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ORIGINAL ARTICLE

Therapeutic Trajectory of Hyaluronic Acid Versus Corticosteroids in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis

RAVEENDHARA R. BANNURU,[1] NIKOLA S. NATOV,[2] ISI E. OBADAN,[1] LORI L. PRICE,[1] CHRISTOPHER H. SCHMID,[1] AND TIMOTHY E. McALINDON[1]

Objective. **To compare the efficacy of intraarticular hyaluronic acid with corticosteroids for knee osteoarthritis (OA).**
Methods. **Our data sources were Medline, EMBASE, CINAHL, BIOSIS, and the Cochrane database, as well as hand-searched reviews, manuscripts, and supplements. For unpublished data we used author contacts. Randomized trials that reported effects of intraarticular hyaluronic acid versus corticosteroids on knee OA were selected based on inclusion criteria. Two reviewers extracted data independently. Using a random-effects model, we computed effect sizes for pain change from baseline at 2, 4, 8, 12, and 26 weeks. We also performed multivariate analyses accounting for within and between-study covariance. We performed sensitivity analyses for trials that reported intent-to-treat (ITT) analysis and blinding, and directly compared Hyalgan with methylprednisolone.**
Results. **The 7 eligible trials included 606 participants. Five reported ITT analyses. At week 2 the effect size was −0.39 (95% confidence interval [95% CI], −0.65, −0.12) favoring corticosteroids; at week 4 it was −0.01 (95% CI −0.23, 0.21) suggesting equal efficacy. At week 8 the effect size was 0.22 (95% CI −0.05, 0.49) favoring hyaluronic acid, and at week 12 it was 0.35 (95% CI 0.03, 0.66) favoring hyaluronic acid. At week 26 the effect size was 0.39 (95% CI 0.18, 0.59), favoring hyaluronic acid. The multivariate analyses and sensitivity analyses generated consistent results.**
Conclusion. **From baseline to week 4, intraarticular corticosteroids appear to be relatively more effective for pain than intraarticular hyaluronic acid. By week 4, the 2 approaches have equal efficacy, but beyond week 8, hyaluronic acid has greater efficacy. Understanding this trend is useful to clinicians when treating knee OA.**

INTRODUCTION

Knee osteoarthritis (OA) is a common and progressive joint disease. With an estimated incidence rate of 240 per 100,000 person-years (1), it is a major public health problem in the US and often results in early retirement and joint replacement. In the absence of effective disease-modifying medical interventions for knee OA, treatments are primarily symptomatic in nature, often including intraarticular injections of a corticosteroid or hyaluronic acid.

Corticosteroids have been employed for years in the treatment of OA, and as a result rheumatologists have substantial clinical experience of their utility and effectiveness. Consensus statements widely recommend corticosteroids as useful adjunctive treatment in the management of knee OA (2–4). Clinical trials and meta-analyses have demonstrated their efficacy (5). Hyaluronic acid, a large viscoelastic glycosaminoglycan that is naturally present in healthy joint fluid, is a relatively new intervention that is now widely used. It confers to joint fluid a number of protective properties, including shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication (6).

The original biologic rationale for the therapeutic use of synthetic hyaluronic acid in knee OA was its potential to increase the viscosity of synovial fluid (7). Therefore, the basis for the Food and Drug Administration's approval for hyaluronic acid was as a medical device rather than a pharmaceutical, and despite many placebo-controlled

[1]Raveendhara R. Bannuru, MD, Isi E. Obadan, MBBS, MPH, Lori L. Price, MAS, Christopher H. Schmid, PhD, Timothy E. McAlindon, DM, MPH: Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [2]Nikola S. Natov, BSc: Tufts University School of Medicine, Boston, Massachusetts.

Address correspondence to Timothy E. McAlindon, DM, MPH, Center for Arthritis and Rheumatic Diseases, Tufts Medical Center, Tufts University School of Medicine, 800 Washington Street, Box 406, Boston, MA 02111. E-mail: tmcalindon@tuftsmedicalcenter.org.

