AMSSM Scientific Statement Concerning Viscosupplementation Injections for Knee Osteoarthritis: Importance for Individual Patient Outcomes

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Objective: Osteoarthritis (OA) is a disabling disease that produces severe morbidity reducing physical activity. Our position statement on treatment of knee OA with viscosupplementation injection [hyaluronic acid (HA)] versus steroid [intra-articular corticosteroid (IAS)] and placebo [intra-articular placebo (IAP)] is based on the evaluation of treatment effect by examining the number of subjects within a treatment arm that met the Outcome Measures in Rheumatoid Arthritis Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria, which is different and more relevant than methods used in other reviews which examined if the average change across the treatment groups was clinically different.

Data Sources: We performed a systematic literature search for all relevant articles from 1960 to August 2014 in the MEDLINE, EMBASE, and Cochrane CENTRAL. We performed a network meta-analysis (NMA) of the relevant literature to determine if there is a benefit from HA as compared with IAS and IAP.

Main Results: Eleven articles met the inclusion criteria from the search strategy. On NMA, those subjects receiving HA were 15% and 11% more likely to respond to treatment by the OMERACT-OARSI criteria than those receiving IAS or IAP, respectively ($P < 0.05$ for both).

Conclusions: In light of the aforementioned results of our NMA, the American Medical Society for Sport Medicine recommends the use of HA for the appropriate patients with knee OA.

Key Words: viscosupplementation, knee osteoarthritis, OARSI-OMERACT, network analysis, corticosteroid

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INTRODUCTION

Osteoarthritis (OA) is a disabling disease that produces severe morbidity reducing physical activity.[1,2] The purpose of this statement is to provide an evidence-based, best practices summary to assist physicians with the nonoperative treatment of OA and to establish the level of evidence, knowledge gaps, and areas requiring additional research. The American Medical Society for Sport Medicine (AMSSM) represents over 2100 nonsurgical sports medicine physicians who have completed additional training in sports medicine after a residency program in family medicine, internal medicine, pediatrics, emergency medicine, or physical medicine and rehabilitation, many of whom have extended expertise in OA evaluation and management. The American Medical Society for Sport Medicine is committed to development and maintenance of a strong relationship with our patients and communities through high-quality patient-centered care.

Osteoarthritis is one of the leading causes of disability in adults in the United States,[1] and knee OA specifically is ranked within the top 10 noncommunicable diseases for global disability-adjusted life years.[3] In 2005, arthritis-related conditions represented the second most common reason for medical visits, and it was the fifth most expensive US inpatient condition for 2008.[3] The lifetime risk of suffering symptomatic knee OA is estimated to be 44.7% [95% confidence interval (95% CI) 40.0% to 49.3%][4] and approximately 1 in 11 of the US population is diagnosed with symptomatic knee OA by 60 years of age.[5]

Knee arthritis compromises physical activity and thus contributes to rising obesity, type-2 diabetes, and general chronic disease, thereby markedly escalating health care expenditures.[2] Patients with knee OA have significantly poorer quality of life when compared with healthy controls.[6] The dose–response relationship between weight and arthritis pain underscores the importance of managing pain to improve activity level in those afflicted with knee OA.[4]

There is general consensus that the initial management of knee OA treatment should include weight loss and strengthening exercises.[7] However, certain aspects of treatment for knee OA are controversial. Other societies have recommended against, supported the use, or consider the data inconclusive concerning the use of viscosupplementation.[8–10] Many physicians have seen patients with OA experience clinical

benefit after hyaluronic acid (HA) injections while others do not.[11]

Our position statement on treatment of knee OA with viscosupplementation injection versus placebo and steroid is based on the evaluation of treatment effect by examining the number of subjects within a treatment arm that met the Outcome Measures in Rheumatoid Arthritis Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria, which is different and more relevant than methods used in other reviews which examined if the average change across the treatment groups was clinically different.[12,13] We believe it is important to look at the potential for an individual to improve because of a treatment given by injection when compared with the potential for improvement of another therapeutic or placebo injection. We performed a network meta-analysis (NMA) of the relevant literature to determine if there is a benefit from high molecular weight and/or low molecular weight HA as compared with intra-articular corticosteroids (IASs) and intra-articular placebo (IAP). To do so, we compared the percentage of individuals with knee OA who achieved improvement as defined by the OMERACT-OARSI responder criteria[13] among those treated with HA, IAS, or IAP injection.

METHODS

Data Sources and Searches

We performed a systematic literature search for all relevant articles from 1960 to August 2014 in the MEDLINE, EMBASE, and Cochrane CENTRAL. The search strategy combined the Medical Subject Heading (MeSH) and key words for viscosupplementation, hyaluronic acid, intra-articular corticosteroid, and osteoarthritis. Our MEDLINE search strategy can be found in Appendix 1. In addition, we performed a manual search of references from reports of randomized controlled trials (RCTs), previous meta-analyses, and review articles to identify additional relevant studies. All relevant articles referenced in the American Academy of Orthopaedic Surgeons (AAOS) Treatment of Osteoarthritis of the Knee Evidence-Based Guidelines were also reviewed. The results of identified studies were supplemented with data identified through the gray literature including regulatory agency reports, www.clinicaltrials.gov, and contacting investigators for clarification of or additional data. Two investigators reviewed each potentially relevant citation independently.

