Osteoarthritis and Cartilage 19 (2011) 611–619

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis – meta-analysis

R.R. Bannuru †, N.S. Natov ‡, U.R. Dasi §, C.H. Schmid †, T.E. McAlindon †*

† *Tufts Medical Center, Boston, MA, USA*
‡ *Tufts University School of Medicine, Boston, MA, USA*
§ *Nagarjuna University, India*

ARTICLE INFO

Article history:
Received 10 March 2010
Accepted 4 September 2010

Keywords:
Osteoarthritis
Knee
Intra-articular
Hyaluronic acid
Meta-analysis

SUMMARY

Objective: To evaluate the therapeutic trajectory of intra-articular hyaluronic acid (IAHA) vs *placebo* for knee osteoarthritis (OA).

Design: Our data sources include Medline, EMBASE, CINAHL, BIOSIS, Web of Science, Google Scholar, Cochrane database; hand searched reviews, manuscripts, and, supplements; author contacts for unpublished data. Randomized trials that reported effects of IAHA vs *placebo* on knee OA were selected based on inclusion criteria. We computed effect sizes for change from baseline at 4, 8, 12, 16, 20 and 24 weeks, using Bayesian random effects model. We performed multivariate analyses adjusting for correlation between time points. Meta-regressions were performed adjusting for potential confounders.

Results: The 54 eligible trials included 7545 participants. The conduct and quality of these trials varied in number of aspects. The effect size (ES) favored IAHA by week 4 (0.31; 95% CI 0.17, 0.45), reaching peak at week 8 (0.46; 0.28, 0.65), and then trending downwards, with a residual detectable effect at week 24 (0.21; 0.10, 0.31). This therapeutic trajectory was consistent among the subset of high quality trials and on multivariate analysis adjusting for correlation between time points.

Conclusions: Our meta-analysis highlights a therapeutic trajectory of IAHA for knee OA pain over 6 months post-intervention. With this additional perspective, we are able to infer that IAHA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks. On the other hand, the peak effect size (0.46; 0.28, 0.65), is greater than published effects from other OA analgesics [acetaminophen (ES = 0.13; 0.04, 0.22); NSAIDs (ES = 0.29; 0.22, 0.35); COX-2 inhibitors (ES = 0.44; 0.33, 0.55)]. An effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. Thus, its properties could have utility for certain clinical situations, or in combination with other therapies.

Introduction

Intra-articular injections of synthetic hyaluronic acid are widely employed in the medical management of knee osteoarthritis (OA) pain, based on potentially therapeutic physicochemical properties[1–3]. A range of hyaluronic acid products are now available, on which expenditure in the US is estimated at $725 million each year[4]. The therapeutic justification of the expense of hyaluronic acid injections rests heavily on the duration of effect, which is claimed to be prolonged[5–8].

However, despite many clinical trials of hyaluronic acid, there remains contention regarding the efficacy of these products, with markedly discordant interpretations of the collective data between experts. Among the six meta-analyses performed to date[9–14], two drew positive conclusions[9,10], two reported a small effect[11,12], and two refuted any evidence of efficacy on the basis of low methodological quality[13,14]. These meta-analyses evaluated intra-articular hyaluronic acid (IAHA) therapy from the perspective of more traditional interventions, generally analyzing two fixed time points. However, as suggested by a more recent systematic review comparing hyaluronic acid with intra-articular corticosteroids[15], the benefit of hyaluronic acid appears to be time-varying. Therefore, evaluation of the post-intervention time course of the effect of hyaluronic acid (the "therapeutic trajectory") could provide additional informative perspectives on its overall efficacy.

* Address correspondence and reprint requests to: Timothy E. McAlindon, Center for Arthritis and Rheumatic Diseases, Tufts Medical Center, Tufts University School of Medicine, 800 Washington Street, Box 406, Boston, MA 02111, USA. Tel: 1-617-636-5645; Fax: 1-617-636-1542.
E-mail address: tmcalindon@tuftsmedicalcenter.org (T.E. McAlindon).

1063-4584/$ – see front matter
doi:10.1016/j.joca.2010.09.014

The number of clinical trials of hyaluronic acid has expanded since the last pooled analysis[10], and includes new studies of high methodological rigor[7,8,16–20]. Therefore, in order to reach a definitive conclusion about the efficacy of hyaluronic acid for knee OA, we performed an updated meta-analysis evaluating its effect at specified post-treatment intervals in relation to the minimally clinically important effect. We also evaluated the potential biases that have limited interpretation of prior systematic analyses of the pooled data[9–14].

Methods

Search strategy

Two reviewers (RB and NN) independently performed a systematic electronic literature search for citations comparing the efficacy of IAHA injections with *placebo* in the management of knee OA. We searched Medline, EMBASE, CINAHL, BIOSIS, Web of Science, Google scholar and the Cochrane Central Register of Controlled Trials from inception to March 2010. The key terms ("arthritis" or "osteoarthritis" or "osteoarthrosis" or "gonoarthrosis" or "degenerative arthritis") and ("viscosupplementation" or "hyaluronic acid" or "hyaluronan" or "hyaluronate" or "Hyalgan" or "Synvisc" or "Orthovisc" or "Artzal" or "Supartz" or "Suplasyn" or "BioHy" or "Euflexxa" or "Nuflexxa" or "Hylan GF-20") were entered as medical subject heading terms and as text words for searches. All searches were limited to human randomized clinical trials. No limits were applied for language, publication date or publication status and foreign language papers were translated. The last full search was run on March 3, 2010. We also hand searched the reference lists of all retrieved studies and conference proceedings of the American Association of Orthopedic Surgeons, the American College of Rheumatology, the British Society for Rheumatology, the European League against Rheumatism, the International League of Associations of Rheumatology, and the Osteoarthritis Research Society International. The conference proceedings were searched from January 1990 to February 2010. Product inserts of viscosupplements were consulted. We attempted to identify unpublished data by contacting experts, study authors and manufacturers. We also contacted the primary authors of abstracts with incomplete data. The exact full search strategy is available upon request.