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trials of hyaluronic acid products, contention remains regarding their effectiveness. Although numerous clinical trials reported durable benefits on knee OA (8,9), others failed to show benefits compared with placebo (10,11). This raised the question about the magnitude of therapeutic effects of hyaluronic acid products and stimulated a number of meta-analyses (12–17). However, the conclusions of meta-analyses were also inconsistent: 2 analyses drew strongly positive conclusions but had potential conflicts of interest (12,13); 2 reported a small effect (14,15); and 2 others inferred that hyaluronic acid is not more effective than saline as a placebo (16,17).

In the face of this controversy, we aimed to reexamine the clinical usefulness of hyaluronic acid products from the perspective of their relative efficacy when compared with intraarticular corticosteroids, a widely used intervention with which clinical rheumatologists have considerable familiarity. In addition, we sought to determine their relative efficacy over time, since prior trials suggest that they have different response trajectories.

MATERIALS AND METHODS

Selection of trials. Two reviewers (RRB and NSN) performed an electronic literature search for citations comparing the efficacy of intraarticular hyaluronic acid injections with intraarticular corticosteroid injections in the management of knee OA. We searched Medline, EMBASE, CINAHL, BIOSIS, and the Cochrane Controlled Trials Register from inception to February 2009. The key terms osteoarthritis, osteoarthrosis, gonarthrosis, degenerative arthritis, hyaluronic acid (and the trade names for hyaluronic acid), hyaluronan, hyaluronate, viscosupplementation, and corticosteroids (and the trade names for corticosteroids) were entered as medical subject heading terms and as text words for searches. All searches were limited to human randomized clinical trials reported in journals with no language restrictions. We also hand searched the reference lists of all retrieved studies and abstracts presented at scientific meetings of the American College of Rheumatology, the British Society for Rheumatology, and the Osteoarthritis Research Society International to ensure that no eligible studies were excluded. The conference proceedings were searched from January 1990 to February 2009. 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 search was performed independently by the same 2 reviewers to ensure an exhaustive review of the literature.

Inclusion criteria. We included all clinical trials that were randomized, used human subjects, and compared the therapeutic effects of intraarticular hyaluronic acid with that of intraarticular corticosteroids to treat knee OA. Each included trial was required to contain extractable data for at least 1 of the outcome measures of pain currently recommended for OA clinical trials (Table 1).

Table 1. Hierarchy of outcome measures used in the meta-analysis*

Outcome measures
Western Ontario and McMaster Universities
Osteoarthritis Index Pain Subscale (visual analog scale or Likert)
Index joint pain when walking (visual analog scale or Likert)
Index joint pain during activities other than walking (visual analog scale or Likert)
Spontaneous index joint pain (visual analog scale or Likert)

* To be eligible for our analysis, studies had to report results for ≥1 of these outcomes.

Data extraction. Two reviewers (RRB and NSN) independently extracted data from each trial using a standardized data form. The year of publication, trial design, number and mean age of participants, percentage of women, withdrawal rate, duration of study, study design, dosage and number of treatment doses used, and outcome measures were extracted for each trial. Where necessary, means and measures of dispersion were approximated from the figures in the studies. We determined whether concealment of allocation was reported, the degree of blinding, and whether or not there was an intent-to-treat (ITT) analysis. The type and extent of sponsorship were also noted. The data were checked for consistency between the 2 reviewers, and any discrepancy identified was discussed until a consensus was reached.

Time points. Since the treatment duration and the post-treatment assessment time points varied among the trials, we grouped the time points of outcome assessments of individual trials into 5 intervals: 2 weeks (1–2 weeks), 4 weeks (3–6 weeks), 8 weeks (7–10 weeks), 12 weeks (11–16 weeks), and 26 weeks (17–29 weeks). This grouping was designed to best capture the data presented in all of the studies.

Assessment of trial quality. Two reviewers (RRB and NSN) independently assessed the methodologic quality of each trial for randomization, appropriateness of the randomization method (computer generated, centralized randomization), blinding, and appropriateness of the blinding method (investigator blinded to the intervention, participant blinded to the intervention, assessor of the end point blinded to the intervention). We assessed the way all withdrawn participants were reported and how their data were treated, and we determined whether concealment of allocation to intervention was reported.