Study Selection

To be included in this meta-analysis, studies had to[1] be in English[2]; be a RCT in patients with OA of the knee[3]; evaluate the efficacy of either IAS or intra-articular HA (regardless of molecular weight) to placebo/no treatment (control) or each other; and[4] report on the OMERACT-OARSI responder rates or mean change from baseline in Western Ontario and McMaster University Arthritis Index (WOMAC) pain, stiffness, or function subscales after at least 8 weeks after the last injection and no longer than 26 weeks. Studies comparing one of the above mentioned therapies to tidal irrigation or arthroscopic lavage were excluded, as these therapies were not deemed to be inactive (a true control).

Validity Assessment

Two independent investigators assessed the quality of each included RCT using the Cochrane Risk of Bias Tool. This checklist includes 6 quality questions encompassing the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome reporting, and selective reporting. Each item was scored as a low, unclear, or high risk of bias.

Data Extraction

Two investigators used a standardized tool to independently extract all data with disagreements resolved by discussion or a third investigator. The data were extracted for each RCT[1]: author identification[2]; year of publication[3]; study design and methodological quality information needed to complete the Cochrane Collaboration's tool for assessing risk of bias[4]; sample size[5]; inclusion/exclusion criteria[6]; baseline characteristics[7]; HA (and molecular weight) and corticosteroid doses and schedules used; and[8] duration of follow-up.

End point data collected included OMERACT-OARSI responder rate and mean change from baseline in WOMAC pain, stiffness, and function subscale scores. When an end point was reported at multiple time points between 8 and 26 weeks, we chose the time of optimal response to active therapy. The OMERACT-OARSI response was defined as having an improvement in WOMAC pain or WOMAC function $\geq$50% and absolute change $\geq$20 mm on the 100-mm visual analogue scale (VAS) or improvement in at least 2 of the following 3 categories: pain $\geq$20% and absolute change $\geq$10 mm; function $\geq$20% and absolute change $\geq$10 mm; and/or patient's global assessment $\geq$20% and absolute change $\geq$10 mm.[13] The WOMAC index is a standardized and validated methodology for assessing pain associated with OA and is routinely used as a primary end point in clinical trials studying the effect of drugs and devices for OA.[14] It is self-administered and consists of the following 3 domains: pain (5 items), stiffness (2 items), and physical function (17 items) measured on a Likert scale (score 0-5) or on a 100-mm VAS, with higher value indicating more severe symptoms. In cases where more than 1 published time point on the same study population was available in multiple publications, the most comprehensive article and the primary end point time point of best response (between 8 and 26 weeks) were used in the meta-analysis to optimize the amount of analyzable data.

Statistical Analysis

We performed traditional pairwise meta-analyses analyzing mean change from baseline in WOMAC pain, stiffness, and function subscale scores as continuous variables using StatsDirect version 2.7.8 (StatsDirect Ltd, Cheshire, United Kingdom). Pairwise meta-analyses were performed for each therapy, combining data from approved doses of the same therapies using the method recommended by the Cochrane Collaboration. For these continuous end points, standardized mean differences as Hedges' g and associated

95% CIs were calculated using a random-effects approach. In instances where variances for net changes were not reported directly, they were calculated from CIs, *P*-values, or individual variances. If the variances for paired differences were not reported, we calculated it from variances at baseline and at the end of follow-up; assuming a correlation coefficient of 0.5 between initial and final values. The OMERACT-OARSI responder rate was meta-analyzed using a random-effects model as a dichotomous end point with weighted averages reported as relative risks and associated 95% CIs. For all pairwise meta-analyses containing at least 3 studies, the likelihood of statistical heterogeneity (using the I^2 statistic with a value >50%, representing important statistical heterogeneity) and publication bias (using the Egger weighted regression statistic with a $P < 0.05$, suggesting a higher likelihood of publication bias) were assessed.[15]

We then performed NMA, a generalization of traditional pairwise meta-analysis that compares all pairs of treatments within a set of treatments for the same disease state (in this case OA of the knee). Along with analyzing direct within-trial comparisons between 2 treatments, the NMA framework enables incorporation of indirect comparisons constructed from 2 trials that have 1 treatment in common. This type of analysis safeguards the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. We used the package "netmeta" (version 0.5-0) in R (version 3.0.2, The R Foundation for Statistical Computing). The package uses a novel graph-theory methodology that exploits the analogy between treatment networks and electrical networks to construct an NMA model accounting for the correlated treatment effects in multiarm trials. We implemented a random-effects model, assuming common heterogeneity across all comparisons. Inconsistency was assessed by comparing the results from direct and indirect estimates of effect. Incoherence was said to be present if direct and indirect evidence estimates varied to a statistically significant extent as depicted by a test for interaction.[16]

