range 0–10] of <5 versus ≥ 5) and by unilateral versus bilateral knee disease. We used central randomization to conceal allocation: recruiting physicians sent details and written informed consent of included participants by mail to the central trial coordination office at the University of Berne (Berne, Switzerland). Study secretaries not involved with patient care checked completeness of information, entered the data into the trial database, and subsequently opened sealed, opaque, sequentially numbered envelopes containing the allocation information. Allocated preparations were sent by mail to treating physicians. For logistical reasons and pursuant to liability insurance law, different experimental preparations had different syringes and packs. Treating physicians were required not to inform patients about the allocated treatment. To determine their degree of blinding, patients were asked at 6 months to guess which intervention they had received.

Second cycle. It was originally planned to offer patients a maximum of 2 additional treatment cycles during months 7–18. Due to resource limitations, patients were offered only 1 additional treatment cycle of 3 injections per knee during

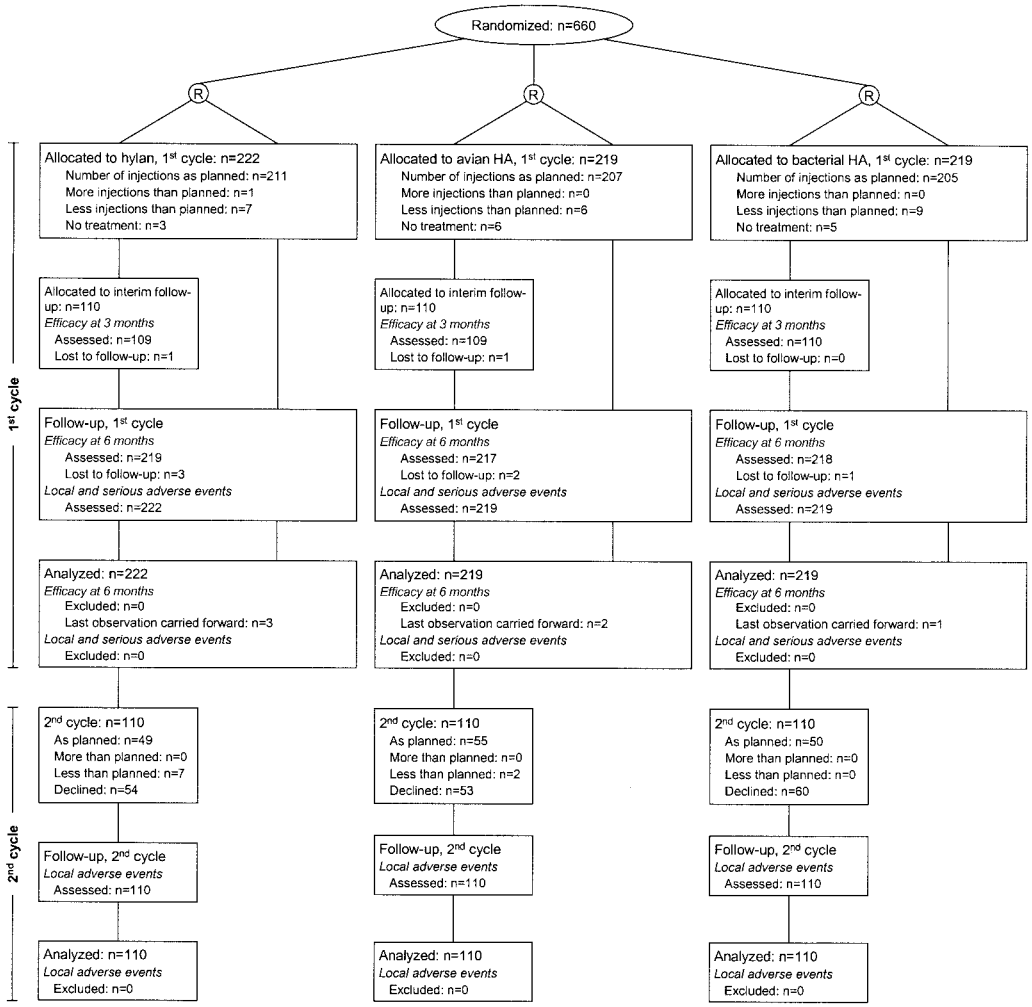

Figure 1. Flow of patients through the various stages of the trial. R = randomized; HA = hyaluronic acid.