Each study was evaluated for the type of analysis performed (ITT versus no ITT). An analysis was considered to be ITT if it was characterized by its investigators as such and if there was an attempt to analyze data from all randomized participants, or if there were no dropouts (even if the analysis was not specifically described as ITT). In trials for which both ITT and no ITT analyses had been performed, and that included extractable data for each analysis, we used the ITT analyses. Within each study, the

number of participants randomized and the number analyzed were evaluated.

Statistical analysis. We computed an effect size for each study at each time point using Hedges' g statistic (18) corrected for small samples as follows:

$$g = [(M_{HA} - M_{CS})/S_{pooled}]$$

$$S_{pooled} = \sqrt{\{[(n_{HA}-1)S^2_{HA} + (n_{CS}-1)S^2_{CS}]/(n_{HA}+n_{CS}-2)\}}$$

$$\text{Corrected Hedges' } g = g^*[1 - 3/\{4(n_{HA}+n_{CS})-9\}]$$

where M_{HA}, S_{HA}, and n_{HA} are the mean change, SD, and the number of participants studied from baseline to a given time point in the hyaluronic acid group, respectively. M_{CS}, S_{CS}, and n_{CS} are the corresponding values in the corticosteroid group. Throughout this article, negative Hedges' g favors corticosteroids and positive Hedges' g favors hyaluronic acid.

We calculated the pooled effect size at each time point separately using a random effects model with between-study variance calculated by the DerSimonian-Laird method (19). The pooled data are presented as forest plots with 95% confidence intervals (95% CI). We assessed statistical heterogeneity with the help of the I^2 statistic (20). We then ran multivariate analyses at each time point separately to check robustness of the effect sizes while accounting for within- and between-study covariance (21). We used SAS statistical software, version 9.1 and R, version 2.7.2 (SAS Institute, Cary, NC) for the analysis.

Wherever necessary, we imputed the SD according to a published method (22). Of note is that one can only accurately estimate the 95% CI around change scores when the raw data are presented in all relevant articles or when the correlation between pretest and posttest scores is known. Neither quantity was published in the available studies, so we used a correlation of 0.5 to calculate the measure of the change score dispersion. This is a conservative assumption that will artificially widen the 95% CI around the summary statistic.

Analyses of sensitivity. We did sensitivity analyses restricted to trials that reported ITT analysis, blinding methodology, and that directly compared Hyalgan (Fidia SPA, Abano Terme, Italy) with methylprednisolone. We were unable to perform sensitivity analysis restricted to trials with adequate allocation concealment, because only one trial reported adequate allocation concealment. We also ran meta-regressions adjusting for blinding status and ITT status.

RESULTS

Trials. Our search yielded 1,238 studies, of which 1,108 were excluded after title and abstract screening. Full reports were retrieved for 130 studies, and 121 of those studies were excluded since they were not relevant to the study question. Nine randomized clinical trials fulfilled our inclusion criteria (23–31). Two of those 9 trials did not report sufficient information for data extraction and analysis and were excluded (30,31). One trial reported only median values of the outcome measures and no mean values or any measures of variance (31). The other trial did not use a validated scale for reporting outcomes (30). Therefore, our meta-analysis was based on 7 trials (Figure 1).

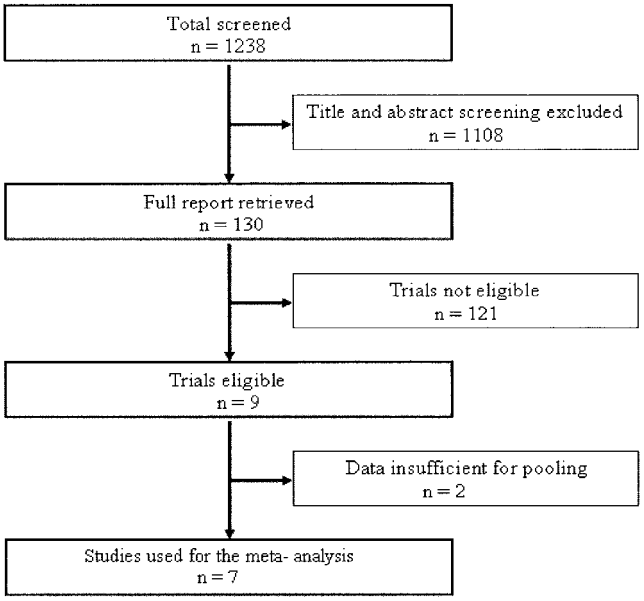

Figure 1. Summary of the search results and trial selection.

