Systematic Review

Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses

Kirk A. Campbell, M.D., Brandon J. Erickson, M.D., Bryan M. Saltzman, M.D., Randy Mascarenhas, M.D., F.R.C.S.C., Bernard R. Bach Jr., M.D., Brian J. Cole, M.D., M.B.A., and Nikhil N. Verma, M.D.

Purpose: To conduct a systematic review of overlapping meta-analyses comparing treatment of knee osteoarthritis (OA) with intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]) versus oral nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids (IA-corticosteroids), intra-articular platelet-rich plasma (IA-PRP), or intra-articular placebo (IA-placebo) to determine which meta-analyses provide the best current evidence and identify potential causes of discordance. **Methods:** Literature searches were performed for meta-analyses examining use of IA-HA versus NSAIDs, IA-corticosteroids, IA-PRP, or IA-placebo. Clinical data were extracted, and meta-analysis quality was assessed. The Jadad algorithm was applied to determine which meta-analyses provided the highest level of evidence. **Results:** Fourteen meta-analyses met the eligibility criteria and ranged in quality from Level I to IV evidence. In studies reporting patient numbers, there were a total of 20,049 patients: 13,698 receiving IA-HA, 355 receiving NSAIDs, 294 receiving IA-corticosteroids, and 5,702 receiving IA-placebo. Ten studies examined the effects of IA-HA versus IA-placebo; of these, 5 found that IA-HA improved pain and 4 found that IA-HA improved function. No clinically relevant differences in the efficacy of IA-HA versus NSAIDs regarding pain and function were found. Regarding IA-HA versus IA-PRP, IA-HA improved knee function at 2 and 6 months after injection but the effects were less robust than those of IA-PRP. Regarding IA-HA versus IA-corticosteroids, the positive effects of IA-HA were greater at 5 to 13 weeks and persisted for up to 26 weeks. After application of the Jadad algorithm, 2 concordant high-quality meta-analyses were selected and both showed that IA-HA provided clinically relevant improvements in pain and function compared with IA-placebo. **Conclusions:** This systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA shows that the current highest level of evidence suggests that IA-HA is a viable option for knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks. IA-HA has a good safety profile, and its use should be considered in patients with early knee OA. **Level of Evidence:** Level IV, systematic review of Level I to IV studies.

Knee pain due to osteoarthritis (OA) is one of the most common complaints in patients presenting to orthopaedic clinics, resulting in significant societal costs including cost of treatment and lost time from work or activities.[1,2] Several nonoperative and operative treatment options exist to mitigate this pain and the resulting limitations in function occurring in patients with arthritis. The goal of nonoperative treatment modalities is to minimize

From Midwest Orthopaedics at Rush, Rush University Medical Center (K.A.C., B.J.E., B.M.S., B.R.B., B.J.C., N.N.V.), Chicago, Illinois; and the Division of Sports Medicine, Department of Orthopaedic Surgery, The University of Texas Health Science Center at Houston (R.M.), Houston, Texas, U.S.A.

The authors report the following potential conflict of interest or source of funding: B.R.B. receives support from Arthrex, Ossur, Linvatec, and Smith & Nephew. B.J.C. receives support from Arthrex, DJ Orthopaedics, Johnson & Johnson, Regentis, Zimmer, and Smith & Nephew. N.N.V. receives support from Minivasive, Smith & Nephew, Arthrosurface, Omeros, Arthrex, Athletico, ConMed Linvatec, Miomed, and Mitek.

Received December 10, 2014; accepted March 19, 2015.

Address correspondence to Kirk A. Campbell, M.D., Midwest Orthopaedics at Rush, Rush University Medical Center, 1611 W Harrison St, Ste 300, Chicago, IL 60612, U.S.A. E-mail: Kirk.anthony@gmail.com

0749-8063/141037/$36.00

http://dx.doi.org/10.1016/j.arthro.2015.03.030

pain and restore function in a noninvasive manner while prolonging the need for a total knee arthroplasty (TKA). These options include intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]), intra-articular corticosteroids (IA-corticosteroids), oral nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular platelet-rich plasma (IA-PRP).

Viscosupplementation is the injection of an intra-articular compound made of high-molecular-weight fluid containing hylan products (derivative of hyaluronan) that essentially functions as a viscoelastic glycosaminoglycan. Hyaluronic acid (HA) is naturally present in joint fluid and serves multiple purposes including shock absorption, joint lubrication, and energy dissipation; in addition, it coats the articular cartilage surfaces of the femur, tibia, and patella to protect them.[3]

The desire to delay the treatment of knee OA with TKA lies in the desire to reduce the possibility of the need for early revision TKA. Although the failure rate varies on an individual basis, it is generally accepted that the revision rate for knee arthroplasty is slightly less than 1% per year with a 10-year survivorship rate of approximately 95% and a 20-year survivorship rate of approximately 85%.[4-8] Recent evidence has shown that approximately 4 million persons in the United States are living with a TKA and that over half of the adults in the United States diagnosed with knee OA will eventually undergo TKA.[9]

Despite the plethora of studies examining the array of less invasive treatment options that exist for knee OA prior to performing a TKA, there has been no definitive consensus as to which treatments are the most effective at improving pain and function.[10,11] Arrich et al.[10] performed a meta-analysis to determine if IA-HA improved pain or function in patients with knee OA and found that it did improve activity-related knee pain. Conversely, Bannuru et al.[11] conducted a meta-analysis comparing IA-HA with oral anti-inflammatory medications, and although both treatments showed improvements in function and stiffness, there were no differences between the groups.

Therefore the purpose of this study was to conduct a systematic review of overlapping meta-analyses comparing treatment of knee OA with IA-HA versus oral NSAIDs, IA-corticosteroids, IA-PRP, or intra-articular placebo (IA-placebo) to determine which meta-analyses provide the best current evidence and identify potential causes of discordance. The main objectives of this study were (1) to conduct a systematic review of meta-analyses comparing the aforementioned treatment options for knee OA, (2) to provide an analytical framework for interpreting the presently discordant best available evidence to develop treatment recommendations, and (3) to identify gaps in the literature that require continued investigation. We hypothesized that intra-articular injections of HA would provide significant improvement in pain and function with minimal side effects compared with IA-corticosteroids, IA-PRP, IA-placebo, or oral anti-inflammatory medications.

Methods

A systematic review of the literature was performed using the PubMed database, CINAHL (Cumulative Index to Nursing and Allied Health Literature) Complete database, Cochrane Database of Systematic Reviews, Scopus database, and Embase database. The following search terms were used: meta-analysis AND hyaluronic acid AND (knee [arthritis OR osteoarthritis]) AND (corticosteroid OR NSAID OR placebo OR [platelet rich plasma OR PRP]). The search was performed on August 24, 2014, and was limited to articles written in English. Broad search query terms were used to include all possibly applicable studies. All reviewed articles were then manually cross-referenced to ensure that all potential studies were included.

The abstracts that resulted from these searches were reviewed by 2 of the authors (K.A.C. and R.M.). The inclusion criteria were meta-analyses that compared the use of IA-HA in knee OA with the use of IA-placebo, IA-PRP, IA-corticosteroids, or oral NSAIDs. Cadaveric, animal, and biomechanical studies were excluded. The exclusion criteria included narrative reviews, reviews without an organized and reported search algorithm, reviews that did not directly compare IA-HA versus another treatment modality, studies without clinical outcome data, and non−English-language studies. Systematic reviews that did not pool data or perform a meta-analysis were also excluded. Full-text articles were then obtained for those studies that met both the inclusion and exclusion criteria. The references for each of these citations were manually screened to ensure that no studies were missed. The tables of contents for the past 2 years of *Arthroscopy*, *The Journal of Bone and Joint Surgery*, *The American Journal of Sports Medicine*, *Clinical Orthopaedics and Related Research*, *Osteoarthritis and Cartilage*, and *The New England Journal of Medicine* were manually searched for any additional studies that were not identified in our prior search. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram shows our study selection algorithm (Fig 1).