RESULTS

Eleven articles met the inclusion criteria from the search strategy (Appendix 1).[17–27] The average age of the subjects in the studies included in this analysis was older than 60 years (Table 1 Study Demographics). In most studies, the subjects' severity was Kellgren–Lawrence (K-L) grade 2 or 3. The average body mass index of the subjects in all studies was categorized as overweight or obese. Most studies followed the subjects for a total duration of 6 months or equivalent 26 weeks, with one at 12 weeks and one at 18 weeks. The number of injections varied from a single dose to 5 weekly injections depending on preparation. The sample size of all but 1 study was more than 200 with a maximum of 588 subjects with a mean of 336 subjects. Women were subjects in the studies more often than men.

Cochrane bias tool assessment (Table 2) demonstrated that most studies exhibited a lower risk of bias for the majority of domains assessed. When potential for bias was present among studies, it was most commonly because of incomplete data reporting, selective reporting, or the absence of blinding of participants and personnel. For evaluating analyses, Egger *P*-values suggested a lower likelihood of publication bias (Egger $P > 0.05$ for all).

On NMA (Table 3), those subjects receiving HA were 15% and 11% more likely to respond to treatment by the OMERACT-OARSI criteria than those receiving IAS or IAP, respectively ($P < 0.05$ for both); although IAS use was not associated with an improved OARSI responder rate. Hyaluronic acid significantly decreased WOMAC pain and function scores compared with control, and WOMAC function scores compared with IAS. Hyaluronic acid trended toward improving WOMAC stiffness scores compared with control and IAS; however, statistical significance was not reached for this analysis. No significant reduction in WOMAC pain, stiffness, or function scores was observed with IAS compared with control. The median optimal timing used in this analysis was OARSI: 26 weeks (13-26 weeks), WOMAC pain: 25 weeks (13-26 weeks), WOMAC function: 13 weeks (12-26 weeks), and WOMAC stiffness: 13 weeks (13-26 weeks).

Moderate degrees of statistical heterogeneity were observed in the HA versus control WOMAC pain, stiffness, and function analyses (I^2 = 49%, 55%, and 51%, respectively), whereas minimal heterogeneity was observed in the HA versus control OARSI responder analysis. All other analyses had too few direct comparisons to assess statistical heterogeneity. On comparison of available direct and indirect estimates of effect, no statistically significant incoherence was noted.

Safety concerns about the HA products were evaluated in the studies. The most common side effects were arthralgia, swelling, and stiffness that occurred in equivalent percentages in each treatment and control group. One study had a significant difference[24] in arthralgia of 17% in HA and 3.2% in IAS with resolution symptoms within 2 to 3 weeks. The other studies did not demonstrate a difference between HA and control in treatment-related adverse events (Table 4).

DISCUSSION

We conducted a NMA of the efficacy of intra-articular injection of HA versus IAS and IAP injections in OA of the knee. To our knowledge, this is the first study to use a NMA to assess the effectiveness of HA injection for knee OA through comparison of OMERACT-OARSI responder rates. Our results demonstrate evidence of small but statistically significant improvement for the group of subjects treated with HA injections compared with those treated with IAS or IAP injections with regard to pain and function as assessed by the relevant WOMAC subscales. Furthermore, on an individual level, our results indicate that HA instillation led to a 15% and 11% greater chance of achieving OARSI responder status than did IAS and IAP, respectively, each statistically significant. The OMERACT-OARSI criteria were developed in 2003 to standardize the assessment of individuals in clinical trials for knee OA who demonstrate a significant clinical response as a consequence of one or more treatment interventions (Pham et al, 2003). As such, by its very definition, statistically significant changes in OMERACT-OARSI responder rates represent clinically

TABLE 1. Study Demographics

Study	Sample Size	Mean Age	% Female	Mean BMI (kg/m^2)
Altman et al[17]	346	63.1	46 vs 64	29.9
Altman et al[18]	588	61.6	63	32.7
Caborn et al[19]	216	63.1	56.9	31
Chevalier et al[20]	253	62.9	74 vs 68	27.9
Day et al[21]	240	62	56 (HA) vs 61 (P)	Reported height and weight but not BMI but needed to be below 40
DeCaria et al[22]	30	72.4	47	29.9
Housman et al[23]	391	60.9	71 vs 61 vs 69	31.2
Huang et al[27]	200	65	76	25.6
Leighton et al[24]	442	61.7	51 vs 47	28.3
Navarro-Sarabia et al[25]	306	63.5	83.7	28.4 vs 28.7
Strand et al[26]	379	60.6	59.5 vs 60.2	28.5