Trial characteristics. The characteristics of the 7 included trials are presented in Table 2, and the characteristics of the participants involved in these trials are presented in Table 3. These trials were published between 1987 and 2004. Overall, these 7 trials randomized 606 participants (representing 610 knees). Three hundred twelve participants (101 men, 211 women) were assigned to the hyaluronic acid arm and 294 participants (298 knees, 99 men, 195 women) received corticosteroids. These trials included participants with a mean age range of 49–72 years.

Of the 7 trials used in the analysis, 4 compared Hyalgan with methylprednisolone acetate (23–25,27), one compared Hyalgan with triamcinolone hexacetonide (26), one compared Orthovisc (Anika Therapeutics, Woburn, MA) with methylprednisolone acetate (28) and the seventh compared Synvisc (Genzyme, Ridgefield, NJ) with triamcinolone hexacetonide (29). Therefore, all of the included trials used Hyalgan as their hyaluronic acid product except 2, which used Orthovisc (28) and Synvisc (29). Hyalgan has a molecular weight of 500–730 kd, Orthovisc has a molecular weight of 1,000–2,900 kd and Synvisc is a cross linked product with a molecular weight of 6,000 kd.

As a comparator, 5 of the trials used methylprednisolone acetate, at a frequency of 3 weekly injections for a total dose of 120 mg. One trial used a single 20-mg dose of triamcinolone hexacetonide and 4 weekly placebo injections (26). The seventh trial used a single 40-mg dose of triamcinolone hexacetonide (29).

Trial quality. All trials were reported as randomized. Only 1 was double-blinded (26), 3 were single-blinded toward the evaluator (23,27,29), and 3 were open-label (24,25,28). Five trials reported to have performed an ITT

Table 2. Characteristics of trials included in the meta-analysis

Trial author, year (ref.)	Dose	Sponsor	Blinding	Allocation concealment	Intent to treat
Leardini et al, 1987 (23)		Industry	Single evaluator	Unclear	Yes
Hyalgan	2 ml (20 mg), 3 weekly injections				
Methylprednisolone	1 ml (40 mg), 3 weekly injections				
Leardini et al, 1991 (24)		Industry	Open label	Unclear	Yes
Hyalgan	2 ml (20 mg), 3 weekly injections				
Methylprednisolone	1 ml (40 mg), 3 weekly injections				
Pietrogrande et al, 1991 (25)		Industry	Open label	Unclear	Yes
Hyalgan	2 ml (20 mg), 5 weekly injections				
Methylprednisolone	1 ml (40 mg), 3 weekly injections				
Jones et al, 1995 (26)		Industry	Double	Unclear	No
Hyalgan	20 mg, 5 weekly injections				
Triamcinolone hexacetonide	20 mg single injections followed by 4 placebo injections				
Frizziero and Pasquali Ronchetti, 2002 (27)		Unclear	Single evaluator	Adequate	Yes
Hyalgan	2 ml (20 mg), 5 weekly injections				
Methylprednisolone	1 ml (40 mg), 3 weekly injections				
Tascioglu and Oner, 2003 (28)		Unclear	Open label	Unclear	No
Orthovisc	2 ml (30 mg), 3 weekly injections				
Methylprednisolone	1 ml (40 mg), 3 weekly injections				
Caborn et al, 2004 (29)		Industry	Single evaluator	Unclear	Yes
Synvisc	2 ml (16 mg), 3 weekly injections				
Triamcinolone hexacetonide	2 ml (40 mg), single injection				

analysis (23–25,27,29). One trial reported allocation concealment (27).

Sponsorship and heterogeneity. None of the trials reported independent funding from any governmental or not-for-profit organization. Five trials were sponsored by manufacturers of hyaluronic acid (23–26,29), and the other 2 were unclear if they were sponsored or not (27,28). The analysis exhibited heterogeneity (I^2) scores of 47% at 2 weeks, 37% at 4 weeks, 47% at 8 weeks, 49% at 12 weeks, and 0 at 26 weeks.