Data were extracted from the studies that met the inclusion criteria and included information about levels of evidence included in the studies, length of follow-up, duration of symptomatic relief, adverse events, knee function, knee pain outcomes, and pooled effect size. Standardized outcome scores that were collected included Lequesne scores, visual analog scale (VAS) pain scores, and Western Ontario and McMaster Universities Osteoarthritis Index pain subscores. Data specific to the methodology of the included meta-analyses

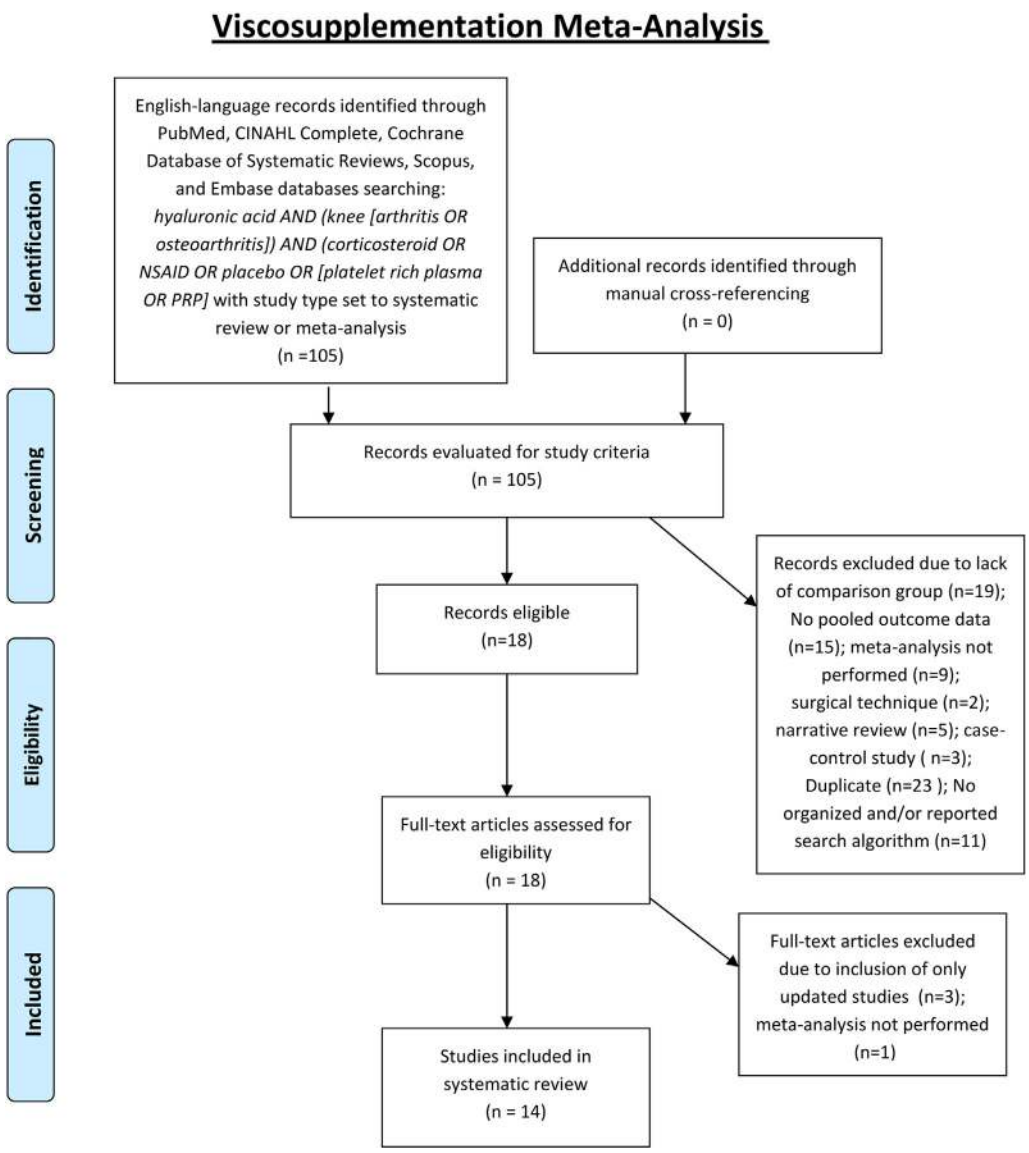

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the results of application of the study algorithm to the number of studies included, with the number of studies removed after application of each exclusion criterion. (NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.)

were extracted and included the rationale for repeating the systematic review, the databases that were used for the review, a comparison of the number of "possible" previous systematic reviews cited versus the number that were actually cited in the study, and the conclusions of the review regarding whether IA-HA was more clinically effective than the treatment modality with which it was compared in terms of pain relief and adverse events.

Meta-analysis quality was scored using the Quality of Reporting of Meta-analyses (QUOROM) system.[12] This system provides a method for evaluating meta-analyses based on the quality of their reporting and methodology in 18 categories. Each meta-analysis was awarded a point in each category if it met over half of the criteria given in that category, for a total of 18 points possible. Meta-analysis quality was also graded using the Oxman-Guyatt quality-appraisal tool.[13] The modified Coleman Methodology Score[14] was extracted from individual studies when available. In addition, when known biases within the literature were reported by individual trials, these were recorded.

The Jadad decision algorithm[15] was used to guide interpretation of discordant reviews. Sources of discordance among meta-analyses as described by Jadad et al.[15] include differences in the clinical question, inclusion/exclusion criteria, data pooling, data extraction, quality assessment, and statistical analysis. Scoring was performed based on the assessment of randomization, randomization methodology, double blinding, withdrawals or dropouts from the study, and allocation concealment. This algorithm was independently applied by 3 of the authors, and their results were compared to determine which of the included systematic reviews provided the best current evidence to make recommendations (K.A.C., B.M.S., R.M.). All statistical

analyses were performed with the use of Microsoft Excel X (Microsoft, Redmond, WA).

Results

The initial search yielded 105 abstracts, and after application of the study selection algorithm, 14 studies fulfilled our inclusion and exclusion criteria and were included (Fig 1). These studies were published between 2003 and 2014, with all 14 performing a meta-analysis. Industry funding for the studies was provided to 4 of the 14 included meta-analyses,[16-19] which introduces the possibility of a conflict of interest.

Of the studies, 7 included Level I evidence,[11,17,18,20-23] 4 included Level I and Level II evidence,[10,19,24,25] 1 included Level II and Level III evidence,[26] and 2 included Level I and Level IV evidence.[16,27] The number of included patients ranged from 606 patients[23] to 12,667 patients,[25] with mean follow-up periods ranging from 3 weeks[21] to 135.2 weeks.[16] In studies that reported the number of patients in each group, there were a total of 20,049 patients: 13,698 receiving IA-HA, 355 receiving NSAIDs, 294 receiving IA-corticosteroids, and 5,702 receiving IA-placebo.

Authors' Assessment of Prior Systematic Review Literature

The majority of the included studies only cited a few of the available pre-existing meta-analyses or systematic reviews (Table 1), with only 7 of 14 studies citing more than 50% of prior systematic reviews or meta-analyses.[10,11,19,21-23,25] None of the studies cited all of the previous systematic reviews that were available at the time of publication. Eleven of the 14 studies provided a rationale for repeating the systematic review (Tables 1 and 2), with several of them highlighting the discordant findings of prior meta-analyses as the rationale for repeating the study.[17,22] The remaining studies cited either differing methodologies,[19,22] the inclusion of other outcome variables,[10,18,20] or a comparison with other treatments as their rationale.[11,21,23,27] Appendix Table 1 (available at www.arthroscopyjournal.org) provides a list of the primary studies used in each meta-analysis.

Outcome Measures

The included studies were heterogeneous in both the standardized and nonstandardized patient outcome measures that were reported (Appendix Table 2, available at www.arthroscopyjournal.org). There was a high level of variance seen in the mean differences in VAS scores (on a 100-mm VAS) for IA-HA versus IA-placebo. The studies by Arrich et al.[10] and Modawal et al.,[20] in which the mean differences ranged from −3.8 to 18.1, highlight these differences. In terms of a weighted mean difference between the efficacy of IA-HA and intra-articular saline solution, a value of just 10.20 using the VAS was found at 3 months' follow-up,[18] whereas standardized mean difference (SMD) values representing only a small (SMD <0.5) effect on knee pain were found at follow-up.[19,24] For reference, the SMD values of 0.2, 0.5, 0.8, and 1.0 are defined as small, medium, large, and very large, respectively.[28]

When IA-HA was compared with IA-placebo, the patient-reported mean percent improvement in pain from baseline at the 5- to 13-week post-injection time point ranged from 28% to 54% whereas the mean percent improvement in function ranged from 9% to 32%.[22] In terms of the effect size for IA-HA versus NSAIDs, no clinically relevant differences were found between the 2 treatments.[11,16] IA-PRP was found to have a greater pooled effect size regarding knee function (when pooled using a random-effects model) compared with IA-HA at both 2 months and 6 months after injection. This effect was maintained for up to 1 year.[27]

The included studies were also heterogeneous with respect to their method of analysis of the response to treatment with IA-HA. Some studies reported on pain outcome scores and knee function, whereas others reported on knee range of motion, activity-related knee pain, pooled effect size, VAS pain score, Lequesne score, Western Ontario and McMaster Universities Osteoarthritis Index score, or adverse reactions (Appendix Table 3, available at www.arthroscopyjournal.org).