Inclusion & exclusion criteria

We included all clinical trials that were randomized, used human subjects and compared therapeutic effects of IAHA with *placebo* to treat knee OA. To be eligible for inclusion, we required that each trial report extractable outcome data for at least one measure of pain or function or stiffness, as currently recommended for OA clinical trials (Table I).

Outcome measures & time points

Our primary outcome measure was pain reduction at pre-specified time points. Since the treatment duration and the post-treatment assessment time points varied among the trials, *a priori* we grouped the time points of outcome assessments of individual trials into seven intervals: 2 weeks (1–2 weeks), 4 weeks (3–6 weeks), 8 weeks (7–10 weeks), 12 weeks (11–14 weeks), 16 weeks (15–18 weeks), 20 weeks (19–22 weeks) and 24 weeks (23–26 weeks). This grouping was designed to best capture the data presented in all of the studies. When an article provided data on more than one pain scale, we referred to a hierarchy of pain-related outcomes (Table I) and extracted the outcome that was highest on the list. Our secondary outcome measures were function and stiffness at a pre-specified end point of 8 weeks or 12 weeks or at the end of the trial, whichever appeared first.

Table I
Hierarchy of outcome measures used in the meta-analysis*

Pain:
- Western Ontario and McMaster Universities (WOMAC) OA Index Pain Subscale (visual analog or Likert version)
- Pain on walking for index joint (visual analog or Likert scale)
- Pain in index joint during activities other than walking (visual analog or Likert scale)
- Spontaneous pain in index joint (visual analog or Likert scale).

Function:
- WOMAC OA Index Function Subscale (visual analog or Likert version)
- Function score for index joint (visual analog or Likert scale).

Stiffness:
- WOMAC OA Index Stiffness Subscale (visual analog or Likert version)
- Stiffness score for index joint (visual analog or Likert scale).

* To be eligible for our analysis, studies had to report results for at least one of these outcomes.

Data collection process

We developed a data extraction form, tested it on 10 randomly selected included studies and refined it accordingly. Two reviewers (RB and UD) independently, in a blinded manner extracted data from each trial using this standardized data extraction form. The data were checked for consistency between the two reviewers. All disagreements were resolved by consensus. The reviewing team completed an *a priori* training exercise and had an inter-rater agreement of 99.4%. Duplicate publications were carefully checked and excluded by juxtaposing the author names, treatment comparisons, sample sizes, outcomes and location of trials.

Data items

Information was extracted from each included trial on: (1) characteristics of trials (including trial design, number of participants, withdrawal rate, trial duration, publication status, type and extent of sponsorship); (2) characteristics of trial participants (including mean age, sex, stage and severity of disease, duration of disease); (2) type of intervention (including type, dose, duration and frequency of hyaluronic acid and *placebo*); (3) type of outcome measure (including the level of pain, function and stiffness).

Risk of bias in included trials

Two reviewers (RB and NN) independently, in a blinded manner and with adequate reliability ascertained the quality of eligible randomized trials. We determined the adequacy of randomization (computer generated, centralized randomization), allocation concealment, blinding of participants, healthcare providers, data collectors and outcome assessors. We assessed the way all withdrawn participants were reported and how their data were treated. The type and extent of sponsorship were also noted.

Each study was evaluated for the type of analysis performed (intention-to-treat vs non–intention-to-treat). An analysis was considered to be intention-to-treat if: (1) it was characterized by its investigators as such and there was an attempt to analyze data from all randomized participants, or (2) there were no dropouts (even if the analysis was not specifically described as intention-to-treat). Within each study, the number of participants randomized and the number analyzed were evaluated. Where possible, data from an intention-to-treat analysis were extracted. We defined "*high quality trials*" as those with more than 100 randomized participants and

also reporting intention-to-treat analysis, adequate blinding, and allocation concealment.

Statistical methods

We computed an effect size for each study at each time point separately using Hedges' g statistic[21] corrected for small samples as follows:

$$g = \left[(M_{HA} - M_{PL})/S_{pooled}\right]$$

$$S_{pooled} = \text{sqrt}\left\{\left[(n_{HA}-1)S_{HA}^2 + (n_{PL}-1)S_{PL}^2\right]\Big/(n_{HA}+n_{PL}-2)\right\}$$

$$\text{Corrected Hedges's } g = g \times [1 - 3/\{4(n_{HA}+n_{PL}) - 9\}]$$

M_{HA}, S_{HA} and n_{HA} are the mean change, standard deviation and number of participants studied from baseline to a given time point in the hyaluronic acid group. M_{PL}, S_{PL} and n_{PL} are the corresponding values in the *placebo* group. Negative g values favor *placebo* and positive g values favor hyaluronic acid.

Three studies[22–24], compared *placebo* with two formulations of hyaluronic acid and one study[18] compared *placebo* with three formulations. We treated these as separate trials and compared outcomes from each formulation with those of the *placebo* group. To adjust for the within-study correlation induced by the common *placebo* group, we apportioned the control group into as many equal-sized groups as treatments studied and compared the treatment to the divided control group.