Meta-analysis. At week 2 we found an effect size of −0.39 (95% CI −0.65, −0.12) favoring corticosteroids (Fig-

Table 3. Characteristics of the participants in the pooled trials

	All participants				Hyaluronic acid group				Corticosteroid group			
Trial author, year (ref.)	N	Mean age, years	Withdrawn, %	Women, %	N	Mean age, years	Withdrawn, %	Women, %	N	Mean age, years	Withdrawn, %	Women, %
Leardini et al, 1987 (23)	40*	64	20	81	20	64	25	80	20†	65	15	81
Leardini et al, 1991 (24)	40	65	0	88	20	65	0	85	20	65	0	90
Pietrogrande et al, 1991 (25)	90	63	1	73	45	64	2	78	45	62	0	69
Jones et al, 1995 (26)	63	71	66	62	32	71	59	56	31	70	74	68
Frizziero and Pasquali Ronchetti, 2002 (27)	99	50	29	53	52	49	27	54	47	50	32	53
Tascioglu and Oner, 2003 (28)	60	59	8	100	30	57	7	100	30	60	10	100
Caborn et al, 2004 (29)	218	63	30	57	113	63	27	59	105	64	33	54

* In 36 patients and 40 knees.
† In 16 patients and 20 knees.

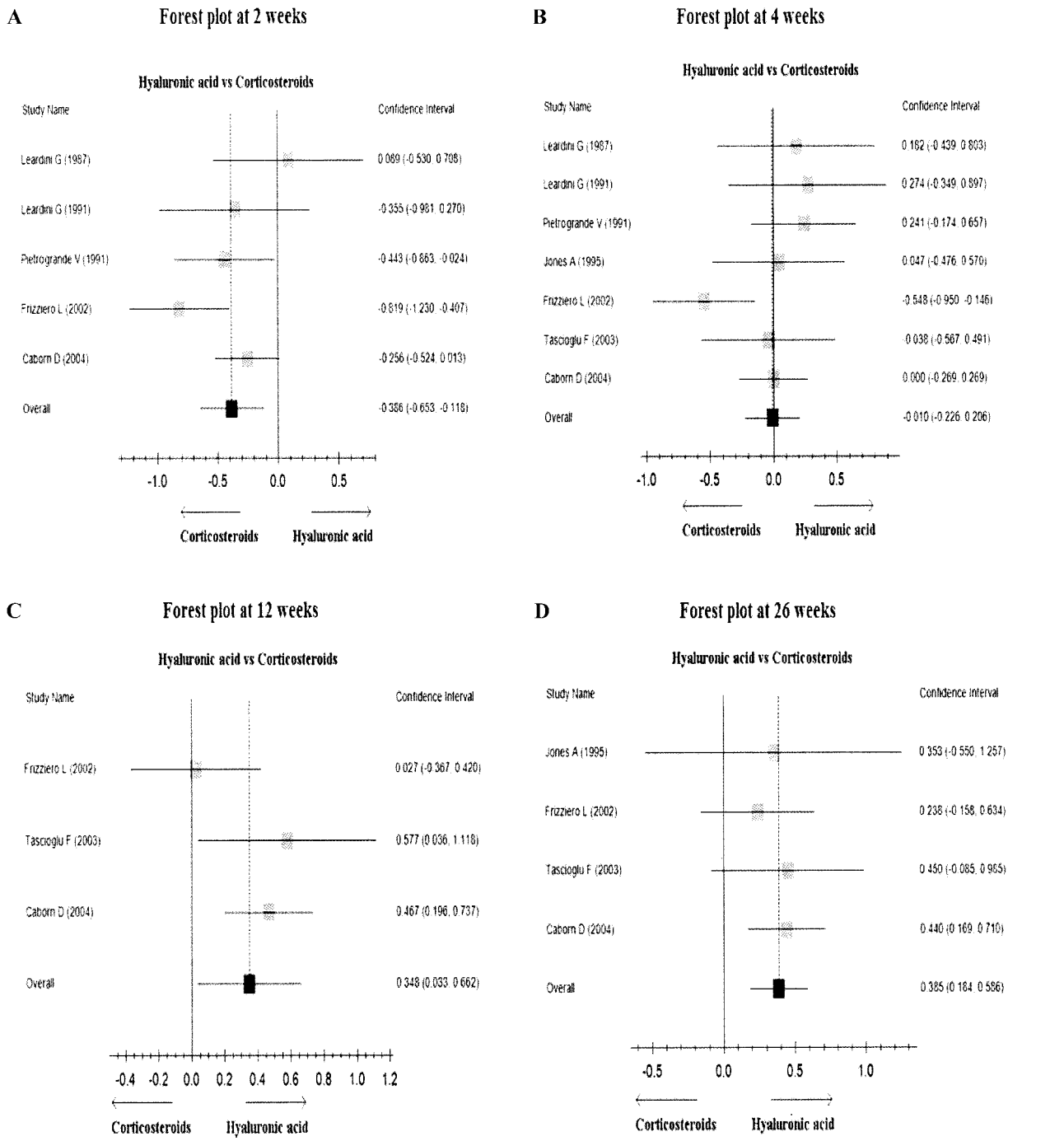

Figure 2. Forest plots of pain change from baseline at **A,** 2 weeks, **B,** 4 weeks, **C,** 12 weeks, and **D,** 26 weeks.

