Current Therapeutic Research 90 (2019) 39–51

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Intra-Articular Hyaluronic Acid in the Symptomatic Treatment of Knee Osteoarthritis: A Meta-Analysis of Single-Injection Products

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ARTICLE INFO

Article history:
Received 12 September 2018
Accepted 25 February 2019

ABSTRACT

Background: Viscosupplementation of the synovial fluid with intra-articular hyaluronic acid (IA HA) is a well-known symptomatic treatment of knee osteoarthritis. The question arises whether a monoinjection (ie, single injection) could be as efficient as multi-injection (ie, 3–5 injections) regimens.

Methods: A meta-analysis of published studies relating to IA HA monoinjection trials was performed. The efficacy criterion was the Western Ontario and MacMaster Universities pain subscore. Any study design was accepted, from randomized control trials to single-arm observational open-label studies. An extensive search was performed using PubMed, Google, Google Scholar, and references found in recent meta-analyses, for all articles published before end of April 2018. Population profiles were analyzed in terms of age, sex, body mass index (BMI), and Kellgren-Lawrence (KL) radiology grades. Results of intra-articular single injection of placebo were collected to create a database allowing post hoc comparisons. Each IA HA study arm was compared to an IA placebo arm (either pooled or not), to present a similar KL profile controlled with the χ^2 test. The effect size (ES) (95% CI) and *P* values were calculated and synthesized for each follow-up visit at 1, 2, 3, and 6 months. In parallel, a global approach was used to represent the variations from baseline for each group or subgroup studied.

Results: From 1547 citations, 28 studies were included in the meta-analysis, representing 4129 patients treated with monoinjection: 3360 received IA HA and 769 patients received IA placebo. The mean (SD) IA HA patient was 61.2 (9.6) years, 63% women, BMI 28.0 (4.1), 47% KL III, and 3% KL IV. A good placebo KL profile matching was obtained for 26 of the 31 IA HA arms. For the whole IA HA population, ES = 0.30 (95% CI, 0.25–0.35) at 3 months and ES = 0.39 (95% CI, 0.33–0.44) at 6 months. In a restricted analysis, after removal of outliers, poorly KL matched and active arms <30 patients, results remained unchanged, ES = 0.29 (95% CI, 0.23–0.34) and ES = 0.40 (95% CI, 0.34–0.45) at 3 and 6 months respectively, whilst heterogeneity was improved.

Conclusions: There are certainly limits to the post hoc placebo comparison method, for individual studies. But for each synthesis per subgroup or group, the results were properly confirmed using multiple statistical approaches and weighing methods. This meta-analysis suggests that monoinjections produce results similar to multi-injections of IA HA in terms of pain relief in the treatment of knee osteoarthritis. (*Curr Ther Res Clin Exp*. 2019; 80:XXX–XXX)

Introduction

Viscosupplementation (VS) of the synovial fluid by intra-articular (IA) injections of hyaluronic acid (HA) is a well-known symptomatic treatment of knee osteoarthritis (OA), in use for more than 30 years. Typically, the treatment consisted of 3 to 5 injections at 1-week intervals, but more recently—in the past 10 to 15 years—alternative regimens have been proposed, consisting of 1 injection only. The question therefore arises whether a single injection (ie, monoinjection) of IA HA has the same level of efficacy as multi-injection regimens, particularly in comparison to injected placebo.

Objectives

To evaluate the efficacy of a single IA injection of HA, in the symptomatic treatment of knee OA, by comparing clinical results obtained through various trials using the Western Ontario and MacMaster universities pain subscore (WOMAC A), to those obtained with a single injection of placebo.

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https://doi.org/10.1016/j.curtheres.2019.02.003

A meta-analysis of published studies was performed, to collect the largest quantity of clinical results. No systematic review was anticipated.

Methods

The methods were adapted from the preferred reporting items for systematic reviews and meta-analyses statement[1] recommendations.

Protocol and ethic statements

The protocol was to extract and explore all data results for the WOMAC A, from published studies without limiting the investigation to randomized controlled trials (RCTs). Consequently, with inclusion of all types of study, a high level of evidence is not claimed for this meta-analysis, and no registration was needed. Institutional review board/ethics committee approval was not required for this retrospective meta-analysis that was based solely on published statistical results, without need of any individual patient results.