months 7–12. Since we were unable to administer the expensive hylan and avian HA to all patients according to the original allocation, we a priori selected a 50% random sample of patients, who were administered the originally allocated preparations, using a concealed randomization schedule stratified by allocated preparation. The schedule was computer generated before the beginning of the trial and held centrally at the trial coordination office. The remaining participants were offered the less expensive bacterial HA regardless of the previous treatment and were excluded from the analysis of the second cycle.

Outcome measures. The primary outcome measure was the change in the pain score of the WOMAC, version 3.1, between baseline and 6 months (21), with individual items graded on a 5-point Likert scale from 0 to 4. Secondary outcome measures were the WOMAC global score and subscores on stiffness and disability (21); health-related quality of life based on the 5 dimensions and visual analog scale (VAS) of the European Quality of Life (EuroQol) questionnaire (22); self-reported health care utilization for knee disease (23); the frequency of local adverse events, defined as the occurrence of an effusion (evidence from clinical examination or arthrocentesis) or a flare (hot, painful, swollen knee occurring within 48 hours of injection of the study preparation); corticosteroid injections or treatment interruptions due to local adverse events; and the frequency of serious adverse events (adverse events leading to serious disability, hospital admission, or prolongation of hospitalization; life-threatening events; or death). Finally, we determined direct health care costs in each of the 3 groups.

All efficacy outcomes were assessed at 6 months using patient-administered mailed questionnaires and, if necessary, telephone calls by blinded interviewers. For exploratory purposes we performed an interim followup at 3 months, which was restricted to the prespecified 50% random sample described above. After completion of each treatment cycle, information on serious and local adverse events was actively gathered from patients and physicians using mailed question-

naires or telephone calls by blinded interviewers. All suspected events were adjudicated by 2 investigators (PJ and SR) who were blinded to the assigned treatment, based on medical records. Any disagreements were resolved by consensus. During the second cycle (months 7–12), only local adverse events were recorded, using the same procedures as described above.

Sample size. SVISCOT-1 was a superiority trial. The sample size was calculated to detect a difference between groups of 0.8 units in standardized WOMAC pain scores for the pairwise comparisons of the hylan with each of the 2 conventional HAs, using Bonferroni correction and assuming an SD of 2. The difference of 0.8 units in standardized WOMAC pain scores corresponds to a difference in effect sizes of ~0.4 SD units between hylan and HA that was expected from indirect comparisons derived from the meta-analysis by Lo et al (12). We calculated that a sample size of 200 patients per trial arm would provide >96% power to detect this difference with P set at 0.025.

Statistical analysis. Two primary treatment comparisons were performed: 1) the high molecular weight hylan versus the medium molecular weight avian HA and 2) the hylan versus the low molecular weight bacterial HA. The efficacy and safety of the 2 HAs were nearly identical, and no evidence of a difference in efficacy between the hylan and either of the 2 HAs was found in any of the prespecified primary and secondary analyses. Therefore, we report the comparison of the hylan with the 2 HAs combined. Finally, we stratified analyses of the primary outcome according to age, sex, body mass index, unilateral versus bilateral knee disease, and radiographic and clinical severity. These stratified analyses were not defined in the protocol but were specified before the data analysis. All WOMAC scores were standardized to range from a minimum of 0 to a maximum of 10. Higher values indicate more severe symptoms, and differences between groups were calculated so that negative values indicate a benefit of hylan compared with HAs. WOMAC scores were analyzed using analysis of covariance adjusted for baseline values (24). In sensitivity analyses, we also adjusted for the concomitant use of 3 types of cointervention (physiotherapy, chondroitin, and pain medications). For stratified analyses, we performed formal tests of interaction between allocated treatment and patient characteristics in multivariable least squares linear regression models (25).