Study	Severity	Product	Control	No. Injections	Duration
Altman et al[17]	K-L II-IV	NASHA (Durolane)	Saline	1	26 wk
Altman et al[18]	K-L II-III	BioHA	Saline	3	26 wk
Caborn et al[19]	Not reported	Hylan G-F 20 (Synvisc)	Triamcinolone hexacetonide	3, 1	26 wk
Chevalier et al[20]	K-L II-III	Hylan G-F 20 (Synvisc)	Saline	1	26 wk
Day et al[21]	Mild to Moderate; <K-L IV	25 mg of sodium HA in 2.5 mL of phosphate buffered saline (ARTZTM; batch no. C4F27S). The sodium HA was extracted from rooster combs and the purified material has a molecular weight of 6.2-11.7 × 105 Da	2.5 mL of the PBS vehicle (batch no. C4F28S)	5	18 wk
DeCaria et al[22]	K-L II-III	HA 20 mg/mL	HA 0.001 mg/mL	3	6 mo
Housman et al[23]	K-L II-III	Hylastan 2, 1	IAS	2, 1	26 wk
Huang et al[27]	K-L II-III	Hyalgan	Saline	5	26 wk
Leighton et al[24]	K-L II-III	NASHA (Durolane)	MPA	1	12 wk
Navarro-Sarabia et al[25]	K-L II-III	1% Sodium hyaluronate	Saline	5	40 mo
Strand et al[26]	K-L I-III	Gel-200	Saline	1	13 wk

BMI, body mass index; MPA, methylprednisolone.

significant differences. Thus, the statistically significant results that we have identified for HA versus IAS and IAP also represent a clinically relevant difference.

We found no statistical or clinical benefit for IAS injection versus IAP injection, despite using the time point of maximal IAS benefit for comparison with IAP. Similarly, we were unable to identify significant differences in treatment response when comparing the efficacy of low versus high molecular weight HA products compared with IAP injection, a finding that was influenced by the limitation in power imposed by the paucity of studies of adequate quality to compare the effects of products of different molecular weights.

Our results of statistically significant benefit of HA injections over IAP injections are consistent with several of the previous meta-analyses of HA injections for knee OA.[28–31] When analyzed in terms of mean rather than individual responses, the small effect size in our study (0.2) was also consistent with the majority of previous studies[29] except for 1 study with smaller effect size.[32] By way of context, the effect size identified by our study, although small, is similar to that found in a meta-analysis of nonsteroidal anti-inflammatory drugs (NSAIDs) for knee OA.[32] The interpretation of the clinical relevance of the small statistical benefit has varied among reviews and has been considered controversial.[33] Accordingly, our interpretation of the data, specifically our OMERACT-OARSI results reflecting superiority of HA injection over IAS and IAP, concurs with certain previous reviews[28,31] by demonstrating a meaningful clinical correlate to the statistical benefit from HA injections, although not with other studies[29,32] that have interpreted the data as reflecting no clinical benefit. The divergent conclusions from previous studies have been attributed to the varied methodology used in study selection, the assessment of effect size, and the interpretation of the clinical relevance of the statistical results.[33] Furthermore, the relatively large and persistent placebo effects found in trials of knee OA in general, but particularly seen among trials using intra-articular saline controls, have been recognized as substantial barriers to OA therapeutics[34] including viscosupplements.[35] In fact, given that arthrocentesis with or without saline injection has been recognized as an effective intervention in knee OA patients presenting with

TABLE 2. Cochrane Bias Rating Table

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting
Altman 2004	+	+	+	+	-	?
Altman 2009	+	?	?	+	+	+
Caborn 2004	-	-	-	+	-	+
Chevalier 2008	+	+	+	+	+	+
Day 2004	+	?	+	+	+	?
Decaria 2011	+	?	+	+	+	+
Housman 2013	+	+	+	+	+	+
Huang 2011	?	?	?	?	+	?
Juni 2007	+	+	+	+	+	+
Lee 2006	+	?	-	+	?	+
Leighton 2013	+	+	+	+	+	?
Navarro 2011	+	+	+	+	-	+
Pavelka 2011	+	+	+	+	-	-
Raman 2008	+	?	?	+	+	+
Strand 2012	+	+	+	+	?	?

a significant knee effusion,[36] some researchers have suggested that intra-articular saline "placebo" injections might better be categorized as active controls rather than as "placebos."[33] As a consequence of the uncertainty generated by these issues, when the results of previous systematic reviews and meta-analyses have been used to generate evidence-based guidelines for the treatment of knee OA, recommendations regarding the use of HA injections have typically been measured. Thus, in their latest iterations, the American College of Rheumatology[37] makes no official recommendation for the use of HA injections and the OARSI guidelines rate the benefit from HA as uncertain.[38] A notable exception to this trend was the recent guideline published by the AAOS[10] that changed their previous recommendation regarding the use of HA injections for knee OA from "inconclusive" to "strongly recommending against" its use. Of note, the latest AAOS review demonstrated the statistically significant benefit for HA injection on the WOMAC pain, stiffness, and function subscales that have been noted in most other reviews, including the previous AAOS review. The AAOS panel strongly recommended against the use of HA injections based on a re-evaluation of the existing literature according to a change in the analytic method by which clinical relevance was assessed.