We calculated the pooled effect sizes using Bayesian random effects models[25]. This model incorporates within and between-study variances and uncertainty in the between-study variance, which is slightly more conservative (wider uncertainty intervals) than non-Bayesian random effects models. The study pain scores were assumed to be randomly drawn from a normal distribution with mean equal to the overall treatment effect and a variance representing the heterogeneity between the study means. The random effect mean and variance were given non-informative prior distributions, specifically N(0, 1000000) for the mean and Uniform(0,100) for the standard deviation. For the meta-regression models, the mean was represented as a linear regression function with both intercept and slope given N(0,1000000) prior distributions. To compute the Bayesian estimates, we used Markov chain Monte Carlo implement through the BRugs package running OpenBUGS within the R statistical software. To check convergence of the Markov chains, we ran three parallel chains and monitored convergence with the Gelman-Rubin diagnostic using a between to within ratio of 1.1[26]. On convergence, which generally occurred within 1000 runs, we saved 15,000 samples from each chain to estimate posterior distributions of model parameters.

The pooled data are presented as Forest plots with Bayesian 95% confidence intervals (CIs). We assessed statistical heterogeneity with the help of the I^2 statistic, which describes the percentage of total variation across the trials that is attributable to chance[27]. I^2 values of 25%, 50% and 75% correspond to low, moderate, and high between-trial heterogeneity.

We performed two types of analyses. First, we meta-analyzed overall pain, function and stiffness as well as pain at each time point separately. Second, to incorporate the correlation induced by the multiple measurements at different time points within the same study we used a multivariate longitudinal regression model that adjusted for time[28].

Where necessary, means and measures of dispersion were approximated from the figures in the manuscripts. When a published study only reported the median, range and size of the trial[29], we estimated their means and variances according to a published method[30].Wherever necessary, we imputed the standard deviation according to a published method[31].Of note is that one can only accurately estimate the CIs around change scores when the raw data are presented in all relevant articles or when the correlation between pre- and post-test scores is known. Neither quantity was published in some of the available studies, so we used a correlation of 0.5 to calculate the measure of the change score dispersion. In a sensitivity analysis we tried other correlations (0.4, 0.6, and 0.7) and they did not change the result.

For the secondary outcomes of stiffness and function, as well as to obtain an overall effect of pain, we calculated an overall effect size at the earliest pre-specified end point of 8 weeks or 12 weeks or the end of the trial. This reflects the expert consensus opinions, existing literature[10,15] and the manufacturers' recommendations of the peak effect of hyaluronic acid. We also estimated the 95% prediction interval for overall pain.

Using meta-regression, we performed sensitivity analyses to examine how trial quality, allocation concealment, intention-to-treat analysis, blinding methodology, trial size, publication status, publication date, molecular weight and origin of hyaluronic acid preparation modified the treatment effect for overall pain. Each meta-regression used a random effects model[32] and examined one variable at a time.

Results

Trial selection

We identified 1257 references in our literature search, of which 1117 were excluded after title and abstract screening and removing duplicates (Fig. 1). Full reports were retrieved for 140 studies for detailed evaluation. Forty-nine reports describing 54 trials met our inclusion criteria and were included in the meta-analysis[5–8,16–20,22–24,29,33–67].

Trial characteristics

The 54 trials in the meta-analysis were published between 1983 and 2009 and randomized 7545 participants. Forty-nine trials (6962 participants) contributed to the meta-analysis of pain-related outcomes; 16 trials (2571 participants) of function-related outcomes; and 15 trials (2488 participants) of stiffness-related outcomes contributed to the meta-analysis. The average age of

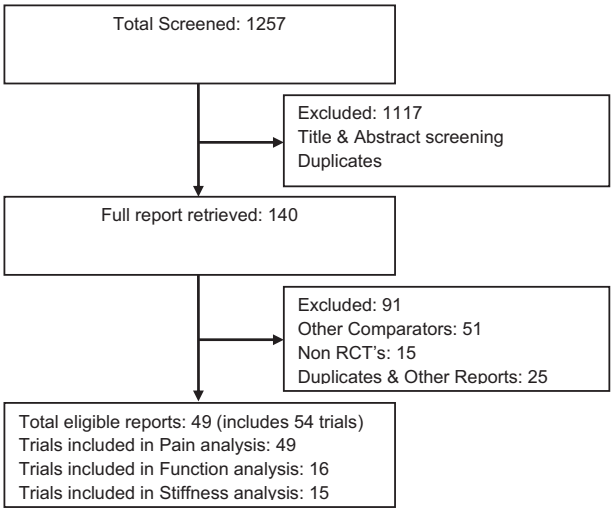

Fig. 1. Study flow chart.

the participants ranged from 45 to 72 years. Women represented between 28% and 100% of participants. Participant samples included in trials were heterogeneous with respect to age, sex, knee radiographic grade, and baseline pain, reflecting varied patient selection among the trials.

Risk of bias within trials

The conduct and quality of the 54 randomized trials varied in a number of aspects (Table II). The sample sizes varied between 24 and 586 with a mean of 140; 19 trials had a sample size less than 100. Trial duration ranged from 4 to 52 weeks with a mean of 23 weeks; 15 were fewer than 10 weeks duration. Allocation concealment was adequate in 28 trials (52%); and was either unclear or not reported in 26 trials (48%). Intention-to-treat analysis results were reported in 28 trials (52%); 26 trials (48%) reported per protocol analyses or the analytical approach was either unclear or not reported. Double blinding was adequate and clearly reported in 38 trials (70%); 16 trials were single blind/unclear/not reporting. Dropout rates or losses to follow-up ranged from 0% to 50% with 11 trials reporting 20% or greater loss to follow-up. Sixteen trials (30%) met our criteria for high quality trials.