The 5 dimensions of the EuroQol were mapped onto a single health state index based on the European value set and standardized to range from a minimum of 0 to a maximum of 10 (26). Higher values indicate better health-related quality of life; accordingly, positive differences indicate a benefit of the hylan. Using average estimates, direct health care costs were calculated for each treatment group. The following health care utilization measures and costs were recorded during the trial and used for calculations: viscosupplementation (hylan, Swiss francs [CHF] 224.45 per injection; avian HA, CHF 195.78 per injection; bacterial HA, CHF 122.45 per injection); number of inpatient days (CHF 500 per day); knee replacement (CHF 12,320 for 1 knee and CHF 18,419 for both knees); other knee operation (CHF 5,572); number of visits to general practitioner (CHF 67 per visit), rheumatologist (CHF 111 per visit), orthopedic surgeon (CHF 120 per visit), physiotherapist (CHF 51 per visit), occupational therapist (CHF 125 per visit), and ambulatory nurse (CHF 40 per visit); use of pain and other medication (paracetamol, CHF 116 for a treatment duration of 6 months; NSAIDs, CHF 361; opioids, CHF 257; food supplements, CHF 151); number of steroid injections (CHF 68.78 per injection); and knee puncture plus specimen examination (CHF 116.28 per procedure). In a sensitivity analysis, no difference in costs was assumed for viscosupplementation preparations (CHF 200 per injection).

Results of health care utilization and costs were analyzed using the Kruskal-Wallis test and analysis of variance for continuous outcomes and the chi-square test for binary outcomes. Success of blinding of patients was assessed using a modification of a blinding index originally described by James et al (27), which ranges from 0 to 1, where 0 denotes complete failure of blinding and 1 indicates complete success of blinding (28).

Analyses were conducted using an intent-to-treat (ITT) approach, whereby all randomized patients were included in the analysis in the group to which they were allocated regardless of the treatment received. Missing values were imputed for continuous outcomes by carrying forward the most recent nonmissing value. All P values are 2-sided. The data analyst (SW) was kept blinded to the allocated interventions for all analyses. Analyses were performed using Stata 9.2 software (StataCorp, College Station, TX).

RESULTS

Study flow and patient characteristics. Between June 2003 and April 2004, a total of 660 patients were included in the trial. Figure 1 presents the flow of participants through the trial. Two hundred twenty-two patients were allocated to receive hylan, 219 to receive avian HA, and 219 to receive bacterial HA. The groups had similar clinical characteristics at baseline (Table 1). Of the patients listed above, 211 in the hylan group (95%), 207 in the avian HA group (95%), and 205 in the bacterial HA group (94%) received all injections as planned (Figure 1). Less than 1% of patients were lost to followup at the 6-month assessment of the primary outcome, and a blinding index of 0.96 (95% confidence interval [95% CI] 0.95, 0.98) indicated that blinding of patients was successful.

WOMAC pain score. Figure 2 indicates that we were unable to detect a difference in the WOMAC pain score between the hylan group and the HA groups at 3 and 6 months. In unadjusted analyses, the difference between hylan and HAs was 0.1 at 3 months (95% CI −0.3, 0.5) and 0.1 at 6 months (95% CI −0.2, 0.3). Nearly identical results were seen in the analysis adjusted for concomitant treatments at 3 months (0.1 [95% CI −0.3, 0.4]) and 6 months (0.0 [95% CI −0.3, 0.2]). No differences were observed in the number of patients receiving intraarticular steroid injections in the 4 weeks before the 6-month assessment; 27

(12%) in the hylan group received steroids, 22 (10%) in the avian HA group, and 26 (12%) in the bacterial HA group ($P = 0.75$). Figure 3 presents the results of stratified analyses, again with no evidence of differential effects across various groups of patients.