ure 2A). At week 4 the effect size was −0.01 (95% CI −0.23, 0.21) suggesting equal efficacy (Figure 2B). At week 8 there was an effect size of 0.22 (95% CI −0.05, 0.49) favoring the hyaluronic acid preparations. At week 12 the effect size was 0.35 (95% CI 0.03, 0.66) favoring hyaluronic acid (Figure 2C). Even at week 26 we found an effect size of 0.39 (95% CI 0.18, 0.59) favoring hyaluronic acid (Figure 2D). At 26 weeks we had the same results, even if we excluded an outlier trial with a high withdrawal rate (26).

Multivariate analyses. The results were consistent when we ran multivariate analyses accounting for within- and between-study covariance. At week 2 the effect size was −0.37 (95% CI −0.57, −0.18) favoring corticosteroids; the effect size at week 4 was −0.001 (95% CI −0.19, 0.18) suggesting equal efficacy; at week 8 the effect size was 0.24 (95% CI 0.05, 0.44) favoring hyaluronic acid; at week 12 the effect size was 0.45 (95% CI 0.23, 0.66) favoring hyaluronic acid; and at week 26 the effect size was 0.45 (95% CI 0.22, 0.68) favoring hyaluronic acid.

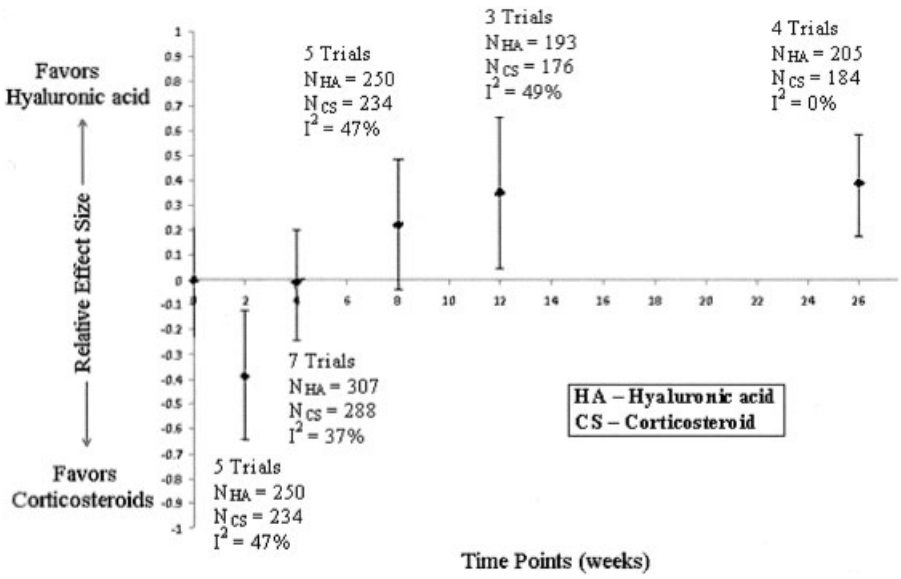

Figure 3. Relative effect size at each time point (95% confidence intervals).