Power calculations were reported in 30 trials (56%). Mean sample size in these trials was 210 compared to 62 in 16 trials without those calculations in the published manuscripts. Industry involvement was reported in 53 trials (98%) either in the form of

Table II
Risk of bias indicators of included trials

Author Year	Groups comparable at baseline	Adequate allocation concealment	Adequate double blinding	Intention-to-treat analysis	Dropout (percent)	
					HA	*Placebo*
Shichikawa *et al.*[33]	Yes	Yes	Yes	No	7.7	9.1
Shichikawa *et al.*[34]	Yes	Yes	Yes	No	15.8	10.5
Bragantini *et al.*[35]	No	No	No	No	0	5.3
Grecomoro *et al.*[36]	NR	No	Unclear	No	0	10
Dixon *et al.*[37]	No	No	Yes	No	16.7	15.2
Russell *et al.*[38]	NA	No	No	No	19.0*	
Dougados *et al.*[39]	No	No	No	No	10.9	16.4
Moreland *et al.*[40]	NR	Yes	Yes	Yes	4.3	6.3
Puhl *et al.*[41]	No	Yes	Yes	No	6.9	6.5
Cohen *et al.*[42]	Yes	No	Yes	No	5.1*	
Creamer *et al.*[43]	Yes	No	No	Yes	0	0
Dahlberg *et al.*[29]	Yes	Yes	Yes	Yes	7.1	8.3
Henderson *et al.*[44]	Yes	No	Yes	No	11.1	4.3
Scale *et al.*[45]	Yes	Yes	Yes	No	NR	NR
Carrabba *et al.*[46]	Yes	No	Unclear	Yes	0	0
Corrado *et al.*[47]	Yes	No	Unclear	No	9.5	15.8
France 1995	Yes	Yes	Yes	Yes	10.3	15.0
Sala and Miguel[49]	Unclear	Yes	Unclear	Yes	0	0
Guler *et al.*[50]	NA	No	Yes	NA	NR	NR
Lohmander *et al.*[51]	Yes	Yes	Yes	No	20.0	22.5
UK 1996	NA	Yes	Yes	Yes	NR	NR
Wu *et al.*[52]	Yes	No	Unclear	No	48.4	51.9
Altman and Moskowitz[53]	Yes	No	Yes	No	35.6	32.3
Wobig *et al.*[5]	No	Yes	Yes	Yes	1.8	1.7
Hizmetli *et al.*[54]	NA	No	Yes	No	20	20
Huskisson and Donnelly[6]	Yes	No	Yes	Yes	20	18
Brandt *et al.*[55]	Yes	Yes	Yes	No	20.2	25.0
Bunyaratavej *et al.*[56]	Yes	No	Yes	Yes	NR	NR
Dickson *et al.*[57]	Yes	Yes	Yes	Yes	18.9	14.0
Tamir *et al.*[58]	Yes	No	No	No	20.0	29.2
Karlsson *et al.*[22]	Yes	Yes	Yes	No	28.2	27.3
Karlsson *et al.*[22]	Yes	Yes	Yes	No	20.5	27.3
Petrella *et al.*[59]	Yes	Yes	Yes	Yes	16.7	6.7
Jubb et al[60]	Yes	No	Yes	Yes	23.1	20.5
Tsai *et al.*[61]	NA	No	Yes	Yes	NR	NR
Altman *et al.*[62]	Yes	Yes	Yes	Yes	23.1	20.1
Day *et al.*[63]	Yes	Yes	Yes	Yes	16.4	16.1
Pham *et al.*[64]	Yes	Yes	Yes	Yes	6.9	5.9
Cubukcu *et al.*[65]	Yes	No	No	Yes	0	0
Neustadt *et al.*[66]	Yes	Yes	Yes	No	7.0	12.2
Rolf *et al.*[23]	Yes	No	Yes	Yes	6.0	12
Rolf *et al.*[23]	Yes	No	Yes	Yes	8.0	12
Sezgin *et al.*[67]	Yes	No	No	Yes	0	0
Kotevoglu *et al.*[24]	Yes	No	Unclear	No	23.1	30.7
Kotevoglu *et al.*[24]	Yes	No	Unclear	No	19.2	30.7
Petrella and Petrella[16]	Yes	Yes	Yes	Yes	7.5	7.5
Lundsgaard *et al.*[17]	Yes	Yes	Yes	Yes	2.4	4.8
Petrella *et al.*[18]	Yes	Yes	Yes	Yes	8.0	6.0
Petrella *et al.*[18]	Yes	Yes	Yes	Yes	2.0	6.0
Petrella *et al.*[18]	Yes	Yes	Yes	Yes	4.0	6.0
Altman *et al.*[7]	Yes	Yes	Yes	Yes	11.5	11.6
Baltzer *et al.*[19]	Yes	No	Unclear	Yes	11.1	7.5
Chevalier *et al.*[8]	Yes	Yes	Yes	Yes	7.3	9.3
Baraf *et al.*[20]	Yes	Yes	Yes	Yes	7.3	10.2

NA: not available; NR: not reported.
* Numbers for separate groups were not reported.