Eligibility criteria

Inclusion of articles was done after passing the following criteria:

- Clinical prospective studies on human patients with knee OA, with all designs permitted, from double-blind RCT to open-label single arm studies. Any kind of comparator was allowed, including injected placebo (ie, saline solution), another IA HA (single or multi-injections), or any other alternative treatment (preferably injected). At minimum, a comparison to baseline was required.
- At least 1 population arm treated with a single injection of HA, positioned as the product analyzed or as the control.
- The WOMAC A—the single criterion used for this meta-analysis—with at least 2 measures made: 1 at inclusion (ie, baseline) and 1 at follow-up.
- Known patient profile for each population, with data documented for age, body mass index (BMI), distribution of Kellgren-Lawrence (KL) radiology grades, and OA anteriority to allow the assessment of comparability between groups.
- Quantitative results allowing analysis, preferably given as mean, standard deviation (SD) and number of patients, for each measure.
- Qualitative results provided as frequency (percentage or population).

Placebo-injected comparators were analyzed similarly, and their results were pooled in various combinations to match the patient profile of each trial. Other comparator arms present in these studies, such as IA steroids, multi-injection HA, or alternative treatments (eg, plasma rich in growth factors), were not considered for this analysis.

Information sources

A systematic research was done to select proper results, all published before end of April 2018. No limitation to the past was set, because single-injection of IA HA is a relatively recent regimen for the VS in knee OA. There was no restriction placed on the country in each study was done, but only articles published in English were considered. Articles were selected among references found in PubMed, Google, Google Scholar, and from recent meta-analyses.[2–12] We used the following key words, sequentially associated, to get limited lists of properly oriented citations: *single, hyaluronic acid, sodium hyaluronate, intra-articular, injection, knee, osteoarthritis, viscosupplementation, cross-linked, G-F 20, Hylan, Synvisc-One, Durolane, NASHA, Monovisc, Gel-200,* and *clinical trial.*

Search and study selection

A first selection was done after screening the titles and abstracts, then full-text articles were assessed for their eligibility. Special care was taken to eliminate duplicate publications at different levels of the search. Animal or laboratory testing, general articles, reviews, meta-analyses, recommendations (ie, guidelines), or author's opinions were also eliminated.

At the end, articles were also not included if they described:

- A specific context different from the current practice of VS of knee OA: other joint, surgery context, or other pathology associated;
- A multi-injection regimen (more than 1 IA HA injection per treatment);
- A clinical trial done with a nonmarket-approved mono-injection IA HA (European Community or United States);
- A planned combination of treatments, without use of IA HA alone; or
- Insufficient data for the WOMAC A.

Data process

Data extracted from the articles were taken as published and no question has been addressed to any of the authors. A strong effort was made to include all possible studies; when needed and justified, the standard error (SE) was calculated from the *P* value, or data was measured on the available graphs. No alternative pain assessment was considered to compensate or complete any missing WOMAC A data.

Data were collected and processed using Excel (Microsoft Corp, Redmond, Washington). Interpretation was done following the description made within each study. Data was recorded per study arm either for the IA HA mono-injection or, when present, the injected placebo comparator. These data included the arm size (ie, population), the average patient profile at inclusion (ie, number, sex, age, BMI, OA anteriority), and the WOMAC A subscore (SD) at each observation time from the inclusion to the last control visit. For a comprehensive assessment, all these scores were recalculated on a 0 to 100 scale, and the observation times were classified at months M1 (2–5 weeks), M2 (6–9 weeks), M3 (10–18 weeks), and M6 (22–26 weeks).

Many studies did not have their own IA placebo control arms, so our approach consisted of using the available IA placebo results as an independent database, and subsequently selecting the best placebo comparator for each study by matching the KL profile. Proper matching was controlled with the χ^2 test and considered as satisfactory if $P > 0.05$. Each RCT versus placebo kept its own control arm.

Summary measures

In the first phase, each individual study and its matching placebo were analyzed. The variations from baseline (or inclusion) were calculated with the SD for each population seen at each visit (M1, M2, M3, and M6). Then, the comparison to placebo was done, calculating the difference of variation from baseline, the pooled SD and SE, the effect size (ES)—which is defined here as Cohen's d[13] with the attached 95% CI—and *P* value.