Other WOMAC scores and quality of life. The difference in changes between baseline and 6 months between hylan and the HAs was 0.1 (95% CI −0.2, 0.4) for the WOMAC overall score, 0.1 (95% CI −0.3, 0.4) for the WOMAC stiffness score, and 0.1 (95% CI −0.2, 0.4) for the WOMAC disability score. There was little evidence for a difference between groups on the EuroQol VAS (0.1 [95% CI −0.2, 0.4]) and health state index (0.2 [95% CI −0.1, 0.4]).

Health care utilization. There was no statistical evidence for differences between groups in the use of pain medication or other disease-specific treatments, including surgical interventions (data not shown). Seventeen percent of all patients had undergone, or were on the waiting list for, knee replacement surgery at the end of the trial, again with no evidence for a difference between groups. Median direct costs were CHF 1,824 ($1,459) in the hylan group, CHF 1,548 ($1,238) in the avian HA group, and CHF 1,271 ($1,017) in the bacterial HA group ($P < 0.001$). Corresponding mean costs were CHF 3,181 ($2,545), CHF 2,834 ($2,267), and CHF 2,640 ($2,112), respectively ($P = 0.52$). Assuming identical costs of the 3 preparations in the sensitivity analysis, little differences were found between groups (median costs were CHF 1,684 for hylan, CHF 1,564 for avian HA, and CHF 1,533 for bacterial HA) ($P = 0.37$).

Safety. Serious adverse events during the first cycle, which occurred in 15 of 222 patients allocated to receive hylan and in 25 of 438 patients allocated to receive HAs are shown in Table 2. There was little evidence for a difference between groups. Two serious adverse events were judged to be probably related to the evaluated intervention. These included 1 episode of septic arthritis, which occurred after injection of the

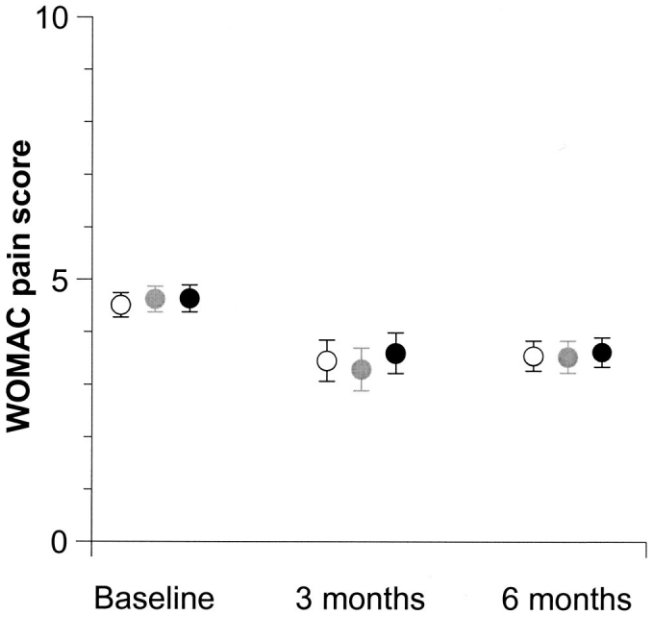

Figure 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (mean and 95% confidence interval) in groups receiving hylan (open circles), avian hyaluronic acid (HA) (shaded circles), or bacterial HA (solid circles) at baseline and at 3 months and 6 months. The analysis of baseline and 6-month scores was based on 660 patients, while the analysis of 3-month scores was based on a random sample of 330 patients (see Figure 1).