The guideline relied on a relatively new outcome measure, the minimum clinical important improvement (MCII). The MCII and a closely-related concept that relates either improvement or worsening, the minimal clinically important difference,[39] represent an effort by investigators to incorporate subjects' expectations for improvement from a given intervention into the assessment of its efficacy.[39,40] Although these outcome measures are recognized as an important innovation for use in assessing the clinical relevance of statistical results in OA research trials, the methodology applied in certain guidelines has been criticized on several accounts.[41] It should be noted that the MCII has not been adequately validated for use in isolation to guide clinical decision making.[2] Furthermore, the application of the MCII in some guidelines does not seem to account for the variance in MCII by baseline symptom severity,[39] treatment type,[42] age, and trial assessment intervals.[43] Thus, when the AAOS investigators used studies of NSAIDs and rehabilitation to generate a single cut-off value to assess MCII responses to HA injection with placebo controlled between group comparisons, the cut-off values to assess the MCII as a determinant of HA efficacy may have been higher than the appropriate level, thus biasing the results toward fewer studies achieving clinically relevant results.[41] We used an alternative approach to capture the experience of individual subjects undergoing treatment in OA studies, the OMERACT-OARSI responder criteria,[44] which seeks to identify the proportion of subjects who meet preset criteria for response as individuals. Using the OARSI

TABLE 3. HA (Combined HMW and LMW) Versus CONT or IAS at Time of Best Response

Outcome	Comparison	NMA ES (95% CI)	No. Studies	TMA ES (95% CI)	I^2 (%)	Egger *P*
WOMAC pain	HA vs CONT	−0.19 (−0.32 to −0.06)	7	−0.19 (−0.32 to −0.06)	48.9	0.26
	HA vs IAS	−0.06 (−0.28 to 0.16)	2	−0.06 (−0.28 to 0.17)	NA	NA
	IAS vs CONT	−0.13 (−0.39 to 0.13)	NA	NA	NA	NA
WOMAC stiffness	HA vs CONT	−0.12 (−0.27 to 0.03)	6	−0.12 (−0.27 to 0.03)	55.1	0.51
	HA vs IAS	−0.17 (−0.50 to 0.16)	1	−0.17 (−0.36 to 0.01)	NA	NA
	IAS vs CONT	0.05 (−0.31 to 0.41)	NA	NA	NA	NA
WOMAC function	HA vs CONT	−0.19 (−0.32 to −0.05)	7	−0.19 (−0.32 to −0.05)	50.8	0.38
	HA vs IAS	−0.29 (−0.53 to −0.05)	2	−0.30 (−0.58 to −0.01)	NA	NA
	IAS vs CONT	0.10 (−0.18 to 0.38)	NA	NA	NA	NA
OARSI responder	HA vs CONT	1.11 (1.01 to 1.20)	4	1.10 (1.01 to 1.19)	0	0.27
	HA vs IAS	1.15 (1.02 to 1.30)	2	1.15 (1.01 to 1.30)	NA	NA
	IAS vs CONT	0.96 (0.82 to 1.11)	NA	NA	NA	NA

Likelihood of statistical heterogeneity (I^2 statistic with a value >50% representing important statistical heterogeneity) and publication bias (Egger weighted regression statistic with a $P < 0.05$, suggesting a higher likelihood of publication bias).

CONT, control; ES, effect size; NA, not available; TMA, traditional meta-analysis.