Synthesis of results

In the second phase, different pooling methods were tested. Using MIX 2.0 software (BiostatXL, Frederick, Maryland) (fixed effect,

inverse-variance pooling), a synthesis at each visit time was proposed, representing the results as forest plots. The clinical efficacy was therefore assessed for each individual study, from the absolute difference with placebo (relevant or not) and the statistical significance (P value). Also, ES = 0.2 was a priori considered small, 0.5 was considered medium, and 0.8 was considered large. Heterogeneity was assessed from funnel plots and from the indexes I^2 and τ^2.

Additional analysis

In a separate approach, single-injection HAs were pooled per product to form subgroups >500 patients. Alternatively, they were pooled together into a subgroup called "other IA HA." Intergroup comparisons were performed between each subgroup (product) and its matched placebo group. Finally, a synthesis was done for all single IA HA products. Graphs were made to illustrate these results, representing the score variations from baseline and ES as a function of time that follows the concept of a therapeutic trajectory.[2]

Risk of bias within or across studies

There was no systematic review of each characteristic of the studies. Our intention was to explore widely existing data, so we included all types of studies. Consequently, factors like the presence of a control arm, the allocation technique, or the quality of the blinding could not apply. To assess the risk of bias, we first used the funnel plots to detect outlying results and potential publication bias, demonstrated by asymmetry of the funnel plot. Then, to limit the risk of selection bias, special care was given to the quality of the placebo matching for each active study arm. In summary, for the included studies, outlying results, other potential bias, heterogeneity assessment results, and other abnormalities were analyzed. This led us to discard several studies that are further detailed in the Results.

Results

Study selection

Study selection results are described by the flow chart (Figure 1). The research was initiated via PubMed, proceeded with Google, and subsequently with Google Scholar. As complement, 55 miscellaneous citations (35 abstracts and 20 full-text articles) were added from various sources. A final search of the lists of references generated numerous duplicates that were eliminated during our selection process. A total of 1547 citations were identified. After screening from title and/or abstract and removal of the duplicate publications, 112 full-text articles of interest were assessed for eligibility. Of these, 57 included data for IA HA mono-injection.[14–70] At the end, 28 studies were included,[43–70] whereas 29 studies were removed for 1 or several of the following reasons:

- Two studies were in combination with surgery: anterior cruciate ligament reconstruction,[26] or arthroscopy[27];
- Eight with experimental regimens from a multi-injection product: single-shot,[26–28] or large shot grouping several syringes,[29–31] or smaller shot,[32] or retreatment[33];
- Three nonapproved products for VS in European Community or United States[16,17,34];
- Seventeen did not include a WOMAC A result[14–30];
- Six with missing data: no SD or SE,[35–38] no score at inclusion (set at 100% = major bias),[39] or inappropriate data (population ratio for gain >15 mm or 40%)[40]; and
- Two had duplicate datasets: the dataset used by Frampton[41] was the same as that used by Chevalier et al[43] and the dataset used by Belzile et al[42] was the same as that used by Hangody et al.[60]

In summary, 25 of the 28 included studies were successively identified from PubMed (19 during the first search), 3 from Google, and none additional from the other sources.

Study characteristics and placebo matching

Among the 28 included studies, 8 were single-arm, observational studies and 20 were RCTs. Of those RCTs, 14 were described as double-blind. In the 6 remaining RCTs,[49,55,57,59,64,65] there were numerous differences in treatments (eg the number of injections) and, although it seemed possible to maintain study blinding for the patient, it was unclear whether the assessment was made by a blinded investigator. The comparators within the 20 RCTs were:

- IA saline solution (ie, placebo) for 6 studies;[43,51,52,60–62]
- IA autologous preparation for 4 studies:[56,57,64,65] platelet rich plasma (PRP), plasma rich in growth factors (PRGF), or mesenchymal stem cells (MSC);
- IA ozone for 1 study[64];
- IA drug (ie, corticosteroid) for 3 studies[47,49,53];
- Another IA HA monoinjection for 3 studies, here analyzed as separate arms,[45,46,48] or ignored for 2 other experimental, nonapproved products[45]; and
- IA HA multi-injection for 4 studies.[54,55,59,70] To maintain the same number of injections per patient in both trial arms, 1 study used sham injections from empty syringes[54] and another used IA saline injections.[70]

In Table 1, studies have been organized per subgroups (Synvisc-One [Sanofi-Aventis, Bridgewater, New Jersey], Durolane [Bioventus LLC, Durham, North Carolina], or other products), allowing intermediate and global syntheses. The active arms were identified from #1 to #31. The reference index of each citation is given with the principal author's name and later in the document, we attached the year of publication, as given in the citation.