Search Methodology

Although 13 of the 14 included studies searched PubMed/Medline, there was heterogeneity in the other databases that were used. These included Embase, the Cochrane Database of Systematic Reviews, and the CINAHL among others. One study did not identify the databases used in the search.[17] Ten of the included studies used the Embase or Cochrane Database of Systematic Reviews (or both) to find articles. Three studies used the CINAHL database,[10,21,23] and all studies that reported their search strategy searched at least 3 databases (Table 2). The total number of unique primary studies cited by the included systematic reviews was 107. The number of primary studies varied widely from 5 in those reviews performed in 2006 and 2014[11,17] to 89 in a study published in 2012,[25] with a median of 18 primary studies cited (Table 2 and Appendix Table 1 [available at www.arthroscopyjournal.org]).

Study Results

IA-HA Versus IA-Placebo. Of the 10 studies that examined the effects of IA-HA versus IA-placebo, 5 found that IA-HA resulted in improvements in pain and 4 found that it resulted in improvements in function. However, 3 meta-analyses found no difference between IA-HA and IA-placebo in terms of pain, and

Table 1. Number of Prior Systematic Reviews or Meta-analyses Actually Cited as Compared With Maximum Number That Could Possibly Have Been Cited, in Addition to Authors' Rationale for Repeating Systematic Review

Authors	Date of Publication (Month/Day/Year)	Date of Last Literature Search (Month/Day/Year)	No. of Systematic Reviews or Meta-analyses Possible to Cite	No. of Systematic Reviews or Meta-analyses Cited	Rationale for Repeating Meta-analysis as Abstracted From Article
Espallargues and Pons[16]	1/—/2003	—/—/1999	0	0	NA
Lo et al.[24]	12/17/2003	2/—/2003	1	0	NA
Wang et al.[26]	3/—/2004	12/—/2001	0	0	NA
Arrich et al.[10]	4/12/2005	4/—/2004	3	2	"In contrast to 2 previous meta-analyses on this subject, we used a different approach to data synthesis and interpretation: instead of analyzing a composite effect size over time, we allocated trial data, when possible, to 3 outcome groups that we assumed would be relevant for patients with osteoarthritis. We specifically looked at pain at rest, pain during exercise and joint function as distinct outcomes, measured repeatedly over time. In addition, we assessed adverse events and the impact of both trial quality and molecular mass of the product. This analysis allows us to provide important additional insight into the effects of intra-articular administration of hyaluronic acid for the treatment of osteoarthritis of the knee."
Modawal et al.[20]	9/—/2005	8/—/2004	3	1	"We provide here a stringent test of the efficacy of viscosupplementation for relieving knee pain from osteoarthritis with a meta-analysis that includes only data from randomized, double-blinded, controlled trials of hyaluronic acid that measured pain using a visual analogue scale (VAS), the most widely accepted method for pain evaluation."
Strand et al.[17]	—/—/2006	NA	5	2	"Divergent interpretations from 3 recent meta-analyses have added to this controversy . . . To supplement evidence provided by recent meta-analyses of IA-HA treatment, an integrated analysis of five RCTs examining a single IA-HA product is presented … This provides a comparison that avoids some limitations inherent to meta-analyses, because it circumvents the need for any type of data transformation."
Reichenbach et al.[21]	12/15/2007	11/—/2006	6	4	"All of these studies compared hyaluronic acid and hylan with a sham intervention, but only one study included trials comparing hylan with hyaluronic acids directly … heterogeneity of the studies limited conclusions … did not pool results of included trials … The safety of hylan compared with conventional hyaluronic acids was rarely addressed … but sample sizes of included trials precluded any definitive conclusions … Previous claims that hylan has greater benefits compared with conventional preparations of hyaluronic acids were mainly based on implicit indirect comparisons from placebo-controlled trials."
Bellamy et al.[22]	—/—/2009 (update—original 4/19/2006)	1/—/2006	6	5	"These publications employ different methodologies and have shown conflicting results … but they recommended further work on the effect of multiple courses of hylan … Given this diversity of opinion there is, therefore, a rational basis for performing a Cochrane review of viscosupplementation in knee OA."

(continued)

Table 1. Continued

Authors	Date of Publication (Month/Day/Year)	Date of Last Literature Search (Month/Day/Year)	No. of Systematic Reviews or Meta-analyses Possible to Cite	No. of Systematic Reviews or Meta-analyses Cited	Rationale for Repeating Meta-analysis as Abstracted From Article
Bannuru et al.[23] (2009)	12/15/2009	2/—/2009	8	5	"However, the conclusions of meta-analyses were also inconsistent … In the face of this controversy, we aimed to reexamine the clinical usefulness of HA products from the perspective of their relative efficacy when compared with intraarticular corticosteroids, a widely used intervention with which clinical rheumatologists have considerable familiarity."
Rutjes et al.[25]	6/12/2012	1/31/2012	9	7	"Several trials have since been published [since previous reviews]. In addition, we were aware of unpublished trials, which were never included in any meta-analysis to date. Therefore, we did a comprehensive, up-to-date systematic review to determine whether viscosupplementation is clinically effective and safe to treat symptomatic knee OA."
Colen et al.[18]	8/1/2012	6/27/2011	9	4	"In this systematic review we will compare the efficacy of intra-articularly administered HA with intra-articularly administered placebo in randomized controlled trials (RCTs) using the visual analog scale (VAS) for pain as a primary outcome measurement at 3-months follow-up. Using this approach we make some recommendations concerning the efficacy of HA compared with the effects of placebo and discuss the differences in efficacy between the different HA products and the differences between the different HA products and placebo."
Miller and Block[19]	9/1/2013	6/—/2013	11	8	"In contrast, we only included data from full-text manuscripts published in peer-reviewed journals. Lastly, Rutjes et al analyzed all safety data using an odds ratio, a statistic that excludes zero total event trials. Considering that 30 of 38 SAE treatment effects in the current meta-analysis reported zero total events, the odds ratio is arguably an inappropriate statistic for this type of analysis since most data are disregarded."
Chang et al.[27]	3/—/2014	9/—/2013	12	4	"However, to our knowledge, no meta-analytic research has quantified the effectiveness of PRP treatment and analyzed the factors that modify the outcomes. Therefore, we undertook a systematic review and meta-analysis to investigate the clinical results in patients with knee chondral degenerative lesions, with regard to functional changes, compared with the pretreatment condition, after PRP injections, placebo controls, and HA administration."
Bannuru et al.[11] (2014)	4/—/2014	4/—/2013	13	9	"Several meta-analyses have examined the effects of IA-HA in the treatment of knee OA compared with placebo and with intra-articularly injected corticosteroids and found inconclusive results … Although NSAIDs are among the most efficacious and widely used treatments for knee OA, no meta-analysis has been performed to assess these medications against IA-HA, which is considered to have a more favorable safety profile. The objectives of this study were to systematically evaluate the relative efficacy of IA-HA for symptomatic knee OA in comparison with NSAIDs."

HA, hyaluronic acid; IA-HA, intra-articular hyaluronic acid; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PRP, platelet-rick plasma; RCTs, randomized controlled trials; SAE, serious adverse event.