Table 1. Characteristics of the patients at baseline*

	Hylan (n = 222)	Avian HA (n = 219)	Bacterial HA (n = 219)
Age, mean ± SD years	63.3 ± 12.3	63.5 ± 11.1	63.3 ± 11.5
Women, no. (%)	144 (64.9)	150 (68.5)	143 (65.3)
Weight, mean ± SD kg	78 ± 15	78 ± 15	79 ± 15
Height, mean ± SD meters	1.67 ± 0.10	1.67 ± 0.09	1.67 ± 0.10
BMI, mean ± SD kg/m^2	28.2 ± 4.9	28.1 ± 5.0	28.6 ± 5.2
Affected knee, no. (%)			
Left	52 (23)	60 (27)	58 (26)
Right	64 (29)	57 (26)	61 (28)
Both	106 (48)	102 (47)	100 (46)
Radiographic severity, no. (%)†			
Slight	53 (24)	44 (20)	48 (22)
Moderate	126 (57)	127 (58)	131 (60)
Severe	43 (19)	48 (22)	40 (18)
Clinical severity, no. (%)‡			
Slight	37 (17)	35 (16)	29 (13)
Moderate	42 (19)	39 (18)	52 (24)
Severe	143 (64)	145 (66)	138 (63)
WOMAC, mean ± SD score§			
Pain	4.5 ± 1.8	4.6 ± 1.9	4.6 ± 1.8
Stiffness	4.6 ± 2.4	4.5 ± 2.3	4.7 ± 2.3
Disability	4.6 ± 1.9	4.7 ± 2.0	4.7 ± 1.9
Overall	4.6 ± 1.8	4.6 ± 1.9	4.7 ± 1.8
EuroQol, mean ± SD score§			
Health state index	6.0 ± 1.9	6.0 ± 1.8	6.0 ± 1.9
VAS	6.4 ± 2.0	6.2 ± 1.9	6.4 ± 1.9

* HA = hyaluronic acid; BMI = body mass index; EuroQol = European Quality of Life; VAS = visual analog scale.
† Assessed by treating physicians using a Likert scale ranging from 0 to 3, with 0 indicating no radiographic osteoarthritis and 3 indicating severe radiographic osteoarthritis.
‡ Clinical severity was considered to be slight if the standardized Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score was <2.6, moderate if the score was 2.6–4.0, and severe if the score was >4.0.
§ Standardized to range from a minimum of 0 to a maximum of 10.

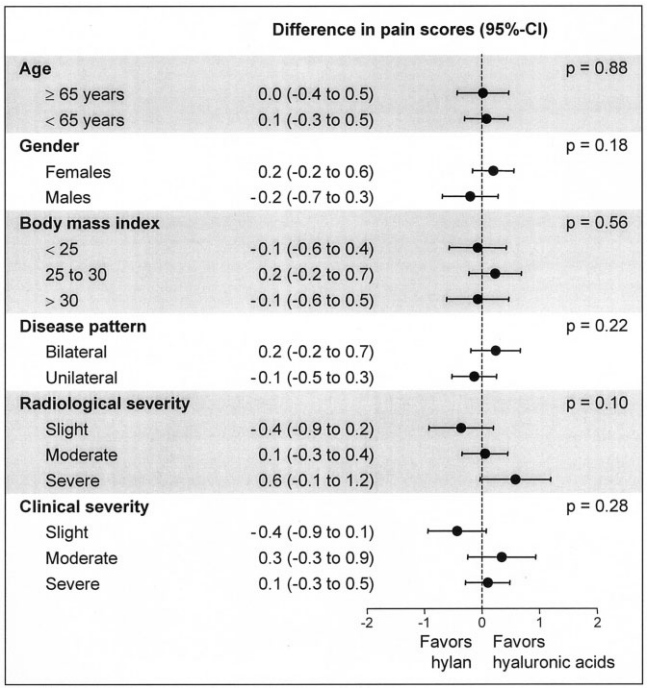

Figure 3. Results of the stratified analyses of the primary outcome according to the indicated characteristics. Values are differences in mean changes between hylan and the hyaluronic acids at 6 months, accompanied by 95% confidence intervals (95% CIs). *P* values are from tests of interaction between allocated treatment and stratum. Body mass index values are kg/m^2.

avian HA, and 1 episode of anaphylactic shock, which occurred after injection of the hylan.