Characteristics of each average patient profile are given in Table 1 for the active IA HA monoinjection arms, and in Table 2 for the injected placebo arms. There were great differences of population size, from 10 to 394 (average 108) per active arm. The follow-up period was from 6 to 52 weeks, with most at 26 weeks. Because we were limited to 26 weeks for the placebo arms, it was not possible to make any longer comparison. Patient profiles were quite homogeneous, in terms of age and BMI, but there was more concern for the KL grades, varying from 0% to 81% grades I and II, with presence of grades IV from 0% to 40%, which is very high. This confirms the choice in the data process session to match in priority the KL profiles for the selection of each placebo arm, and therefore limit the risk of bias for each comparison. For the placebo arms, less population was available, but pooling placebo arms together allowed intermediate profiles, as shown in the second part of Table 2. As for the active arms, placebo profiles were homogeneous in terms of age and BMI.

Matching placebo arms versus active arms is illustrated in Table 3. KL grade are detailed in numbers of patients for grades I and II, III, and IV. The χ^2 test was used to generate the P value by comparing the profiles, study per study. The significant differences were shown by $P < 0.05$. A good profile concordance was obtained for 26 of 29 arms; among failures, #22 was very atypical with 100% grade III, so it was impossible to match. Two arms—#14 and #17— without known KL profile, were allocated to an average placebo based on presumed similar populations. Obviously, the risk of mismatching between any active arm and its placebo exists, and we took care to minimize the bias for the results.