Table III
Pooled effect sizes (95% CI) for pain

Week	All trials			High quality trials		
	N	Effect size	I^2 (%)	N	Effect size	I^2 (%)
4	44	0.31 (0.17,0.45)	75	14	0.27 (0.04,0.49)	75
8	26	0.46 (0.28,0.65)	75	7	0.34 (0.02,0.67)	83
12	31	0.25 (0.15,0.36)	60	12	0.29 (0.13,0.45)	75
16	15	0.20 (0.11,0.30)	7	8	0.22 (0.09,0.36)	0
24	20	0.21 (0.10,0.31)	32	6	0.20 (0.03,0.37)	56

N = Number of trials, I^2 = Heterogeneity score.

funding, providing statistical analyses or having an industry member as a co-author.

Forty-five trials (83%) were published as full-text journal articles, five trials were published as abstracts only[38,40,42,50,61], and three were unpublished[48,54].One recent trial was reported as an abstract[20], which we expect to see as full-text publication in the near future. In addition, an unpublished and unreported trial (382 participants) was identified in the Orthovisc® package insert as OAK 9801. Trials not published in full-text comprise approximately 18% (1345) of the total participant population. Only two non-English manuscripts met the inclusion criteria and were translated[33,34].

In summary, trial characteristics including study quality, sample size and power calculations, duration of the trial, use of intention-to-treat analysis, losses to follow-up, and industry involvement, vary substantially. The known extent of unpublished data includes a large number of individuals.

Heterogeneity

Primary analysis for pain exhibited heterogeneity (I^2) scores of 75% at 4 weeks, 75% at 8 weeks, 59% at 12 weeks, 15% at 16 weeks, zero at 20 weeks and 33% at 24 weeks. The heterogeneity (I^2) score for overall effect size for pain was 70%.

Effects on joint pain

Forty-nine trials (6962 participants) contributed to the meta-analysis of pain-related outcomes (Table III). The effect size favored hyaluronic acid by week 4 (0.31; 95% CI 0.17, 0.45), reaching a peak at week 8 (0.46; 95% CI 0.28, 0.65), and then trending downwards, with a residual detectable effect at week 24 (0.21; 95% CI 0.10, 0.31) [Fig. 2 and Web Fig. 1(A–D)]. This therapeutic trajectory was consistent among the subset of high quality trials (2570 participants) and on multivariate analysis adjusting for correlation between time points.

Sensitivity analyses

Table IV presents meta-regression results for pain based on quality measures. Estimates of effect sizes varied to some degree depending on trial quality, allocation concealment, intention-to-treat analysis, blinding methodology, trial size, publication status, year of publication, molecular weight, and origin of hyaluronic acid preparation. Most significant differences were observed in allocation concealment (adequate vs inadequate 0.29 vs 0.41); double blinding (adequate vs inadequate 0.27 vs 0.53); trial size (>100 vs <100 0.25 vs 0.58) molecular weight (low vs high 0.29 vs 0.60). The 95% prediction interval for overall pain is estimated to be (−0.31, +0.99).

Effects on joint function

The paucity of data at each time point precluded evaluation of the therapeutic trajectory for joint function and stiffness. Sixteen trials (2571 participants) contributed to the meta-analysis of function-related outcomes. The effect size was 0.31 (0.11, 0.51) with heterogeneity score (I^2) of 79% indicating high heterogeneity among the trials. But when two outliers (Cubuku *et al.*, and Sezgin *et al.*) were

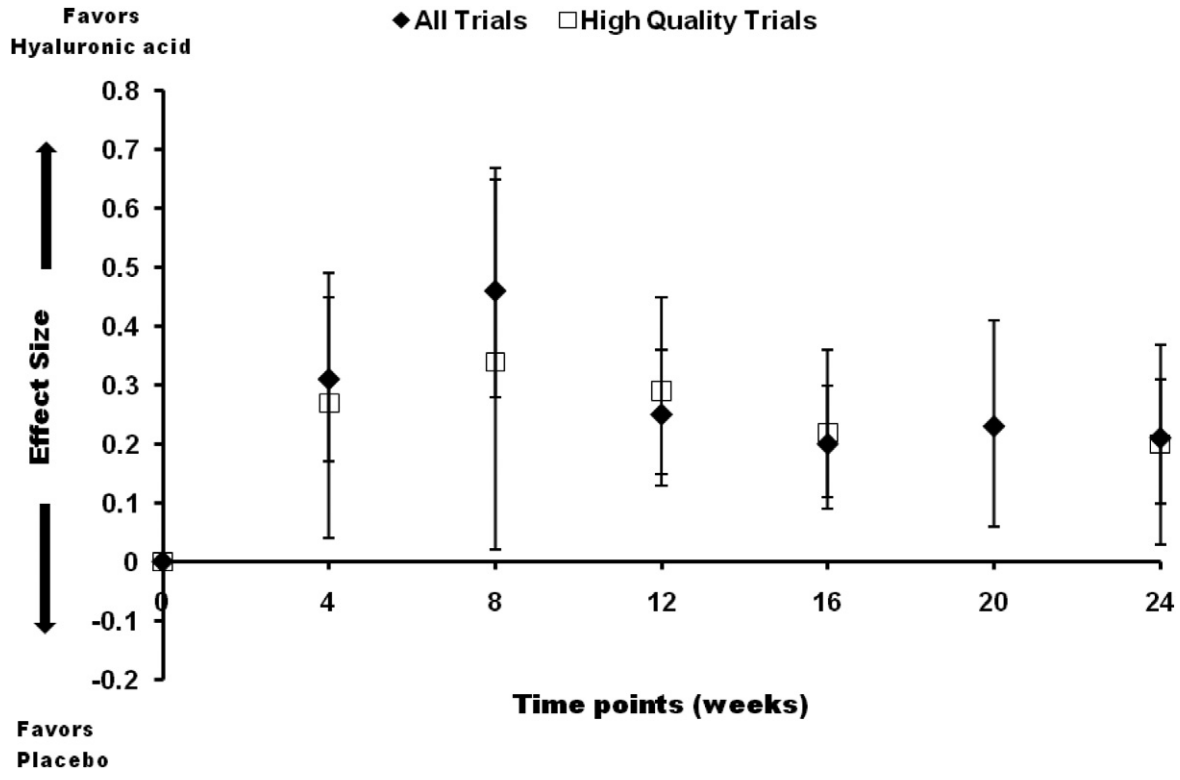

Fig. 2. Graph depicting the effect sizes (95% CI) for pain.