Table 2. Search Methodology Used by Included Studies

Authors	Database						No. of Primary Studies	Primary Studies Included Only RCTs
	PubMed/ Medline	Embase	Cochrane Library	CINAHL	Science Citation Index	Other		
Espallargues and Pons[16]	+	+	+	−	−	+	14	−
Lo et al.[24]	+	−	+	−	−	+	22	+
Wang et al.[26]	+	+	+	−	−	+	20	+
Arrich et al.[10]	+	+	+	+	−	+	22	+
Modawal et al.[20]	+	−	−	−	−	−	9 (11 comparable cohorts)	+
Strand et al.[17]	NR	NR	NR	NR	NR	NR	5	+
Reichenbach et al.[21]	+	+	−	+	+	+	13 (15 comparable cohorts)	+
Bellamy et al.[22]	+	+	+	−	−	+	76	−
Bannuru et al.[23] (2009)	+	+	+	+	−	+	7	+
Rutjes et al.[25]	+	+	+	−	+	+	89	−
Colen et al.[18]	+	+	+	−	−	−	74	+
Miller and Block[19]	+	+	−	−	−	−	29	+
Chang et al.[27]	+	−	+	−	−	+	16	−
Bannuru et al.[11] (2014)	+	+	+	−	−	+	5	+

CINAHL, Cumulative Index to Nursing and Allied Health Literature; Embase, Excerpta Medica Database; Medline, Medical Literature Analysis and Retrieval System Online; RCTs, randomized controlled trials; NR, not recorded.

4 studies found no difference in function. The remaining studies showed no clinically relevant differences in either pain or function.[10,16-20,22,24-26]

IA-HA Versus Oral NSAIDs. No clinically relevant differences in the efficacy of IA-HA versus oral NSAIDs on knee pain and function were found in the 3 studies that examined it. However, IA-HA was found to have a slightly more favorable adverse reaction profile than NSAIDs because of the risk of gastrointestinal side effects posed by NSAIDs.[11,16,22] Although both IA-HA and IA-PRP led to improvements in knee function at 2 and 6 months after injection, the positive effects of IA-HA were less robust than those of IA-PRP and there were no differences in adverse reactions.[27]

IA-HA Versus IA-Corticosteroids. IA-corticosteroids provided better pain relief during the first 4 weeks after injection, but the positive effects of IA-HA were greatest at the 5- to 13-week post-injection time point, and this relief persisted for up to 26 weeks in 2 studies.[22,23] No definitive conclusions could be drawn about the best HA product in the studies that compared the different formulations of HA products.[16,18,21,22] In 1 study comparing IA-HA versus intra-articular hylan,[21] the authors discouraged the use of intra-articular hylan because of the increased risk of adverse reactions and their finding of no clinically relevant evidence to support its use.

Study Quality and Validity

The QUOROM scores were assessed for each of the studies and ranged from 11[16] to 17,[22,27] with a median of 15.5 (with the maximum possible score being 18). The Oxman-Guyatt scores ranged from 3[16] to 7[22,27] on a scale from 1 to 7, with a median score of 5. As a reference, Oxman-Guyatt scores lower than 3 are generally considered to indicate that the study in question has "major flaws."[13]

Heterogeneity Assessment

Several methods were used to assess study heterogeneity, and 12 of the 14 included studies performed a statistical heterogeneity analysis.[10,11,18-27] Several performed subgroup analyses assessing parameters such as pain outcomes, physical function, pain by VAS score, pain at rest, pain with activities, and major adverse effects (Appendix Table 2, available at www.arthroscopyjournal.org). Given the heterogeneity in the variables examined, treatment time point assessed, and overall findings of the subgroup analyses that were performed, it was found that the 2 highest-quality studies[22,27] provided the best available evidence about the use of IA-HA in knee arthritis.

Application of Jadad Decision Algorithm

The Jadad decision algorithm was applied to determine which of the 14 included meta-analyses provided the best available current evidence for treatment recommendations in patients with knee OA. The 3 authors applying the Jadad algorithm independently selected the same route through the Jadad decision algorithm. Given that (1) all of the meta-analyses did not address the same study question, (2) our reviews did not include the same primary trials (Table 2 and Appendix Table 1 [available at www.arthroscopyjournal.org]), and (3) our reviews did not have the same selection criteria, the Jadad algorithm suggests that the highest-quality review can be selected based on the publication characteristics of the primary trials, the methodology of the primary trials, the language restrictions, and whether an analysis of data on individual patients was included in the study. The last 2 criteria do

not apply to this study. With respect to publication status, several newer meta-analyses included multiple newly available trials, which may explain some of the discordance in the results and conclusions that were drawn. Regarding the methodology of primary trials, those reviews that included only Level I evidence included trials of superior methodology. Use of the aforementioned criteria facilitated the selection of 2 high-quality meta-analyses with results that represent the best available current evidence.[22,27] These studies were not industry sponsored and concluded that IA-HA leads to improvement in knee pain and function in patients with knee OA versus IA-placebo. The positive effects of IA-HA versus IA-corticosteroids were greatest at 5 to 13 weeks after injection, and this effect persisted for up to 26 weeks after injection. No clinically relevant differences in the efficacy of IA-HA versus oral NSAIDs on knee pain and function were found, but consideration should be given for IA-HA use in patients with knee OA who are unable to tolerate NSAIDs. Although IA-HA leads to improved knee function at 2 and 6 months' follow-up, IA-PRP leads to greater improvements. No definitive conclusions could be drawn about the best HA product in the studies that compared the different formulations of HA products. Overall, the best available evidence in the literature supports the use of the HA class of products in the treatment of knee OA.

Discussion

This systematic review of overlapping meta-analyses found that intra-articular viscosupplementation is a safe and viable treatment option for knee OA with effects that can last up to 26 weeks. Given the high prevalence of knee OA, there have been multiple clinical trials, systematic reviews, and meta-analyses that have attempted to determine the best nonoperative treatment for this condition.[9] However, a clear gold standard has not been identified. Therefore the main purposes of this systematic review of overlapping meta-analyses were to determine the source of discordance between the various meta-analyses and to determine which studies provided the best available current evidence on nonoperative treatment of knee OA. A critical inspection and assessment of the quality of the 14 included meta-analyses using the QUOROM and Oxman-Guyatt guidelines were undertaken to explore the best nonoperative treatment for knee OA. The included meta-analyses used studies of varied levels of evidence including 7 studies with Level I evidence,[11,17,18,20-23] 4 with Level I and Level II evidence,[10,19,24,25] 1 with Level II and Level III evidence,[26] and 2 with Level I and Level IV evidence.[16,27] On the basis of the best available current evidence, the hypothesis that IA-HA provides significant improvement in pain and function with a minimal side-effect profile in the treatment of knee OA was confirmed.

With the changing health care environment, more emphasis has been placed on evidence-based medicine to determine the efficacy and cost-effectiveness of treatments to direct clinical practice guidelines. As such, it is important to identify the best evidence surrounding a particular treatment because there are a multitude of low-level studies with varying results on many different treatment modalities. The topic of nonoperative treatment for knee OA is extremely important because the number of patients with knee OA continues to grow.[9] To minimize knee pain and functional limitations while delaying knee replacement, several nonsurgical options have been implemented, which include IA-HA, IA-corticosteroid injections, oral NSAIDs, and IA-PRP. Although each treatment has proved to relieve pain and improve function on its own, the question remains as to which treatment is superior in eliminating pain and improving function while providing a favorable side-effect profile. In this study we have determined that the highest level of evidence currently available supports the use of intra-articular viscosupplementation for the treatment of patients with knee OA.

The available evidence shows that IA-HA provides small but clinically relevant improvements in knee pain and function when compared with IA-placebo.[10,16-20,22,24-26] Furthermore, although there were no major clinical differences in the efficacy of IA-HA versus oral NSAIDs in relieving knee pain and restoring function, the fact that IA-HA has a more favorable side-effect profile than oral NSAIDs makes IA-HA a good option for patients unable to tolerate oral NSAIDs.[11,16,22] Both IA-HA and IA-corticosteroids were effective in controlling pain, with steroids providing better short-term relief and HA providing more long-term pain relief starting in the 5- to 13-week post-injection period and lasting for up to 26 weeks.[22,23] Although the effects of IA-PRP were greater than those of IA-HA in terms of knee function at 2 and 6 months after injection,[27] the fact that platelet-rich plasma (PRP) is not currently reimbursed by insurance companies limits its availability. Treatment with PRP is cost prohibitive for most patients, and in light of the good outcomes achieved with IA-HA in terms of pain and function, IA-HA may be a better treatment option. Furthermore, more high-quality randomized, double-blinded studies are needed to compare the effects of PRP versus other treatments before it can be fully endorsed as a viable universal option for patients with knee OA.