TABLE 4. HA Adverse Effects

Study	Sample Size	Severity	Product (HA)	Control (Sa, IAS)	No. Injections	Duration	AEs
Altman et al[17]	346	K-L II-IV	NASHA (Durolane)	Saline (Sa)	1	26 wk	Treatment-related AEs: HA = 12.8% vs Sa = 8.0%; arthralgia: HA = 6.4% vs Sa = 2.9%; >70% of treatment-related AEs reported within 2 d in both treatment groups; 9 treatment-related AEs led to withdrawal (HA = 5, Sa = 4), 1 worsening knee OA pain (HA), 1 knee synovitis (Sa); no serious treatment-related AEs
Altman et al[18]	588	K-L II-III	BioHA	Saline (Sa)	3	26 wk	Treatment-related AEs: HA = 10% vs Sa = 11%; arthralgia: HA = 9% vs Sa = 12%; 8 treatment-related AEs led to withdrawal (HA = 3, Sa = 5); no joint effusions in treatment group
Caborn et al[19]	216	Not reported	Hylan G-F 20 (Synvisc)	Triamcinolone hexacetonide (IAS)	3, 1	26 wk	No statistically significant differences observed between treatment groups for overall incidence of AEs or IAS incidence of any single AE; majority of AEs reported were not considered to be related to the study treatments; number and severity of local injection–site reactions comparable between treatment groups; injection site-related events, HA = 7% vs IAS = 10% (P = 0.224); swelling-related events, HA = 8% vs IAS = 12% (P = 0.136); discontinuation due to AEs HA = 10% vs IAS = 10%; 9 serious AEs in 6 patients in IAS group considered not to be treatment-related
Chevalier et al[20]	253	K-L II-III	Hylan G-F 20 (Synvisc)	Saline (Sa)	1	26 wk	No target knee serious AEs; no treatment-related serious AEs; incidence of AEs HA = 5.7% vs Sa = 3.1% (P = 0.366); no difference in treatment-related AEs (P = 0.203) or procedure-related target knee AEs (P = 0.531), all of which were mild or moderate
Day et al[21]	240	Mild to Moderate; <K-L IV	25 mg of sodium HA in 2.5 mL of phosphate buffered saline (ARTZTM; batch no. C4F27S). The sodium HA was extracted from rooster combs, and the purified material has a molecular weight of 6.2-11.7 × 10^5 Da	2.5 mL of the buffered saline (Sa) (batch no. C4F28S)	5	18 wk	Treatment-related AEs type and incidence between the active and control groups was similar. Most frequent AE was injection site pain (HA group 16; controls 13); dropout was 4% HA and 6% control

TABLE 4. (*Continued*) HA Adverse Effects

Study	Sample Size	Severity	Product (HA)	Control (Sa, IAS)	No. Injections	Duration	AEs
DeCaria et al[22]	30	K-L II-III	HA 20 mg/mL	HA 0.001 mg/mL	3	6 mo	No significant AEs reported; limited number of patients reported minor discomfort during the injection process
Housman et al[23]	391	K-L II-III	Hylastan 2, 1	Methylprednisolone Acetate (IAS)	2, 1	26 wk	Frequencies of overall AEs and target knee AEs comparable between groups; most frequent target knee AEs in all 3 groups: arthralgia, stiffness, swelling, effusion with no differences between groups; majority mild or moderate; no significant changes in vital signs, antibody testing results or laboratory safety concerns
Huang et al[27]	200	K-L II-III	Hyalgan	Saline (Sa)	5	26 wk	More patients in placebo group experienced at least 1 AE (48% vs 39%), all mild-moderate, none considered related to study treatment; 5 serious AEs reported HA = 3 vs Sa = 2, all considered unrelated to study treatment; statistically significant change from baseline in platelet counts between groups at 5 wk not thought to be clinically significant (P = 0.027)
Leighton et al[24]	442	K-L II-III	NASHA (Durolane)	Methylprednisolone Acetate (IAS)	1	12 wk	During blinded phase, treatment-related AEs: HA = 64 vs IAS = 15 (no P-value reported); arthralgia was the largest component, 38 (17.2%) vs 7 (3.2%) ($P <$ 0.01) with most TRAE reported within 3 days of injection and resolved within 2–3 wk; no treatment-related serious AEs; during OLE, no allergic reactions to the second injections observed
Navarro-Sarabia et al[25]	306	K-L II-III	1% Sodium hyaluronate	Saline (Sa)	5	40 mo	Overall frequency of at least 1 AE = 83%, the same in both treatment groups (n = 11 in each); no serious AEs reported
Strand et al[26]	379	K-L I-III	Gel-200	Saline (Sa)	1	13 wk	Incidence of AEs similar in both treatment groups; 182 treatment-related AEs reported in 100 patients: HA = 26.9% vs Sa = 25.8%; joint swelling, effusion, arthralgia most common and not significantly different between groups; no clinically notable laboratory result changes

AE, adverse event; OLE, open-label extension phase.

responders, we are looking at the benefit to the individual patient rather than the benefit averaged across the group. Our NMA found that subjects undergoing HA injections had 15%, and 11%, greater likelihood of achieving an OARSI response versus IAS and IAP, respectively. This finding contradicts other's assertion, inferred from MCII results, that there is "a low likelihood that an appreciable number of (individual) patients achieved clinically important benefits in the outcomes." Furthermore, the AAOS document seems to lack internal consistency with regard to its recommendations for IAS and HA injections. Unlike the AAOS study, our study design allowed a direct comparison of these treatments through the use of a NMA and has reached different conclusions.