Table IV
Meta-regression results for overall pain based on trial quality indicators

Variable	Total trials	Randomized, *n*	Effect size (95% CI)	I^2%
All trials	49	6962	0.34 (0.22, 0.46)	70
Trial quality				
High	15	2945	0.31 (0.12, 0.51)	74
Low	34	4017	0.35 (0.21, 0.50)	69
Allocation concealment				
Adequate	27	4679	0.29 (0.15, 0.44)	66
Unclear/no	22	2283	0.41 (0.23, 0.59)	75
Intent-to-treat analysis				
Yes	25	4195	0.31 (0.15, 0.49)	72
No	24	2767	0.35 (0.21, 0.51)	69
Double blinding				
Adequate	35	6063	0.27 (0.15, 0.40)	68
Unclear/no/single	14	899	0.53 (0.31, 0.76)	73
Trial size				
>100 Participants	32	6207	0.25 (0.13, 0.38)	60
<100 Participants	17	755	0.58 (0.36, 0.80)	77
Publication status				
Published	44	6310	0.35 (0.23, 0.48)	72
Unpublished	5	652	0.23 (−0.12, 0.57)	35
Year of publication				
After 2000	26	4492	0.28 (0.18, 0.38)	58
Before 2000	23	2470	0.37 (0.18, 0.56)	78
Molecular weight*				
<1000 KDa	28	3500	0.29 (0.14, 0.44)	61
1000–6000 KDa	10	1859	0.29 (0.06, 0.56)	59
>6000 KDa	9	881	0.60 (0.33, 0.88)	82
Origin of hyaluronic acid†				
Avian	42	5598	0.36 (0.23, 0.49)	71
Non-avian	6	1364	0.17 (−0.13, 0.49)	59

Note: these ES were calculated at a pre-specified end point of 8 weeks or 12 weeks or end of the trial whichever occurred earlier.

* Altman *et al.* 2004 and Baraf *et al.* 2009 didn't report the molecular weight of hyaluronic acid used.

† Baraf *et al.* 2009 didn't report the origin of hyaluronic acid used.

taken out of the meta-analysis the effect size was 0.15 (0.01, 0.30) and the heterogeneity score (I^2) was reduced to 58%. The pooled effect size of the five high quality trials (1536 participants) was 0.12 (−0.04, 0.27) showing no effect and the I^2 score was 51%. The effect magnitude in high quality trials was 76% less than in low quality trials. We attempted to present the therapeutic trajectories for function and stiffness with the available data (Web Fig. 2; Web Table I).

Effects on joint stiffness

Fifteen trials (2488 participants) contributed to the meta-analysis of stiffness-related outcomes. The effect size was 0.31 (0.12, 0.49) favoring hyaluronic acid, with an I^2 score of 74%. The pooled effect size of the four high quality trials (1283 participants) was 0.10 (−0.11, 0.31) showing no effect and the I^2 score was 67%. The effect magnitude in high quality trials was 78% less than in low quality trials.

Discussion

This meta-analysis highlights the therapeutic trajectory of IAHA for knee OA pain over 6 months following the intervention. With this additional perspective, we are able to infer that IAHA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks (Fig. 2). On the other hand, the peak effect size (0.46; 0.28, 0.65), is greater than published effects from other OA analgesics. In fact, in comparison to acetaminophen (ES = 0.13; 0.04, 0.22) this is up to four times better[68]; also appears to be better than NSAIDs (ES = 0.29; 0.22,0.35)[69] and equivalent to COX-2 inhibitors (ES = 0.44; 0.33,0.55)[70]. According to the IMMPACT consensus[71], an effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. The effect sizes in our pooled analyses were above this level from weeks 4 to 24 but were subsequently close to, or at that threshold at some time points.

One unique aspect of this meta-analysis is that we examined the therapeutic response over time by pooling the data for each time point separately. The product of this analysis was informative in laying out the pattern of therapeutic response attributable to the intervention. However, two limitations to this approach are that not all trials provided data for each of the time points, and the possibility of correlations among outcomes between time points. We addressed these issues by running a multivariate longitudinal regression model that adjusted for time.

We attempted to minimize publication bias by employing a broad search strategy independently by different reviewers and making author contacts wherever possible. We included eight unpublished trials in our analysis in order to minimize publication bias. We improved reliability on risk of bias assessment and data extraction as two reviewers performed procedures independently before consensus was obtained. We minimized bias through study design and quality by doing sensitivity analyses based on study design and gave an overview of risk of bias assessment.

Another problem in attempting to pool study results was the considerable variety of assessment instruments. To address this, we generated effect sizes by computing Hedges g statistic. Effect sizes provide unit less measures of treatment efficacy centered at zero effect[21]. Bias in clinical trial reports can also theoretically occur from *post-hoc* selection of the outcome measures favoring the study intervention. We tried to reduce this from biasing our pooled estimates by using a hierarchy of recommended outcomes to determine which measure to employ as the index outcome (Table I).