Table 3 presents the number of patients experiencing local adverse events during the first and second cycles. During the first cycle, 9.5% of patients in the hylan group and 7.3% of patients in the HA groups experienced a local adverse event (difference 2.2% [95% CI −2.4, 6.7]). This trend was due to more flares in the hylan group (difference 3.3% [95% CI −0.9, 7.5]), while effusions appeared equally distributed between groups. Three hundred thirty patients were randomly allocated to receive a second cycle of treatment with the originally assigned preparations, 110 in the hylan group and 220 in the HA groups. Figure 1 indicates that 50.9% of the patients randomly allocated to hylan and 48.6% of those randomly allocated to HAs received a second cycle of treatment. Local adverse events occurred more frequently in the hylan group than in the HA groups (difference 6.4% [95% CI 0.6, 12.2]). This difference was most pronounced for flares (difference 6.4% [95% CI 1.8, 10.9]), but was apparent for all outcome measures (Table 3).

DISCUSSION

We found no evidence for clinically relevant differences in efficacy between any of the 3 evaluated viscosupplementation preparations, either in the analysis of WOMAC pain scores or in analyses of secondary outcomes or the stratified analyses. The difference in the WOMAC pain score between hylan and the HAs corresponds to a difference in pain decrease of <1 mm on a VAS ranging from 0 to 100 mm. However, the most expensive, cross-linked, high molecular weight hylan was

Table 2. Patients experiencing serious adverse events during the first cycle (months 0–6)*

	Hylan (n = 222)	Avian HA (n = 219)	Bacterial HA (n = 219)
Serious adverse events	15 (6.8)	12 (5.5)	13 (5.9)
ICD class (code)			
Neoplasms (C or D)	1 (0.5)	0 (0.0)	2 (0.9)
Endocrine and metabolic disorders (E)	1 (0.5)	0 (0.0)	0 (0.0)
Mental and behavioral disorders (F)	1 (0.5)	1 (0.5)	0 (0.0)
Disorders of the nervous system (G)	1 (0.5)	0 (0.0)	0 (0.0)
Disorders of the circulatory system (I)	2 (0.9)	3 (1.4)	2 (0.9)
Disorders of the respiratory system (J)	0 (0.0)	0 (0.0)	2 (0.9)
Disorders of the digestive system (K)	0 (0.0)	2 (0.9)	1 (0.5)
Disorders of the musculoskeletal system and connective tissue (M)	3 (1.4)	1 (0.5)	2 (0.9)
Disorders of the genitourinary system (N)	1 (0.5)	0 (0.0)	2 (0.9)
Symptoms, signs, and other disorders, not classified elsewhere (R)	1 (0.5)	2 (0.9)	0 (0.0)
Injuries and complications of health care, not classified elsewhere (S or T)	4 (1.8)	3 (1.4)	2 (0.9)

* Values are the number (%) of patients. HA = hyaluronic acid; ICD = International Classification of Diseases.