The recommendations from the recent American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline on the non-arthroplasty treatment of knee OA[29] highlights the need for more robust Level I evidence studies on all the aforementioned treatment modalities. Of the treatments investigated in this systematic review, oral NSAIDs were the only treatment modality recommended with a "strong" strength of

recommendation. The AAOS did not recommend the use of HA for patients with symptomatic OA of the knee and graded the strength of this recommendation as strong. The rationale for this rating was based on the fact that although statistically significant outcomes were seen in some studies, those outcomes were not clinically significant, based on a lack of minimum clinically important improvement—defined as the smallest clinical change that would be important to a patient—while also accounting for the fact that there are some statistically significant treatment-related improvements that may be too small to be clinically relevant, despite the fact that they are statistically significant. Similarly, the AAOS was unable to recommend for or against the use of IA-corticosteroids or IA-PRP and rated this recommendation as "inconclusive."[29] Interestingly, Bannuru et al.[30] highlighted that the AAOS clinical practice guideline's use of the minimum clinically important improvement metric may have contained some flaws, so despite the fact that IA-HA was not recommended based on this metric, the best available current evidence suggests that patients may still obtain some benefit from IA-HA use for knee OA. This discrepancy again highlights the need for more high-quality Level I studies exploring the different nonoperative treatment modalities for managing patients with knee OA, as well as the need for more studies on the use of the minimum clinically important improvement metric for these modalities.

The strengths of this study lie in the use of validated quality-assessment tools[12,13,15] to critically appraise the studies included in our review. The use of these tools combined with their application in independent quality assessment by 3 authors with consensus agreement adds support to our main findings that intra-articular viscosupplementation is a viable treatment option for patients with knee OA.

Limitations

Similar to many of the studies that have been included in this review, there are some inherent limitations to our study. One of the major limitations is the fact that the quality of this systematic review is limited by the quality of the studies that were included in prior studies. As such, despite the fact that most of the included studies used data from Level I and Level II studies, the inclusion of Level IV evidence by 2 meta-analyses makes this a Level IV study by default. However, the findings should not be discredited because the conclusions of this study were based on 2 Level I studies.[22,27]

Another limitation lies in the presence of heterogeneity in terms of the number of patients included in the studies, the type of interventions compared, the outcome measures collected, the type of subgroup analysis performed, and the use of the pooled effect size. In addition, the relatively short follow-up periods that were reported in some of the studies are a limiting factor, and little is known about the long-term effects of the described interventions on patients with knee OA. In this study the mean follow-up periods ranged from 3 weeks[21] to 135.2 weeks,[16] but most of the available outcome data regarding the impact of IA-HA on knee pain and function were only available for patients in the 2- to 3-month time period, with even fewer data available for 1 year. This lack of long-term data highlights the fact that more high-quality studies are needed to definitively determine how effective viscosupplementation is for patients with knee OA in the long-term.

Conclusions

According to this systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA, the current highest level of evidence suggests that IA-HA is a viable option for patients with knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks in comparison with other treatment modalities. IA-HA has been shown to have a good safety profile, and its use should be considered in patients with early knee OA.

References

1. MacDonald KV, Sanmartin C, Langlois K, Marshall DA. Symptom onset, diagnosis and management of osteoarthritis. *Health Rep* 2014;25:10-17.
2. Marks R. Perceived health status of women with knee osteoarthritis: A cross-sectional study of the relationships of age, body mass, pain and walking limitations. *Open Orthop J* 2014;8:255-263.
3. Balazs EA. Viscosupplementation for treatment of osteoarthritis: From initial discovery to current status and results. *Surg Technol Int* 2004;12:278-289.
4. Schlueter-Brust K, Kugland K, Stein G, et al. Ten year survivorship after cemented and uncemented medial Uniglide unicompartmental knee arthroplasties. *Knee* 2014;21:964-970.
5. Gudnason A, Hailer NP, W-Dahl A, Sundberg M, Robertsson O. All-polyethylene versus metal-backed tibial components—An analysis of 27,733 cruciate-retaining total knee replacements from the Swedish Knee Arthroplasty Register. *J Bone Joint Surg Am* 2014;96:994-999.
6. Mont MA, Pivec R, Issa K, Kapadia BH, Maheshwari A, Harwin SF. Long-term implant survivorship of cementless total knee arthroplasty: A systematic review of the literature and meta-analysis. *J Knee Surg* 2014;27:369-376.
7. Patil S, McCauley JC, Pulido P, Colwell CW Jr. How do knee implants perform past the second decade? Nineteen- to 25-year followup of the press-fit condylar design TKA. *Clin Orthop Relat Res* 2015;473:135-140.
8. Sabouret P, Lavoie F, Cloutier JM. Total knee replacement with retention of both cruciate ligaments: A 22-year follow-up study. *Bone Joint J* 2013;95-B:917-922.

9. Weinstein AM, Rome BN, Reichmann WM, et al. Estimating the burden of total knee replacement in the United States. *J Bone Joint Surg Am* 2013;95:385-392.
10. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: Systematic review and meta-analysis. *CMAJ* 2005;172:1039-1043.
11. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;43:593-599.
12. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896-1900.
13. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;44: 1271-1278.
14. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: Clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. *Scand J Med Sci Sports* 2000;10:2-11.
15. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *CMAJ* 1997;156: 1411-1416.
16. Espallargues M, Pons JM. Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: A systematic review. *Int J Technol Assess Health Care* 2003;19:41-56.
17. Strand V, Conaghan PG, Lohmander LS, et al. An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee. *Osteoarthritis Cartilage* 2006;14: 859-866.
18. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: A systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs* 2012;26: 257-268.
19. Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: Systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord* 2013;6:57-63.
20. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. *J Fam Pract* 2005;54:758-767.
21. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: A systematic review and meta-analysis. *Arthritis Rheum* 2007;57: 1410-1418.
22. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006;(2):CD005321.
23. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Rheum* 2009;61:1704-1711.
24. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: A meta-analysis. *JAMA* 2003;290:3115-3121.
25. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: A systematic review and meta-analysis. *Ann Intern Med* 2012;157:180-191.
26. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004;86:538-545.
27. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: A systematic review and meta-analysis. *Arch Phys Med Rehab* 2014;95:562-575.
28. Cohen J. *Statistical power analysis for the behavioral sciences*. Hillside, NJ: Lawrence Erlbaum Associates, 1987.
29. Jevsevar DS, Brown GA, Jones DL, et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on: Treatment of osteoarthritis of the knee:2nd edition. *J Bone Joint Surg Am* 2013;95: 1885-1886.
30. Bannuru RR, Vaysbrot EE, McIntyre LF. Did the American Academy of Orthopaedic Surgeons osteoarthritis guidelines miss the mark? *Arthroscopy* 2014;30:86-89.

Appendix Table 1. Primary Studies Included in Meta-analysis

Primary Study	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Adams, 1995	+	−	+	−	−	−	−	+	−	−	+	−	−	+
Altman, 1998	−	+	−	+	+	−	−	+	−	+	+	+	−	+
Altman, 2004	−	−	−	−	−	−	−	+	−	+	+	−	−	−
Altman, 2009	−	−	−	−	−	−	−	−	−	+	+	+	−	−
Anika, 2000	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Anika, 2001	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Ardic, 2001	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Atamaz, 2004	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Atamaz, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Atamaz, 2006	−	−	−	−	−	−	+	−	−	−	+	−	−	−
Atay, 2008	−	−	−	−	−	−	−	−	−	+	+	−	−	−
Auerbach, 2002	−	−	−	−	−	−	−	+	−	−	+	−	−	−
Bach, 1997	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Baltzer, 2009	−	−	−	−	−	−	−	−	−	+	+	−	−	−
Baraf, 2009	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Bayramoglu, 2003	−	−	−	−	−	−	+	+	−	+	+	−	−	−
Beks, 1997	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Bellamy, 2005	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Blanco, 2008	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Bragantini, 1987	−	−	+	+	−	−	−	+	−	+	+	+	−	−
Brandt, 2001	−	+	+	+	−	−	−	+	−	−	+	+	−	−
Brown, 2003	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Bunyaratavej, 2001	−	−	−	+	−	−	−	+	−	+	−	+	−	−
Butun, 2002	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Caborn, 2003	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Caborn, 2004	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Caracuel, 2001	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Carrabba, 1995	−	+	+	+	−	−	−	+	−	+	+	+	−	−
Cerza, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Chevalier, 2010	−	−	−	−	−	−	−	−	−	+	+	−	−	−
Chou, 2009	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Cogalgil, 2002	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Cohen, 1994	−	+	+	−	−	−	−	+	−	+	−	−	−	−
Conrozier, 2009	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Corrado, 1995	−	+	+	+	−	−	−	+	−	+	+	−	−	−
Creamer, 1994	−	+	+	−	−	−	−	+	−	+	+	−	−	−
Cubukcu, 2004	−	−	−	−	−	−	−	+	−	−	−	+	−	−
Cubukcu, 2005	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Dahlberg, 1994	−	+	−	+	−	−	−	−	−	−	+	−	−	−
Day, 2001	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Day, 2004	−	−	−	+	−	+	−	+	−	+	+	+	−	−
DeCaria, 2012	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Dickson, 1998	+	−	+	−	−	−	−	−	−	−	−	−	−	−
Dickson, 2001	−	−	−	−	−	−	−	+	−	+	−	−	−	+
Diracoglu, 2009	−	−	−	−	−	−	−	−	−	+	+	+	−	−