One other limitation this kind of review suffers is from pooling several hyaluronic acid agents which differ in many characteristics including molecular weights, origin, viscosity, cross-linking etc. We addressed this issue by performing several sensitivity analyses wherever possible. We didn't attempt to do sensitivity analyses based on viscosity or cross-linking since that might bias our review as a direct comparison between different agents. Our attempt to do sensitivity analyses based on differing selection criteria specifically knee effusion was not successful mainly due to paucity of data.

The *placebo* effect size in OA trials tends to be large compared to untreated baseline especially in those involving intra-articular injections[72]. Also, there is theoretical possibility that intra-articular saline could have a therapeutic effect to that may be sustained for 6 months or more[73–75]. Furthermore, a therapeutic effect of aspiration of synovial fluid could contribute to a response in patients receiving *placebo*. We would expect all these factors to bias treatment group differences to the null, in which case our effect size would underestimate the clinical benefit.

In summary, using a pooled analysis that accommodates its post-administration trajectory of effect, we confirm IAHA has efficacy for knee OA pain. The magnitude of effect is modest, and exceeds a minimally clinically significant threshold. Thus, its properties could have utility for certain clinical situations, or in combination with other therapies. These data should predicate a re-evaluation of its overall cost-utility.

Funding source

Dr. Bannuru is supported by T32 HS0000060 from Agency for Healthcare Research and Quality and Dr. Schmid is supported by R01 HS018574-01 from Agency for Healthcare Research and Quality. This publication was supported by UL1 RR025752 from the National Center for Research Resources.

Author contributions

All authors were involved in drafting the article and revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bannuru and Dr. McAlindon had full access to all of the data in the article and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE.

Acquisition of data: Bannuru RR, Natov NS, Dasi UR, McAlindon TE.

Analysis and interpretation of data: Bannuru RR, Dasi UR, Schmid CH, McAlindon TE.

Conflict of interest

Bannuru RR; Natov NS; Dasi UR; Schmid CH: None

McAlindon TE: received consulting fees from Stryker Biotech, NiCox, Gelita and GlaxoSmithKline and currently has grant funding from the National Institutes of Health.

Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.joca.2010.09.014

References

1. Peyron JG. Intraarticular hyaluronan injections in the treatment of osteoarthritis: state-of-the-art review. J Rheumatol Suppl 1993;39:10–5.
2. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol Suppl 1993;39:3–9.
3. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 2003;5:54–67.
4. Datamonitor Market Dynamics – Hyaluronic Acid Viscosupplementation, www.datamonitor.com 2002; Reference code DMHC1776.
5. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998;20:410–23.
6. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford) 1999;38:602–7.
7. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum 2009;39:1–9.
8. Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, *et al*. Single, intra-articular treatment with 6 mL of hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multi-centre, double-blind, placebo-controlled trial. Ann Rheum Dis 2008;69(1):113–9.
9. 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-A:538–45.
10. 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; CD005321.
11. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. Jama 2003;290:3115–21.
12. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. J Fam Pract 2005;54:758–67.
13. 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;172:1039–43.
14. Medina JM, Thomas A, Denegar CR. Knee osteoarthritis: should your patient opt for hyaluronic acid injection? J Fam Pract 2006;55:669–75.
15. 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;61:1704–11.
16. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol 2006;33:951–6.
17. Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. Scand J Rheumatol 2008;37:142–50.
18. Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Clin Rheumatol 2008;27:975–81.
19. Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage 2009;17:152–60.
20. Baraf HS, Strand V, Hosokawa H, Akahane O, Lim S, Yaguchi M. Effectiveness and safety of a single intraarticular injection of GEL-200, a new cross-linked formulation of hyaluronic acid (HA) in the treatment of symptomatic osteoarthritis (OA) of the knee. Osteoarthritis Cartilage 2009;(17 Suppl):S174.
21. Cooper H, Hedges LV. The Hand Book of Research Synthesis. New York: Russell Sage Foundation Publications 1994.
22. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford) 2002;41:1240–8.
23. Rolf CG, Engstrom B, Ohrvik J, Valentin A, Lilja B, Levine DW. A comparative study of the efficacy and safety of hyaluronan viscosupplements and placebo in patients with symptomatic and arthroscopy-verified cartilage pathology. J Drug Assess 2005;8:183–200.
24. Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int 2006;26:325–30.
25. Schmid CH, Stark PC, Berlin JA, Landais P, Lau J. Meta-regression detected associations between heterogeneous treatment effects and study-level, but not patient-level, factors. J Clin Epidemiol 2004;57:683–97.
26. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Data Analysis. New York: Chapman and Hall 1996.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