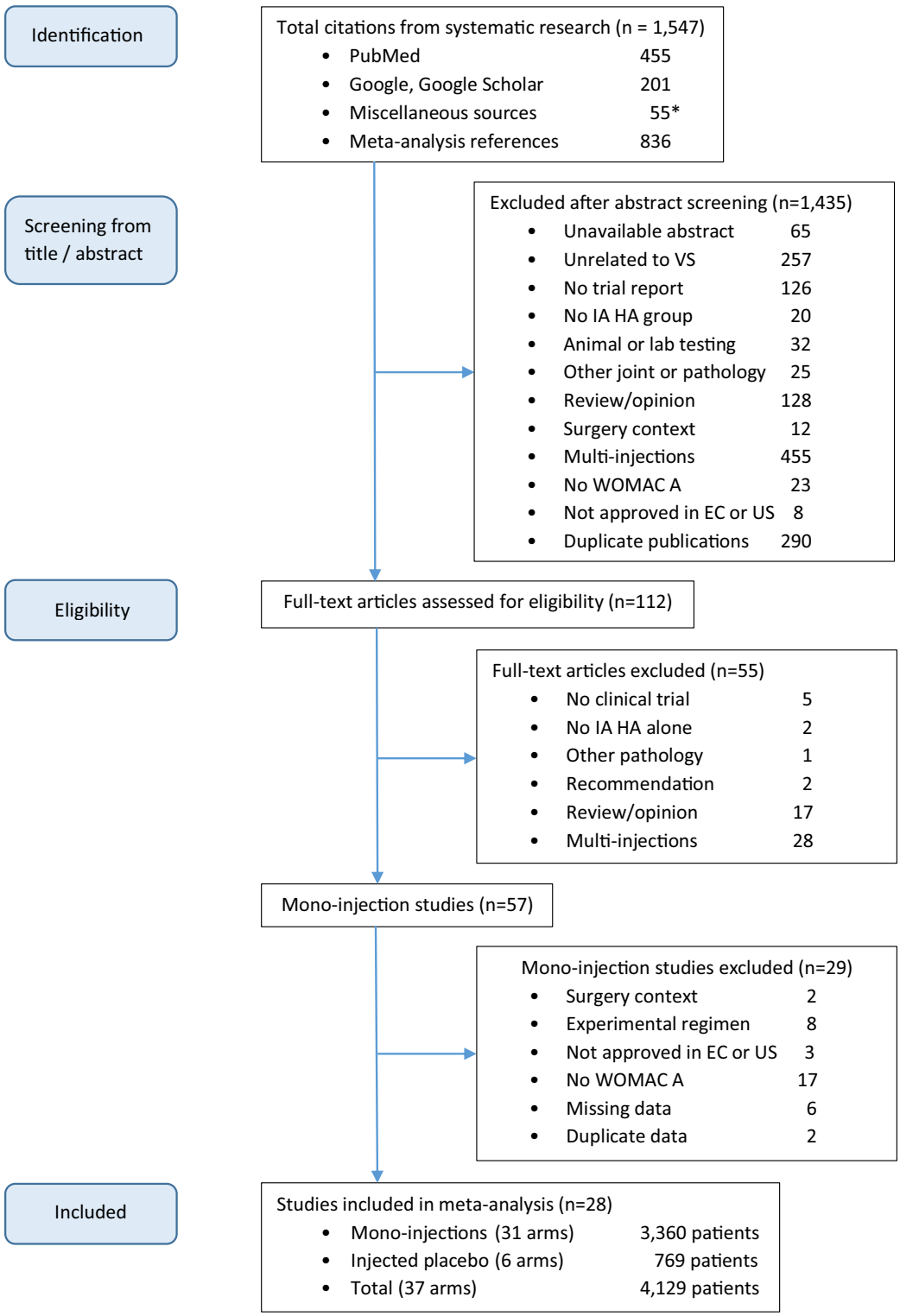


Figure 1. Flow chart. EC = European community; IA HA = intra-articular hyaluronic acid; US = United States; VS = viscosupplementation; WOMAC A = Western Ontario and MacMaster Universities pain subscore. *Thirty-five abstracts and 20 full-text articles.

Results of individual studies and synthesis

Individual results of the placebo comparisons for the WOMAC A are presented in Figures 2, 3, 4, and 5 as ES in the form of forest plots at M1, M2, M3, and M6, for all studies. The bars represent the 95% CI. Positive results are in favor of the IA HA product. In the tabular details, identification of the study is provided (identifier, author's name, and year) along with ES (95% CI). As complement, the percentage of weight for the synthesis and the *P* value are also given.

There are important differences between studies, requiring assessment of heterogeneity. This was first done by funnel plots at M1, M2, M3, and M6 (Figure 6). Outlying studies, #15, #24, and #28, were clearly identified and their spots are filled in red on

Table 1
Selected studies and patient profiles.