(continued)

Appendix Table 1. Continued

Primary Study	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Dixon, 1988	−	+	+	+	−	−	−	+	−	+	+	−	−	−
Dougados, 1993	−	+	+	+	−	−	−	+	−	+	+	−	−	−
Esteve de Miguel, 1995	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Filardo, 2011	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Filardo, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Filardo, 2012a	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Formiguera, 1995	−	−	+	−	−	−	−	+	−	+	−	−	−	−
Forster, 2003	−	−	−	−	−	−	−	+	−	−	+	−	−	−
Frizziero, 2002	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Garcia, 2004	−	−	−	−	−	−	+	−	−	−	−	−	−	−
Genzyme, 2005	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Ghirardini, 1990	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Gobbi, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Graf, 1993	−	−	−	−	−	−	−	+	−	−	+	−	−	−
Graf von der Schulenburg, 1997	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Grecomoro, 1987	−	−	+	+	+	−	−	+	−	+	+	+	−	−
Groppa, 2001	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Groppa, 2004	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Guler, 1996	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Halpern, 2013	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Henderson, 1994	−	+	+	+	+	−	−	+	−	+	+	+	−	−
Heybeli, 2008	−	−	−	−	−	−	−	−	−	+	+	−	−	−
Hizmetli, 1999	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Hizmetli, 2002	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Huang, 2005	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Huang, 2011	−	−	−	−	−	−	−	−	−	+	−	+	−	−
Huskisson, 1999	−	+	+	+	+	−	−	+	−	+	+	+	−	−
Isdale, 1993	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Ishjima, 2012	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Jang, 2013	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Jones, 1995	−	−	−	−	−	−	−	+	+	−	−	−	−	−
Jorgensen, 2010	−	−	−	−	−	−	−	−	−	+	+	+	−	−
Jubb, 2001	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Jubb, 2003	−	+	−	+	−	−	−	+	−	+	+	+	−	−
Juni, 2007	−	−	−	−	−	−	+	−	−	−	+	−	−	−
Kahan, 2001	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Kahan, 2003	−	−	−	−	−	−	−	+	−	+	+	−	−	−
Kalay, 1997	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Karatay, 2004	−	−	−	−	−	−	+	+	−	−	−	−	−	−
Karatay, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Karatosun, 2005	−	−	−	−	−	−	+	+	−	−	+	−	−	−
Karlsson, 1999	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Karlsson, 2002	−	+	−	+	−	−	+	+	−	+	+	+	−	−
Karlsson, 2003	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Karras, 2001	−	−	−	−	−	−	−	+	−	−	−	−	−	−

(continued)

Appendix Table 1. Continued

Primary Study	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Kawabata, 1993	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Kawasaki, 2009	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Kirchner, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Kirchner, 2006	−	−	−	−	−	−	+	+	−	−	+	−	−	−
Kon, 2010	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Kon, 2011	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Kosuwon, 2010	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Kotevoglu, 2002	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Kotevoglu, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Kotevoglu, 2006	−	−	−	−	−	−	+	−	−	+	+	+	−	−
Kul-Panza, 2010	−	−	−	−	−	−	−	−	−	+	+	+	−	−
Lanzer, 2002	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Leardini, 1987	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Leardini, 1991	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Lee, 2006	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Lee, 2011	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Leopold, 2003	−	−	−	−	−	−	−	+	−	−	+	−	−	−
Li, 2011	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Lin, 2004	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Listrat, 1997	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Lohmander, 1996	−	+	+	+	+	+	−	+	−	+	+	+	−	−
Lundsgaard, 2008	−	−	−	−	−	−	−	−	−	+	+	+	−	−
Lussier, 1996	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Marshall, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
McDonald, 2000	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Miller, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Miltner, 2002	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Moreland, 1993	+	−	−	−	−	−	−	+	−	+	−	−	−	−
Nahler, 1996	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Nahler, 1998	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Napolitano, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Navarro-Sarabia, 2011	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Neustadt, 2004	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Neustadt, 2005	−	−	−	−	−	−	−	+	−	−	+	−	−	−
O'Hanlon, 1995	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Onel, 2008	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Ozturk, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Ozturk, 2006	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Patel, 2013	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Patrella, 2002	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Pavelka, 2010	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Payne, 2000	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Pedersen, 1993	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Petrella, 2002	−	+	−	+	+	−	−	+	−	+	−	−	−	+
Petrella, 2006	−	−	−	−	−	−	−	−	−	+	+	−	−	−

(continued)

Appendix Table 1. Continued

Primary Study	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Petrella, 2008	−	−	−	−	−	−	−	−	−	+	+	+	−	−
Petrella, 2009	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Pham, 2003	−	+	−	−	−	−	−	+	−	−	−	−	−	−
Pham, 2004	−	−	−	−	−	−	−	+	−	+	+	−	−	−
Pietrogrande, 1991	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Puhl, 1993	−	+	+	+	+	+	−	+	−	+	+	+	−	−
Puttick, 1995	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Raman, 2006	−	−	−	−	−	−	+	−	−	−	−	−	−	−
Raman, 2008	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Raynauld, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Raynauld, 2002	−	−	−	−	−	−	−	+	−	+	+	−	−	−
Raynauld, 2005	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Redd, 2003	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Rejaili, 2005	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Renklitepe, 2000	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Rolf, 2005	−	−	−	−	−	−	+	−	−	−	−	+	−	−
Roman, 2000	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Russell, 1992	−	+	−	+	−	−	−	−	−	+	−	−	−	−
Rydell, 1972	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Sala, 1995	−	+	−	+	−	−	−	−	−	−	−	+	−	−
Sampson, 2011	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Sanchez, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Sanofi-Aventis, 2010	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Saravanan, 2002	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Scale, 1994	+	+	+	+	+	−	−	+	−	+	+	+	−	−
Schneider, 1997	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Seikagaku, 2001	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Seikagaku, 2001a	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Sezgin, 2005	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Shichikawa, 1983	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Shichikawa, 1983a	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Shimizu, 2010	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Skwara, 2009	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Skwara, 2009a	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Spakova, 2012	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Sripada, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Stittik, 2007	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Strand, 2012	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Tamir, 2001	−	+	+	+	−	−	−	+	−	+	+	−	−	−
Tascioglu, 2003	−	−	−	−	−	−	−	+	+	−	+	−	−	−
Tekeoglu, 1998	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Tetik, 2003	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Thompson, 2002	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Torrance, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Tsai, 2003	−	−	−	−	−	−	−	+	−	+	−	−	−	−

(continued)

Appendix Table 1. Continued

Primary Study	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Tsukamoto, 1995	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Ulucay, 2007	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Vanelli, 2010	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Wang-Saegusa, 2011	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Weiss, 1981	−	−	−	−	−	−	−	−	−	+	+	−	−	−
Weiss, 1981a	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Weiss, 1999	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Westrich, 2009	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Wobig, 1998	+	+	+	+	+	−	−	+	−	+	+	+	−	−
Wobig, 1999	−	−	−	−	−	−	+	+	−	−	+	−	−	−
Wu, 1997	−	−	+	+	−	−	−	+	−	+	−	−	−	−
Wu, 2004	−	−	−	−	−	−	−	+	−	+	−	+	−	−
Yamamoto, 1994	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Yentur, 2003	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Zhou, 2000	−	−	−	−	−	−	+	−	−	−	−	−	−	−

NOTE. The designation "a" after the date of a primary study indicates a separate study from the same author and the same calendar year.