Table 3. Patients experiencing local adverse events during the first cycle (months 0–6) and the second cycle (months 7–12)*

	First cycle			Second cycle		
	Hylan (n = 222)	HAs (n = 438)	Difference (95% CI)	Hylan (n = 110)	HAs (n = 220)	Difference (95% CI)
Local adverse event	21 (9.5)	32 (7.3)	2.2 (−2.4, 6.7)	10 (9.1)	6 (2.7)	6.4 (0.6, 12.2)
Type of local adverse event						
Effusion	7 (3.2)	14 (3.2)	0.0 (−2.9, 2.8)	8 (7.3)	6 (2.7)	4.6 (−0.8, 9.9)
Flare	19 (8.6)	23 (5.3)	3.3 (−0.9, 7.5)	7 (6.4)	0 (0.0)	6.4 (1.8, 10.9)
Corticosteroid injections because of local adverse event	5 (2.3)	5 (1.1)	1.2 (−1.1, 3.3)	4 (3.6)	0 (0.0)	3.6 (0.1, 7.1)
Treatment stopped because of local adverse event	2 (0.9)	6 (1.4)	−0.5 (−2.1, 1.2)	5 (4.5)	0 (0.0)	4.5 (0.7, 8.4)

* Values are the number (%) of patients. HAs = hyaluronic acids; 95% CI = 95% confidence interval.

associated with a trend toward more local adverse events, particularly during the second cycle.

To our knowledge, SVISCOT-1 is the only industry-independent viscosupplementation trial. Empirical research found that studies funded by industry have a higher probability of reaching conclusions in favor of the experimental intervention as compared with independent studies (29). Industry-independent randomized controlled trials are therefore an important element of unbiased and comprehensive assessments of medical interventions. SVISCOT-1 is also the largest viscosupplementation trial to date. It had a power of >95% to detect a clinically relevant difference in effect sizes of 0.4 SD units, which corresponds to a difference of 0.8 units on the standardized 10-point WOMAC pain scale. All between-group differences in primary and secondary efficacy outcomes were close to zero, and confidence intervals excluded any clinically relevant difference.

The trial was covered by the basic health insurance in Switzerland. Therefore, resources were limited. Nevertheless, we were able to reliably answer all relevant questions regarding the comparative efficacy and safety of hylan and conventional HAs. Several measures to reduce the risk of bias were taken, including an adequately concealed random allocation, blinded outcome assessment, and analyses based on the ITT principle (30). In addition, serious adverse events and flares were actively monitored and ascertained by blinded investigators (31). Therefore, underreporting of events and detection bias seem unlikely. Less than 1% of patients were lost to followup for efficacy and none for safety outcomes. This near-complete followup makes attrition bias improbable (32). Finally, the protocol was made publicly available on a Web site, and it was registered with the International Standard Randomized Controlled Trial Number register as a safeguard against selective reporting of trial results (33). These measures might explain some of the differences in results compared with previous trials (34,35).

This trial lacked a placebo control. At the time of initiation of the trial, a meta-analysis found an advantage of viscosupplementation over sham interventions. It suggested that hylan may be more effective than HA and called for an independent trial to establish this difference between hylan and HAs (12). Therefore, it was difficult to justify basic health insurance coverage of a sham control, and our trial can only shed light on the relative efficacy and safety of different preparations and not on the efficacy of viscosupplementation per se. However, changes in pain scores in this trial were comparable with changes in pain scores in large-scale randomized controlled trials comparing viscosupplementation with placebo (36–40). Standardized change scores (41) in these trials ranged from −0.17 (37) to −0.95 (36) SD units (median −0.34) in the active treatment groups and from −0.11 (38) to −0.95 (36) SD units (median −0.33) in the placebo groups compared with −0.50 (hylan), −0.57 (avian HA), and −0.53 (bacterial HA) in SVISCOT-1.

We included patients with OA in 1 or both knees. Perception and reporting of pain in 1 knee might be influenced by moderate-to-severe contralateral disease, resulting in a dilution of effects, as suggested by a post hoc analysis in 1 trial (42). However, our stratified analyses provided no evidence for a difference in effects between patients with unilateral and bilateral disease.

Because of limited resources, we evaluated only 50% of patients at 3 months. These patients were randomly selected using a pregenerated concealed randomization schedule held centrally at the trial coordination office. The 50% sample was still larger than that in most other trials and provided sufficient power to detect clinically relevant differences between groups.