Sensitivity analyses. The results were also consistent when we confined the pooled analysis to the 5 trials that reported using an ITT analysis (23–25,27,29). All 5 trials reported the results at 2, 4, and 8 weeks, but only 2 trials reported the results at 12 and 26 weeks (27,29). In this subset analysis the effect size favored corticosteroids at week 2 (−0.39 [95% CI −0.65, −0.12]), and suggested equal efficacy at week 4 (−0.004 [95% CI −0.30, 0.30]). The effect sizes favored hyaluronic acid at weeks 8, 12, and 26 (week 8 effect size 0.22 [95% CI −0.05, 0.49], week 12 effect size 0.27 [95% CI −0.16, 0.69], and week 26 effect size 0.38 [95% CI 0.15, 0.60]).

These results were also broadly consistent when we confined the pooled analysis to the 4 trials that reported single-blind or double-blind methodology (23,26,27,29). We found an effect size of −0.36 (95% CI −0.82, 0.10) favoring corticosteroids at week 2. At week 4 the effect size of −0.11 (95% CI −0.42, 0.21) slightly favored corticosteroids. At week 8 the effect size of 0.08 (95% CI −0.27, 0.43) favored hyaluronic acid. At week 12 the trend continued with an effect size of 0.27 (95% CI −0.16, 0.70) favoring hyaluronic acid. At week 26 we saw an effect size of 0.37 (95% CI 0.16, 0.59) favoring hyaluronic acid.

Similarly, when we confined the pooled analysis to the 4 trials that compared Hyalgan with methylprednisolone acetate (23–25,27), we found an effect size of −0.43 (95% CI −0.79, −0.08) favoring the corticosteroids at week 2. At week 4 the effect size of 0.01 (95% CI −0.43, 0.45) suggests equal efficacy. At week 8 we saw an effect size of 0.21 (95% CI −0.18, 0.60) favoring the hyaluronic acid. The meta-regression analysis identified no significant interactions with blinding or ITT status.

DISCUSSION

This meta-analysis of trials comparing hyaluronic acid with corticosteroids shows a pattern of relative efficacy that varies over time. In the short term (up to 4 weeks), corticosteroids appear to be more effective for pain. The 2 treatment approaches have equal efficacy 4 weeks after initiation of treatment, but by 8 weeks and beyond, hyaluronic acid products have greater relative effects (Figure 3). Of course, this is a comparative analysis of the relative efficacy of the 2 interventions, which does not directly inform us of their efficacy compared with no treatment. However, together with prior demonstrations of efficacy of corticosteroids when compared with placebo (5), and expert opinions about their clinical utility (2–4), our analysis suggests that both are efficacious, albeit with contrasting onset and duration. However, if we assume that the effect of corticosteroids is largely absent by the 26-week time point (5), we might infer that the absolute effect of hyaluronic acid at this time point is modest.

The validity of the output of any meta-analysis depends on the quality of the pooled clinical trials. This issue has been especially contentious among prior meta-analyses of hyaluronic acid products (12–17), 2 of which based their negative interpretations on poor trial quality. One aspect in particular was the conspicuous absence of ITT data in the trial reports. However, in our analysis, 5 of the 7 included studies did report ITT data (23–25,27,29). A subset analysis confined to these 5 trials yielded results that were consistent with the overall analysis (23–25,27,29). Two trials reported no dropouts (23,24), and 1 trial reported 1 dropout at 8 weeks (25). Two trials did not report dropouts at each time point but performed ITT analyses (27,29), of which 1 used the last observation carried forward approach (29) and the other did not specify the way they dealt with the missing data (27). Two trials performed no ITT analyses (26,28).

It is also possible to test for the influence of methodologic issues among the pooled data through sensitivity analyses around quality parameters. Five of the included trials were of low quality (23–25,28,29), and the other 2 were of higher quality (26,27). The higher quality studies had individual results that were broadly consistent with the lower quality ones. The first of these with adequate allocation concealment had a high withdrawal rate (29%)

(27). Its results favored corticosteroids at 2, 4, and 8 weeks, and at 26 weeks favored hyaluronic acid. The second trial used double-blinding methodology but reported a completer's analysis and experienced a high withdrawal rate (67% at 29 weeks) (26); its results were equivocal at 4 weeks and favored hyaluronic acid at 26 weeks.