Appendix Table 2. Heterogeneity or Subgroup Analyses of Primary Studies

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Statistical heterogeneity analysis	−	+	+	+	+	−	+	+	+	+	+	+	+	+
Subgroup or statistical analysis														
Pooled effect size, IA-HA *v* IA-placebo: after removal of highest-MW formulation HA		+												
Pain outcome, IA-HA *v* IA-placebo: in large trials										+				
Pain outcome, IA-HA *v* IA-placebo: in unpublished trials										+				
Pain outcome, IA-HA *v* IA-placebo: in blinding of outcome										+				
Pain outcome, IA-HA *v* IA-placebo: in large trials with blinding of outcome										+				
Physical function, IA-HA *v* IA-placebo: in large trials with blinding of outcome										+				
Pooled effect size, IA-HA *v* PRP: excluding all but RCTs													+	
Pooled effect size, IA-HA *v* NSAIDs: restricted to double-blinded studies														+
Pooled effect size, IA-HA *v* IA-corticosteroids: in trials using intention to treat									+					
Pooled effect size, IA-HA *v* IA-corticosteroids: in trials reporting single- or double-blind methodology									+					
Pain by VAS scale, IA-HA *v* IA-placebo: good-quality studies					+									
Random-effects regression model, IA-HA: based on pain, with activity					+									
Random-effects regression model, IA-HA: based on HA type—hyaluronan *v* hylan G-F 20					+									
Random-effects regression model, IA-HA: based on study quality—poor *v* good					+									
Pain at rest, IA-HA *v* IA-placebo: high-quality trials				+										
Pain during or after exercise, IA-HA *v* IA-placebo: high-quality trials				+										
Function, IA-HA *v* IA-placebo: high-quality trials				+										
Pain with activities, IA-HA: cross-linked HA *v* non−cross-linked HA trials			0											
Function, IA-HA: cross-linked HA *v* non−cross-linked HA trials			0											
Major adverse events, IA-HA: non−cross-linked HA trials			0											
Major adverse events, IA-HA: cross-linked HA trials			0											
Pain with activities, IA-HA: non−cross-linked trials			+											

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Pain with activities, IA-HA: non−cross-linked, single-blind trials			+											
Pain with activities, IA-HA: non−cross-linked, double-blind trials			+											
Pain with activities, IA-HA: non−cross-linked, single-center trials			+											
Pain with activities, IA-HA: non−cross-linked, multicenter trials			+											
Pain with activities, IA-HA: non−cross-linked, no intention-to-treat trials			+											
Pain with activities, IA-HA: non−cross-linked, only intention-to-treat trials			+											
Pain with activities, IA-HA: non−cross-linked trials with no escape analgesics			+											
Pain with activities, IA-HA: non−cross-linked trials with acetaminophen as escape analgesic			+											
Pain with activities, IA-HA: non−cross-linked, no restriction on escape analgesics			+											
Pain with activities, IA-HA: non−cross-linked, mean age of patients ≤65 yr			+											
Pain with activities, IA-HA: non−cross-linked, mean age of patients >65 yr			+											
Pain with activities, IA-HA: non−cross-linked trials without most advanced OA stage			+											
Pain with activities, IA-HA: non−cross-linked trials with most advanced OA stage			+											
Pain with activities, IA-HA: non−cross-linked, no restrictions on most advanced OA stage			+											
Pain with activities, IA-HA: non−cross-linked trials with effusion as inclusion criteria			+											
Pain with activities, IA-HA: non−cross-linked trials with effusion as exclusion criteria			+											
Pain with activities, IA-HA: non−cross-linked, no restriction on effusion criteria in trials			+											
Pain with activities, IA-HA: non−cross-linked, trial duration ≤12 wk			+											
Pain with activities, IA-HA: non−cross-linked, trial duration >12 wk			+											
Pain with activities, IA-HA: non−cross-linked trials with sample size ≤100			+											
Pain with activities, IA-HA: non−cross-linked trials with sample size >100			+											
Pain with activities, IA-HA: non−cross-linked, non−industry-funded trials			+											
Pain with activities, IA-HA: non−cross-linked, industry-funded trials			+											

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Pain without activities, IA-HA: non−cross-linked trials			+											
Pain without activities, IA-HA: non−cross-linked, single-blind trials			+											
Pain without activities, IA-HA: non−cross-linked, double-blind trials			+											
Pain without activities, IA-HA: non−cross-linked, single-center trials			+											
Pain without activities, IA-HA: non−cross-linked, multicenter trials			+											
Pain without activities, IA-HA: non−cross-linked trials with no intention-to-treat analysis			+											
Pain without activities, IA-HA: non−cross-linked trials with intention-to-treat analysis			+											
Pain without activities, IA-HA: non−cross-linked trials with no escape analgesics			+											
Pain without activities, IA-HA: non−cross-linked trials with acetaminophen as escape analgesic			+											
Pain without activities, IA-HA: non−cross-linked trials with mean age of patients ≤65 yr			+											
Pain without activities, IA-HA: non−cross-linked trials with mean age of patients >65 yr			+											
Pain without activities, IA-HA: non−cross-linked trials without most advanced OA stage			+											
Pain without activities, IA-HA: non−cross-linked trials with most advanced OA stage			+											
Pain without activities, IA-HA: non−cross-linked, no restrictions on most advanced OA stage			+											
Pain without activities, IA-HA: non−cross-linked trials with effusion as inclusion criteria			+											
Pain without activities, IA-HA: non−cross-linked trials with effusion as exclusion criteria			+											
Pain without activities, IA-HA: non−cross-linked, no restriction on effusion criteria in trials			+											
Pain without activities, IA-HA: non−cross-linked, trial duration ≤12 wk			+											
Pain without activities, IA-HA: non−cross-linked, trial duration >12 wk			+											
Pain without activities, IA-HA: non−cross-linked, non−industry-funded trials			+											
Pain without activities, IA-HA: non−cross-linked, industry-funded trials			+											
Functioning, IA-HA: non−cross-linked trials			+											

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Functioning, IA-HA: non−cross-linked trials with no intention-to-treat analysis			+											
Functioning, IA-HA: non−cross-linked trials with intention-to-treat analysis			+											
Functioning, IA-HA: non−cross-linked trials with no escape analgesics			+											
Functioning, IA-HA: non−cross-linked trials with acetaminophen as escape analgesic			+											
Functioning, IA-HA: non−cross-linked trials with no restriction on escape analgesics			+											
Functioning, IA-HA: non−cross-linked trials without most advanced OA stage			+											
Functioning, IA-HA: non−cross-linked, no restrictions on most advanced OA stage			+											
Functioning, IA-HA: non−cross-linked trials with effusion as inclusion criteria			+											
Functioning, IA-HA: non−cross-linked trials with effusion as exclusion criteria			+											
Functioning, IA-HA: non−cross-linked, no restriction on effusion criteria in trials			+											
Functioning, IA-HA: non−cross-linked, trial duration ≤12 wk			+											
Functioning, IA-HA: non−cross-linked, trial duration >12 wk			+											
Functioning, IA-HA: non−cross-linked, non−industry-funded trials			+											
Functioning, IA-HA: non−cross-linked, industry-funded trials			+											
Pain outcome, IA-HA *v* IA-placebo: trials with adequate concealment of allocation										+				
Pain outcome, IA-HA *v* IA-placebo: trials with inadequate concealment of allocation										+				
Pain outcome, IA-HA *v* IA-placebo: trials with adequate *v* inadequate concealment of allocation										+				
Pain outcome, IA-HA *v* IA-placebo: trials with sham intervention										+				
Pain outcome, IA-HA *v* IA-placebo: trials with non-sham intervention										+				
Pain outcome, IA-HA *v* IA-placebo: trials with sham *v* non-sham intervention										+				
Pain outcome, IA-HA *v* IA-placebo: trials with adequate blinding of patients										+				
Pain outcome, IA-HA *v* IA-placebo: trials with inadequate blinding of patients										+				