A strong recommendation against the use of an HA injection is not without consequence, because individual patients find benefit from HA injections, as we demonstrate in this article. An incorrect recommendation against the use of HA may encourage third party payers to limit or eliminate reimbursement for HA as a cost-saving measure (commentary in Washington State Health Care Authority, Health Technology Assessment. "Hyaluronic Acid/Viscosupplementation Draft Evidence Report: Public Comment & Response." Accessed online February 15, 2015, http://hca.wa.gov/hta/Documents/ha-visco_final_report_101113.pdf). Furthermore, given the limited armamentarium of nonoperative interventions available to treat symptomatic knee OA and that HA injections are typically reserved for those patients who are unresponsive to first-line lifestyle interventions, including exercise, weight loss, and oral medications, it is possible that an increase in the number of surgical procedures may result, in the absence of HA injections, although a recent meta-analysis of this question was inconclusive (Newberry et al, 2014). Two recent studies (Bannaru et al, 2015; Newberry et al, 2014) supported with funding from the Agency for Healthcare Research and Quality (ARHQ) have investigated questions related to the efficacy of HA on knee OA that differ from the focus of our research. Bannuru et al (Bannuru et al, 2015) performed the only other NMA of HA in knee OA use of which we are aware as part of a more global investigation of nonoperative treatment options. Although OMERACT-OARSI responder rates were not investigated, the results obtained with regard to HA injections are consistent with those we report. Specifically, HA injections demonstrated statistically significant benefit when prespecified criteria were met for clinical significance, which with regard to pain demonstrated the largest effect size (0.63, CI, 0.39-0.88) of any treatment tested. These investigators also noted greater improvement in response to intra-articular injections, including HA injections, than from oral treatments, and statistically significant improvements from HA injections in function when compared with IAS and IAP and stiffness when compared with IAP. Contrarily, another recent ARHQ-funded review (Newberry et al, 2014) that specifically targeted the population of severe OA of the knee found no functional benefit from HA injections and insufficient evidence to assess delay or avoidance of total knee replacement as a benefit of HA injections. Of note, the methodology of this latter ARHQ-funded study differs from ours in the impact of HA injection on pain, the most frequently assessed outcome parameter in the HA studies included in their analysis (Newberry et al, 2014) was not assessed. The differences reported between these 2 previous studies and our results likely reflect methodological differences.

Substantial heterogeneity in an individual's response to HA injections is suggested by the limited magnitude of the mean changes seen across groups in contrast to the more substantial changes we have demonstrated in individual responsiveness by OARSI responder criteria. It would seem that certain individuals respond more robustly than others to HA injection. Such variation in individual response has also been recognized for IAS injections.[45] Numerous clinical parameters, including subject age,[30] the presence[46] or absence[47] of effusion, higher baseline function,[47] synovial fluid HA concentration,[49] and certain structural measures (eg, the severity[30] or location of joint damage[46]) have been suggested to improve an individual's responsiveness to injection. However, efforts to prospectively identify a set of clinical parameters that predict a favorable response to HA injection have been unsuccessful to date (Koolaee et al, 2014). Furthermore, when assessing the value of HA injections for knee OA, the magnitude of symptomatic benefit may not be the only criterion on which recommendations should be made. For instance, even among those without significant symptomatic improvement, HA injections may have structural benefit to cartilage, a long-held theory[50] which has been supported by a recent study that links a decrease in synovial fluid hyaluronan molecular weight distribution with an increased risk of progressive cartilage loss in OA (Band et al, 2015). Similarly, the benefit of HA injection on symptoms and/or osteoarthritic cartilage may or may not allow delay in total knee replacement surgery.[51] Putative mechanisms through which HA may reduce OA progression include improved cartilage/synovial fluid rheology, increased synthesis of extracellular matrix constituents including better "quality" HA, suppression of inflammatory mediators (eg, cytokines, prostaglandins, nitric oxide), reduction in fibronectin fragment-induced damage, and alteration in immune cell activity.[52] Hyaluronic acid–mediated chondroprotection has been demonstrated in animal, in vitro, and clinical studies,[52] including a recent article[53] that found a decreased rate of medial and lateral tibial articular cartilage degeneration after HA injections through the use of a state-of-the art magnetic resonance imaging–based assessment of cartilage integrity. Other studies of the structural impact of HA injections of similar design have, however, failed to demonstrate structural benefit to cartilage from one series of injections.[54] Thus, for patients with knee OA, HA injections may offer benefits that extend beyond the issues of the statistical significance and clinical relevance of the symptomatic results that they eventuate.

We chose to analyze the data regarding HA injections for knee OA according to a novel temporal scheme. We compared the results for each treatment at the time of the maximal treatment efficacy across studies rather than selecting a consistent single time from injection. Thus, the time at which data were assessed varied between some studies. When comparing HA with IAS, we used the time of optimal HA benefit for analysis of studies of HA versus IAS injections as our intent was to investigate whether HA injections had

significant clinical efficacy at any time point. Our results suggest that maximal benefit occurs at different times after injection with HA and IAS. These results are consistent with previous systematic reviews[28,55,56] that found superiority of IAS injection over HA injection from 0 to 4 weeks after administration but that HA injection was superior to IAS from 4 to 26 weeks. In this regard, each injectable medication may have a different role in treating those with knee OA. Specifically, IAS may have utility to rapidly abort a flare of knee OA,[57] where rapid onset is required as a bridge to additional treatment including physical therapy which might, otherwise, prove too painful. Hyaluronic acid injections, contrarily, may be used to yield longer-term control of baseline symptoms but may not be appropriate for the treatment of acute exacerbations given the longer time to onset of relief.