28. Ishak KJ, Platt RW, Joseph L, Hanley JA, Caro JJ. Meta-analysis of longitudinal studies. Clin Trials 2007;4:525–39.
29. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placebo-controlled study. Arthritis Rheum 1994;37:521–8.
30. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
31. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7–10.
32. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693–708.
33. Shichikawa K, Igarashi M, Sugawara S, Iwasaki Y. Clinical evaluation of high molecular weight sodium hyaluronate (SPH) on osteoarthritis of the knee – a mutli-center well controlled comparative study. Jpn J Clin Pharmacol Therapeut 1983;14:545–58.
34. Shichikawa K, Maeda A, Ogawa N. [Clinical evaluation of sodium hyaluronate in the treatment of osteoarthritis of the knee]. Ryumachi 1983;23:280–90.
35. Bragantini A, Cassini M, De Bastiani G. Controlled single-blind trial of intra-articularly injected hyaluronic acid (Hyalgan) in osteoarthritis of the knee. Clin Trials J 1987;24:333–40.
36. Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. Pharmatherapeutica 1987;5:137–41.
37. Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Curr Med Res Opin 1988;11: 205–13.
38. Russell IJ, Michalek JE, Lawrence VA, Lessard JA, Briggs BT, May GS. A randomized placebo (PL) and no-intervention (NI) controlled, trial of intra-articular (IA) 1% sodium hyaluronate (HA) in the treatment of knee osteoarthritis (OA). Arthritis Rheum 1992;(35 Suppl):S132.
39. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. Osteoarthritis Cartilage 1993;1:97–103.
40. Moreland LW, Arnold WJ, Saway A, Savory C, Sikes D. Efficacy and safety of intra-articular hylan G-F 20 (Synvisc), a visco-elastic derivative of hyaluronan, in patients with osteoarthritis of the knee. Arthritis Rheum 1993;(36 Suppl):S165.
41. Puhl W, Bernau A, Greiling H, Kopcke W, Pforringer W, Steck KJ, *et al.* Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartilage 1993;1:233–41.
42. Cohen MA, Shiroky JB, Ballachey ML, Neville C, Esdaile JM. Double-blind randomized trial of intra-articular (I/A) hyaluronate in the treatment of osteoarthritis of the knee. Arthritis Rheum 1994;(37 Suppl):R31.
43. Creamer P, Sharif M, George E, Meadows K, Cushnaghan J, Shinmei M, *et al.* Intra-articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action. Osteoarthritis Cartilage 1994;2:133–40.
44. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis 1994;53:529–34.
45. Scale D, Wobig M, Wolpert W. Viscosupplementation of osteoarthritis knees with hylan: a treatment schedule study. Curr Ther Res 1994;55:220–32.
46. Carrabba M, Paresce E, Angelini M, Re KA, Torchiana EEM, Perbellini A. The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusion. Eur J Rheumatol Inflamm 1995; 15:25–31.
47. Corrado EM, Peluso GF, Gigliotti S, de Durante C, Palmieri D, Savoia M, *et al.* The effects of intra-articular administration of hyaluronic acid on osteoarthritis of the knee: a clinical study with immunological and biochemical evaluations. Eur J Rheumatol Inflamm 1995;15:47–56.
48. FDA Document: Summary of Safety and Effectiveness Data: Sodium Hyaluronate, www.fda.gov/cdrh/pdf/P980044b.pdf; January 24, 2001. Supartz® Rockville, MD.
49. Sala SF, Miguel RE. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: a short term study. Eur J Rheumatol Inflamm 1995;15:33–8.
50. Guler M, Kuran B, Parlar D, Guler M, Saglam H, Yapici S, *et al.* Clinical trial of intra-articular injection of hyaluronic acid in patients with osteoarthritis of the knee. Turkey: X National Rheumatology Congress; October 29–November 3, 1996.
51. Lohmander LS, Dalen N, Englund G, Hamalainen M, Jensen EM, Karlsson K, *et al.* Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis 1996;55:424–31.
52. Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Zhonghua Yi Xue Za Zhi (Taipei) 1997;59:99–106.
53. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol 1998;25:2203–12.
54. Hizmetli S, Kocagil S, Kaptanoglu E, Elden H, Nacitarhan V. The efficacy and safety of intra-articular hyaluronic acid in osteoarthritis of the knee: a prospective, double-blind trial. 1999, unpublished.
55. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res 2001;385:130–43.
56. Bunyaratavej N, Chan KM, Subramanian N. Treatment of painful osteoarthritis of the knee with hyaluronic acid. Results of a multicenter Asian study. J Med Assoc Thai 2001;2(84 Suppl):S576–81.
57. Dickson DJ, Hosie G, English JR. A double-blind, placebo-controlled comparison of hylan G-F 20 against diclofenac in knee osteoarthritis. J Drug Assess 2001;4:161–226.
58. Tamir E, Robinson D, Koren R, Agar G, Halperin N. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled study. Clin Exp Rheumatol 2001;19: 265–70.
59. Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med 2002;162:292–8.
60. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500–730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. Int J Clin Pract 2003;57:467–74.
61. Tsai C-L, Chang C-C, Chen S-C, Beinat L, Piva S. Treatment of knee osteoarthritis in Asian population with an intra-articular hyaluronan of MW 500–730 KDa. Osteoarthritis Cartilage 2003;(11 Suppl). 119.

62. Altman RD, Akermark C, Beaulieu AD, Schnitzer T. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2004;12:642–9.
63. Day R, Brooks P, Conaghan PG, Petersen M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol 2004;31:775–82.
64. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis 2004;63:1611–7.
65. Cubukcu D, Ardic F, Karabulut N, Topuz O, Hylan G- F. 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment. Clin Rheumatol 2005;24:336–41.
66. Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol 2005;32:1928–36.
67. Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, *et al*. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int 2005;25:264–9.
68. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006; CD004257.
69. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis Part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010;18(4):476–99.
70. Lee C, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. Arthritis Rheum 2005;53:510–8.
71. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, *et al*. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
72. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008;67:1716–23.
73. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. Baillieres Clin Rheumatol 1997;11:769–94.
74. Brandt KD, Smith Jr GN, Simon LS. Intraarticular injection of hyaluronan as treatment for knee osteoarthritis: what is the evidence? Arthritis Rheum 2000;43:1192–203.
75. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. Semin Arthritis Rheum 1997;26:755–70.