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Pain outcome, IA-HA *v* IA-placebo: trials with adequate *v* inadequate blinding of patients										+				
Pain outcome, IA-HA *v* IA-placebo: trials with adequate blinding of outcome assessment										+				
Pain outcome, IA-HA *v* IA-placebo: trials with inadequate blinding of outcome assessment										+				
Pain outcome, IA-HA *v* IA-placebo: trials with adequate *v* inadequate blinding of outcome assessment										+				
Pain outcome, IA-HA *v* IA-placebo: trials with intention-to-treat analysis										+				
Pain outcome, IA-HA *v* IA-placebo: trials with no intention-to-treat analysis										+				
Pain outcome, IA-HA *v* IA-placebo: trials with intention-to-treat *v* no intention-to-treat analysis										+				
Pain outcome, IA-HA *v* IA-placebo: trials with ≥100 patients										+				
Pain outcome, IA-HA *v* IA-placebo: trials with <100 patients										+				
Pain outcome, IA-HA *v* IA-placebo: trials with ≥100 *v* <100 patients										+				
Pain outcome, IA-HA *v* IA-placebo: full journal publications										+				
Pain outcome, IA-HA *v* IA-placebo: other publications										+				
Pain outcome, IA-HA *v* IA-placebo: unpublished studies										+				
Pain outcome, IA-HA *v* IA-placebo: trials based on publication status										+				
Pain outcome, IA-HA *v* IA-placebo: trials with industry-independent funding										+				
Pain outcome, IA-HA *v* IA-placebo: trials with industry-dependent funding										+				
Pain outcome, IA-HA *v* IA-placebo: trials with industry-independent *v* industry-dependent funding										+				
Pain outcome, IA-HA *v* IA-placebo: trials with >1 cycle of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with 1 cycle of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with >1 *v* 1 cycle of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with 1-2 injections of HA										+				

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Pain outcome, IA-HA *v* IA-placebo: trials with 3 injections of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with >3 injections of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials based on No. of injections of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with cross-linked HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with non−cross-linked HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials based on structure of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with very high−MW HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with high-MW HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with low-MW HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials based on MW of HA										+				
Pain outcome, IA-HA *v* IA-placebo: trials with follow-up >6 mo										+				
Pain outcome, IA-HA *v* IA-placebo: trials with follow-up of 3-6 mo										+				
Pain outcome, IA-HA *v* IA-placebo: trials with follow-up <3 mo										+				
Pain outcome, IA-HA *v* IA-placebo: trials based on follow-up duration										+				
Pain-related outcomes, hylan *v* IA-HA: trials with adequate concealment of allocation							+							
Pain-related outcomes, hylan *v* IA-HA: trials with inadequate or unclear concealment of allocation							+							
Pain-related outcomes, hylan *v* IA-HA: trials with inadequate or unclear *v* adequate concealment of allocation							+							
Pain-related outcomes, hylan *v* IA-HA: trials with blinding of patients							+							
Pain-related outcomes, hylan *v* IA-HA: trials without blinding of patients							+							
Pain-related outcomes, hylan *v* IA-HA: trials with blinding *v* without blinding of patients							+							
Pain-related outcomes, hylan *v* IA-HA: trials with intention-to-treat analysis							+							

(continued)

Appendix Table 2. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Pain-related outcomes, hylan *v* IA-HA: trials without intention-to-treat analysis							+							
Pain-related outcomes, hylan *v* IA-HA: trials with intention-to-treat *v* no intention-to-treat analysis							+							
Pain-related outcomes, hylan *v* IA-HA: trials with No. of patients randomized >200							+							
Pain-related outcomes, hylan *v* IA-HA: trials with No. of patients randomized ≤200							+							
Pain-related outcomes, hylan *v* IA-HA: trials with No. of patients randomized >200 *v* ≤200							+							
Pain-related outcomes, hylan *v* IA-HA: trials with follow-up >3 mo							+							
Pain-related outcomes, hylan *v* IA-HA: trials with follow-up ≤3 mo							+							
Pain-related outcomes, hylan *v* IA-HA: trials with follow-up >3 mo *v* ≤3 mo							+							
Pain-related outcomes, hylan *v* IA-HA: large trials							+							
Pain-related outcomes, hylan *v* IA-HA: small trials							+							
Pain-related outcomes, hylan *v* IA-HA: trial comparison of interaction based on size							+							
Flare-ups, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Serious adverse events, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Dropouts due to adverse events, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Overall adverse events, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Effusions, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Local adverse events, IA-HA *v* IA-placebo: large trials with blinded outcome										+				
Overall study withdrawals, IA-HA *v* IA-placebo: large trials with blinded outcome										+				

NOTE. A plus sign indicates formal sensitivity or subgroup analysis was performed, a minus sign indicates formal sensitivity or subgroup analysis was not performed, and a zero indicates descriptive data were provided or discussed but no analysis was performed.

HA, hyaluronic acid; IA, intra-articular; MW, molecular weight; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PRP, platelet-rich plasma; RCTs, randomized controlled trials; VAS, visual analog scale.

Appendix Table 3. Outcomes That Were Assessed for and Reported by Included Studies

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
IA-HA														
Knee function												+		
Improvement in symptoms	0													
No requirement for TKA	0													
Knee pain outcomes												+		
Adverse events	0		+							+				
Mortality			0											
IA-HA (including specific HA products) *v* IA-placebo														
Overall pooled effect size		+												
Lequesne index score						+		+						
Knee function	+			+				+				+		
Physical function										+				
Painful symptoms of knee OA (WB pain)	+													
Pain with activities			+					+						
Pain during or immediately after exercise				+				+						
Patient global assessment								+						
Knee circumference								0						
Pain at rest				+				+						
Percentage of painful days								+						
Knee pain outcomes					+	0		+		+	+	+		
WOMAC scores								+						
Overall adverse events				+				+		+		+		
Flare-ups										+				
Systemic reactions								+						
Injection-site reaction						0								
Injection-site pain						0								
Arthralgia						0								
Arthropathy/arthrosis/arthritis						0								
Back pain						0								
Headache						0								
Knee effusion										+				
Discontinued due to adverse event						0				+				
Overall study withdrawal								+						
No. of clinical failures								+						
No. of survivors								+						
Knee ROM								+						
Joint space width								+						
IA-HA *v* oral NSAIDs														
Overall pooled effect size	+													+
Knee pain outcomes								0						+
WOMAC scores								0						
Knee stiffness														+
Serious adverse events														0
Local adverse events								0						

(continued)

Appendix Table 3. Continued

	Espallargues and Pons[16]	Lo et al.[24]	Wang et al.[26]	Arrich et al.[10]	Modawal et al.[20]	Strand et al.[17]	Reichenbach et al.[21]	Bellamy et al.[22]	Bannuru et al.[23] (2009)	Rutjes et al.[25]	Colen et al.[18]	Miller and Block[19]	Chang et al.[27]	Bannuru et al.[11] (2014)
Study withdrawal								0						
Injection-site pain								0						
Injection-site swelling								0						
IA-HA *v* IA-PRP														
Overall pooled effect size													+	
Risk of adverse reactions													+	
IA-HA (various specific products) *v* IA-corticosteroids (various preparations)														
Overall pooled effect size									+					
Knee pain outcomes								+						
Total Larson rating score								0						
Knee ROM								+						
Function								0						
Patient global assessment								+						
Study withdrawal								+						
Local adverse reactions								+						
Systemic adverse reactions								+						
Analgesic use								0						
Comparison of various specific IA-HA products														
Knee pain outcomes							+	+			+			
Patient global assessment								+						
WOMAC scores								0						
Function								+						
Overall pooled effect size	+						+				+			
Knee ROM								0						
Local adverse events							+	+						
Flare-ups							+							
Joint effusion							+							
Painful injections								+						
Lequesne index score								0						
Clinical failures								0						
Study withdrawal								0						

NOTE. A plus sign indicates formal sensitivity or subgroup analysis was performed, and a zero indicates descriptive data were provided or discussed but no analysis was performed.

HA, hyaluronic acid; IA, intra-articular; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PRP, platelet-rich plasma; ROM, range of motion; TKA, total knee arthroplasty; WB, weight bearing; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.