Our study has several limitations. We did not include unpublished trials, although we searched for these items, a factor which may be biased toward the positive direction because of publication bias. However, the Egger value indicates that it is unlikely that publication bias exists. Furthermore, the outcome measures, assessment times, and study designs used in the included HA studies varied widely. Furthermore, as OARSI responder rates were not collected in all trials, we compared only trials that collected this data in this portion of our analysis. We had access to study level data only, not individual patient data, and were, thus, unable to impute OARSI responses from other trials. Additionally, a wide variety of HA products of different structure and molecular weight are available but we were unable to identify significant changes in efficacy related to these differences. Finally, our study is unable to distinguish whether the accuracy of HA injection affects its efficacy, for example, whether the use of ultrasound-guidance would improve the efficacy of HA injections in knee OA. A recent review by the AMSSM finds that ultrasound-guided (USG) injection in the knee is more accurate and that USG IAS injection is more efficacious than landmark-guided (LMG) injection.[58] The significance of this difference for IAS injection is unknown for HA injections, as we are unaware of any published trials comparing USG versus LMG injections of HA for knee OA. Our data may better approximate the results of those using LMG injections in clinical practice if indeed a difference in efficacy and accuracy with USG exists for HA injection.

CONCLUSIONS

In light of the aforementioned results of our NMA, the AMSSM recommends the use of HA for the appropriate patients with knee OA. Using The Grades of Recommendation, Assessment, Development and Evaluation Working Group system,[15] there are multiple RCTs indicating HIGH-QUALITY evidence.

"We RECOMMEND viscosupplementation injections for K-L grade II-III knee osteoarthritis in those patients above the age of 60 years based on HIGH quality evidence demonstrating benefit using OMERACT-OARSI Responder Rating."

But the evidence should be downgraded because of indirectness for those younger than 60 years.

"We SUGGEST viscosupplementation injections for knee osteoarthritis for those under the age of 60 years based on MODERATE quality evidence due to response of treatment in those over 60 years of age."

We also recommend that clinicians and researchers collect OMERACT-OARSI responder data to track individual response to the viscosupplementation. Furthermore, high-quality studies are needed to address the residual uncertainties regarding the clinical benefit achieved from HA injection, especially in the active 40- to 60-year age group. Prediction rules are needed to identify patient characteristics that prospectively identify members of the subgroup of OA patients that will demonstrate more robust response to HA injection as opposed to those who are unlikely to benefit.

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APPENDIX 1. Search Strategy

Search	Query	Items found
#14	Search (#9 NOT (#10 OR #12))	189
#13	Search ((#9 AND #12) NOT #10)	136
#12	Search ("Clinical Trial"[pt] OR (clinical[tiab] AND trial[tiab]) OR random*[tw] OR "Therapeutic use"[sh])	4115475
#11	Search (#7 AND #10)	168
#10	Search (Medline[tw] OR systematic review[tiab] OR Meta-analysis[pt])	113000
#9	Search (#7 AND #8)	349
#8	Search ("Injections, Intraarticular"[mh] OR corticosteroid*[tiab] OR glucocorticoid*[tw] OR hyaluron*[tw] OR viscosupplement* OR "platelet-rich plasma" OR "Fibroblast Growth Factors"[mh] OR fibroblast*[tw] OR "growth factor" OR "Stem cells"[mh] OR "stem cells" OR mesenchymal OR prolotherap*[tiab] OR "Hypertonic Solutions"[mh])	782643
#7	Search (#4 AND #5 NOT #6)	3188
#6	Search ((animal[mh] NOT human[mh]) OR cadaver[mh] OR cadaver*[titl] OR comment[pt] OR editorial[pt] OR letter[pt] OR "historical article"[pt] OR addresses[pt] OR news[pt] OR "newspaper article"[pt] OR "in vitro"[pt] OR "case report"[title])	5881461
#5	Search ("1966"[dp]:"2014"[dp] AND English[lang] AND "2011/4/22"[edat]:"2014"[edat])	2498692
#4	Search ((#1 OR (#2 AND #3)) NOT arthroplasty[majr])	19061
#3	Search (Osteoarthritis[mh:noexp] OR Arthritis[mh:noexp] OR osteoarthrit*[tiab])	71639
#2	Search ("Knee Joint"[mh] OR "Knee"[mh] OR knee*[tiab])	106867
#1	Search ("Osteoarthritis, Knee"[mh] OR gonitis[tiab] OR gonarthritis[tiab] OR gonarthros*[tiab])	10723