ID	Author	RCT	Follow-up, wk	IA HA mono-injection	N per arm	Sex, W%	Age (SD), y	BMI (SD)	KL %		Anteriority, y
									III	IV	
1	Chevalier, et al[43]	Yes	26	Synvisc-One*	124	74	63.6 (12.6)	29.1 (4.8)	49	0	6.5 (6.4)
2	Pal, et al[44]	No	52	Synvisc-One	394	72	57.6 (9.8)	27.7 (4.5)	57	0	1.4 (2.8)
3	Petrella, et al[45]	Yes	26	Synvisc-One	32	50	59.0 (12.0)	29.0 (3.8)	44	0	5.8 (4.7)
4	Dreiser, et al[46]	Yes	26	Synvisc-One	147	61	66.6 (10.7)	26.3 (2.8)	24	0	6.9 (6.7)
5	Tammachote, et al[47]	Yes	26	Synvisc-One	50	86	62.6 (10.0)	26.3	44	14	NA
6	Sun, et al[48]	Yes	26	Synvisc-One	59	71	62.5 (10.0)	25.2 (4.2)	34	0	5.2 (4.6)
7	De Campos, et al[49]	Yes	26	Synvisc-One	52	75	61.0 (12.0)	30.0 (5.2)	34	25	NA
8	Kearey, et al[50]	No	52	Synvisc-One	119	66	60.2 (11.3)	30.9 (6.4)	55	0	5.3 (6.2)
	Subgroup		***26***	***Synvisc-One***	***977***	***70***	***60.8 (9.5)***	***28.0 (4.0)***	***47***	***2***	***4.0***
9	Altman, et al[51]	Yes	26	Durolane†	172	46	62.9 (10)	30.3 (5.0)	53	23	5.0
10	Arden, et al[52]	Yes	6	Durolane	108	55	64.5 (15.9)	27.2 (5.6)	67	0	2.2 (2.2)
11	Leighton, et al[53]	Yes	26	Durolane	218	51	61.9 (9.6)	28.2 (4.2)	69	0	4.7 (5.4)
12	Zhang, et al[54]	Yes	26	Durolane	161	74	60.2 (8.1)	NA	42	0	3.9 (5.3)
13	Estades-Rubio, et al[55]	Yes	26	Durolane	27	52	52.9 (13.9)	30.0 (4.5)	19	0	2.1 (1.2)
14	Louis, et al[56]	Yes	13	Durolane	24	54	48.5 (11.5)	27.0 (2.9)	NA	NA	8.4 (8.4)
15	Vaquerizo, et al[57]	Yes	48	Durolane	48	54	64.8 (7.7)	31.0 (4.6)	44	19	NA
	Subgroup		***26***	***Durolane***	***758***	***56***	***61.6 (8.9)***	***28.9 (4.2)***	***55***	***7***	***4.4***
16	Baron, et al[58]	No	26	Arthrum 75‡	218	56	62.9 (12.6)	27.2 (4.3)	46	0	4.1 (5.4)
17	Diraçoglu, et al[59]	Yes	26	Monovisc§	20	80	58.0 (7.0)	30.5 (4.9)	NA	NA	NA
18	Hangody, et al[60]	Yes	26	Monovisc	150	66	59.2 (8.6)	28.4 (4.5)	18	1	NA
19	Hangody, et al[60]	Yes	26	Cingal§	149	65	57.5 (8.4)	28.9 (4.7)	19	0	NA
20	Strand, et al[61]	Yes	13	Gel-One‖	247	60	60.9 (10.2)	28.3 (4.1)	53	0	NA
21	Takamura, et al[62]	No	26	Gel-One	152	58	61.0 (9.4)	NA	44	0	0.6 (0.6)
22	Borras-Verdera, et al[63]	No	26	Ostenil-Plus¶	80	NA	> 40	NA	100	0	NA
23	Dreiser, et al[46]	Yes	26	Ostenil-Plus	143	73	67.1 (9.7)	26.4 (2.9)	31	0	5.4 (5.4)
24	Duymus, et al[64]	Yes	52	Ostenil-Plus	34	97	60.3 (9.1)	28.4 (3.6)	29	0	NA
25	Lamo-Espinosa, et al[65]	Yes	52	HyalOne#	10	30	60.3 (4.4)	29.6 (3.4)	20	40	6.0 (4.4)
26	Conrozier, et al[66]	No	26	HappyCross**	40	73	60.7 (13.9)	28.6 (5.0)	43	25	NA
27	Monet, et al[67]	No	28	HappyCross	53	66	62.6 (12.3)	27.5 (5.2)	43	19	4.5 (3.0)
28	Bashaireh, et al[68]	No	39	Crespine Gel††	84	37	55.8 (9.3)	30.5 (4.9)	56	1	NA
29	Sun, et al[48]	Yes	26	Hya-Joint Plus‡‡	62	77	62.7 (8.4)	24.7 (3.3)	35	0	5.4 (4.4)
30	Tuan, et al[69]	No	26	Hya-Joint-Plus	46	80	65.1 (9.3)	24.0 (3.6)	41	0	NA
31	Ha, et al[70]	Yes	15	Hyruan-One§§	137	81	62.0 (8.6)	25.1 (2.9)	43	0	4.0 (4.0)
	Subgroup		***26***	***other IA HA***	***1625***	***65***	***61.3 (10.0)***	***27.7 (4.1)***	***42***	***2***	***3.2***
	Total monoinjections			All IA HA	3360	63	61.2 (9.6)	28.0 (4.1)	47	3	3.7

BMI, body mass index; HA = hyaluronic acid; IA = intra-articular; KL = Kellgren-Lawrence; NA = not applicable; W% = percentage of women.
* Sanofi-Aventis, Bridgewater, New Jersey.
† Bioventus LLC, Durham, North Carolina.
‡ LCA Pharmaceutical, Chartres, France.
§ Anika Therapeutics Inc, Bedford, Massachusetts.
‖ Seikagaku Corporation, Tokyo, Japan.
¶ TRB Chemedica Geneva, Switzerland.
# Fidia Farmaceutici, Abano Terme, Italy.
** Labrha International, Lyon, France.
†† Biopolymer, Dummer, Germany.
‡‡ Hyajoint, SciVision, Taiwan.
§§ LG Life Science Ltd, Seoul, Korea.

the graphs (both funnel plots and forest plots). No important dissymmetry was found in the funnel plots, and the spots distribution seems balanced around the mean (vertical line).

The synthetic results given with the forest plots were obtained by inverse variance pooling (fixed effect) with MIX 2.0 software. Other synthetic results given in Tables 4 and 5 were calculated for each follow-up time at M1, M2, M3, and M6, to complement the mean difference (MD) of the variation to baseline (0–100 scale), and heterogeneity indicators: I^2 is the ratio of the true heterogeneity (moderate at 50% and high at 75%) and τ^2 a measure of the heterogeneity between studies, here in dimensionless units (low at 0.04, moderate at 0.09, and high at 0.16[3]).