Two of the trials reported statistically significant differences in the mean pain scores (visual analog scale [VAS]) between the 2 treatment groups at baseline (23,24). One trial had mean pain scores significantly favoring the corticosteroids group at the baseline and continued to favor the corticosteroids group throughout the study (23). The other trial had mean pain scores significantly favoring the hyaluronic acid group at the baseline and they continued to favor the hyaluronic acid group throughout the study (24). In an attempt to account for this difference, we performed a meta-analysis of change scores. However, the mean change values of pain in these 2 trials showed similar trends to those we observed in the pooled data (23,24).

Another problem in attempting to pool all of the study results was the considerable variety of assessment instruments (e.g., VAS, Western Ontario and McMaster Universities Index-Likert version, VAS version). 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 (19).

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 1).

Another potential source of heterogeneity in efficacy among hyaluronic acid and corticosteroids trials was the use of different drugs in varied doses and regimens. However, the results were consistent when we confined the pooled analysis to the 4 trials that compared Hyalgan with methylprednisolone acetate (23–25,27). The trial that used Orthovisc had equivocal results at 4 weeks and favored hyaluronic acid at 26 weeks (28). The trial that used Synvisc had trends consistent with our results (29).

Six trials allowed the use of analgesics such as nonsteroidal antiinflammatory drugs or acetaminophen, which may have attenuated estimates of efficacy of either drug (23–26,28,29). The other trial was not clear about the usage of concomitant medication (27). Since we would expect this sort of bias to reduce the measured treatment effects, it is unlikely to substantially influence our inferences from this analysis.

One unique aspect of this meta-analysis is that we examined the therapeutic response over time by separately pooling the data for each time point. The product of this analysis was highly informative in contrasting the pattern of therapeutic response attributable to each intervention. However, there are some limitations to this approach, including that not all of the clinical trials provided data relating to each of the time points and the possibility of correlations among outcomes between the time points. We addressed these issues by performing multivariate analyses accounting for within- and between-study variance (21). The multivariate results were consistent with the primary analysis and, in fact, demonstrated an additional significant difference at the 12-week time point.

The contrasting trajectories of treatment response to the 2 interventions are likely predicated on different mechanisms of action and pharmacokinetics. Corticosteroids have potent antiinflammatory influences, which are a plausible explanation for the rapid but short-lived effects (32). Animal model studies of OA also suggest that corticosteroids might have benefits through reducing cytokine and metalloprotease expression (33).

The precise mechanism of action of synthetic hyaluronic acid is unknown. However, proposed mechanisms of hyaluronic acid activity occur in 2 stages: a mechanical/physical stage, and a physiologic stage. Under the mechanical/physiologic stage OA synovial fluid is replaced by higher concentrations of hyaluronic acid, thereby improving viscosity (34). This also restores the shock-absorbing and lubricating abilities of depleted synovial fluid (35) and maintains a boundary layer around nociceptors, reducing pain induction (36,37). The physiologic stage induces the biosynthesis of hyaluronic acid and extracellular matrix components (38), which reduces proteoglycan loss in cartilage (34,35) and apoptosis of chondrocytes (39). It also reduces inflammatory cell activities to reduce hyaluronic acid degradation (34) and acts by reducing induction of pain mediators (34,36,37).

In summary, the evidence suggests that corticosteroids are more effective than hyaluronic acid in the short term (up to 4 weeks), whereas hyaluronic acid is more effective in the long term (4–26 weeks). Awareness of this pattern of response is useful to the clinician in formulating a therapeutic plan for patients with knee OA. It may also be useful to determine in future studies whether coadministration of the 2 agents has a synergistic effect that is useful in clinical practice.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Bannuru, Natov, Price, Schmid, McAlindon.

Acquisition of data. Bannuru, Natov, McAlindon.

Analysis and interpretation of data. Bannuru, Obadan, Price, Schmid, McAlindon.

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