A recently published systematic review identified 9 randomized controlled trials comparing hylan with

another HA (43). The trials used different methods for the assessment of pain, and the review authors made no attempt to combine results of trials with comparable outcome measures, which makes interpretation of results difficult. In a meta-analysis of pain outcomes, which was updated to include results from our trial, we found highly heterogeneous results, with some trials showing an advantage of hylan over HA and others showing the opposite (44). Trials with blinded patients and trials with adequate concealment of allocation, however, had pooled effect sizes near null. The meta-analysis of safety outcomes consistently found that patients allocated to receive hylan were about twice as likely to experience local adverse events as patients allocated to receive HA (44).

During the first treatment cycle, we found a clinically relevant risk of local adverse events in all treatment groups, but there was a trend toward more flares in patients allocated to receive hylan. During the second cycle, 7 of 57 patients allocated to receive hylan experienced flares, but this was true of none of the other patients. The incidence of effusions in the second cycle was also more pronounced in the hylan group. Only about half of the patients had opted for a second treatment cycle in our trial, and the ITT approach used as a measure against attrition bias may have resulted in too-conservative estimates of differences between groups. For example, the calculated difference in the rate of flares during the second cycle of 6.4% translates into a "number needed to harm" of 16 patients to be treated with a second cycle to cause 1 flare. If the analysis is based on treated patients only, the estimated difference between groups increases to 12.5%, and the number needed to harm decreases to 8.

An increased risk of local adverse reactions was also noted in other trials (17,45,46) and in our updated meta-analysis (44). The occurrence of pronounced differences particularly in the second cycle suggests that repeated exposure to hylan might play a role in the development of local adverse events (47). We did not record exposure of patients to hylan before the beginning of the trial, and we are unable to clarify whether previous exposure to 1 of the preparations predisposed patients to flares also during the first cycle. Finally, 2 life-threatening adverse events that occurred during this trial were judged to be probably related to viscosupplementation (1 episode of septic arthritis and 1 episode of anaphylactic shock). This corresponds to a rate of 3 events per 1,000 treatment cycles, which may be considered too high for a treatment with unclear efficacy (48).

Given the consistent and robust lack of an advantage in efficacy of hylan over HAs and the potential for an increased risk of local adverse events, we see no indication for further clinical trials with this preparation (44). Since our trial evaluated only the relative efficacy of different preparations, we are unable to draw any conclusions regarding the advantage of viscosupplementation over sham interventions. The most recent systematic review of 22 trials comparing viscosupplementation and placebo identified major methodologic weaknesses (48). In addition, there was a high degree of heterogeneity between trials that remained unexplained. The authors questioned the efficacy of viscosupplementation and called for a large, well-conducted randomized controlled trial with a sham intervention control group (48). We are aware of at least 3 large-scale randomized controlled trials that remained unpublished and were not included in previous meta-analyses (12,14,48). Therefore, we call for the full disclosure of all data by the manufacturers of these preparations and suggest an updated meta-analysis including all relevant data. Based on the results of this meta-analysis, the need for a large placebo-controlled trial of HAs can be determined. There is no rationale for the continued use of hylan in patients with OA of the knee, either in practice or in clinical research.

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AUTHOR CONTRIBUTIONS

Dr. Jüni had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Jüni, Reichenbach, Tschannen, Züllig, Guetg, Häuselmann, Schwarz, Theiler, Ziswiler, Dieppe, Villiger, Egger.

Acquisition of data. Reichenbach, Tschannen, Jordi, Guetg, Häuselmann.

Analysis and interpretation of data. Jüni, Reichenbach, Trelle, Tschannen, Wandel, Jordi, Züllig, Häuselmann, Schwarz, Theiler, Ziswiler, Dieppe, Villiger, Egger.

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Statistical analysis. Jüni, Reichenbach, Trelle, Wandel.

ROLE OF THE STUDY SPONSOR

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