In Table 4, the first group of results are those obtained for the extended analysis that combined all studies. The second group presents the limited analysis by removal of the outlying studies (ie, removing #15, #24, and #28). Finally, the restricted analysis is presented by also removing the studies with active arms having <30 patients and studies with poor KL placebo matching (ie, also removing #4, #13, #14, #17, #22, and #25). This was done to evaluate how the scores changed (MD, ES), and whether heterogeneity could be improved by removal of the most uncertain studies. As evidenced, the results remained stable whilst a visible improvement was noted on both I^2 (reduced by –10% to –12%) and τ^2 (reduced by –0.05 to –0.09). If the true heterogeneity remains high with I^2 at 71% to 78%, heterogeneity between studies has been clearly shown to an acceptable level.

To summarize, IA HA monoinjections were found to be statistically better than the IA placebo ($P < 0.001$) at any time, for the symptomatic (pain) treatment of knee OA. The ES reached 0.39 or 0.40 at M6, which is clinically relevant.

Risk of bias

There were probably risks of bias for several studies that may raise suspicion. First with the outliers:

- #15: In this autologous preparation study (ie, PRGF),[57] Durolane was used as control and, for the first time in our VS experience, there was absolutely no improvement compared with baseline but rather a slight worsening for the IA HA group (confirmed with graph).

Table 2
Selected placebo arms and patient profiles.

Author	Follow-up, wk	IA comparator	N per arm	Sex, %	Age (SD), y	BMI (SD)	KL %		Anteriority, y
							III	IV	
Altman et al[51]	26	Saline	174	64	63.3 (10.0)	29.5 (5.0)	52	26	6.5
Chevalier et al[43]	26	Saline	129	68	62.5 (9.2)	29.8 (5.7)	60	1	5.8 (5.4)
Strand et al[61]	13	Saline	128	60	60.3 (10.0)	28.7 (3.8)	49	0	NA
Arden et al[52]	6	Saline	110	46	60.9 (20.5)	27.5 (6.1)	64	0	3.1 (3.1)
Hangody et al[60]	26	Saline	69	74	58.0 (9.0)	29.1 (4.5)	20	0	NA
Takamura et al[62]	26	Saline	159	62	62.8 (8.9)	NA	42	0	0.7 (0.5)
Pooled placebo									
A+C	26	Saline	303	66	63.0 (9.7)	29.6 (5.3)	55	15	6.2
A+A'	26	Saline	284	57	62.4 (15.0)	28.7 (5.4)	56	16	5.2
A+T	26	Saline	333	63	63.1 (9.5)	30.3 (5.0)	47	14	3.7
C+S	26	Saline	257	64	61.4 (9.6)	29.2 (4.9)	55	0	5.8
C+A'	26	Saline	239	58	61.8 (15.4)	28.7 (5.9)	62	0	4.6
C+T	26	Saline	288	65	62.7 (9.0)	29.8 (5.7)	50	0	3.0
H+T	26	Saline	228	66	61.3 (8.9)	29.1 (4.5)	36	0	0.7
A+C+S	26	Saline	276	64	62.2 (9.8)	29.3 (4.9)	53	11	6.2
C+S+A'	26	Saline	367	59	61.3 (13.8)	28.7 (5.3)	57	0	4.6
C+S+H	26	Saline	326	66	60.7 (9.5)	29.2 (4.8)	47	0	5.8
A+C+S+A'	26	Saline	541	60	61.9 (12.7)	29.0 (5.2)	56	8	5.4
C+S+H+T	26	Saline	485	65	61.4 (9.3)	29.2 (4.8)	46	0	3.0
C+S+H+T+A'	26	Saline	595	62	61.3 (12.1)	28.8 (5.2)	49	0	3.0
A+C+S+H+T+A'	**26**	**Saline**	**769**	**62**	**61.7 (11.7)**	**29.0 (5.1)**	**50**	**6**	**4.1**

A = Altman et al[51]; A' = Arden et al[52]; BMI = body mass index; c = Chevalier et al[43]; H = Hangody et al[60]; IA = intra-articular; KL = Kellgren-Lawrence; NA = not applicable; S = Strand et al[61]; T = Takamura et al[62].

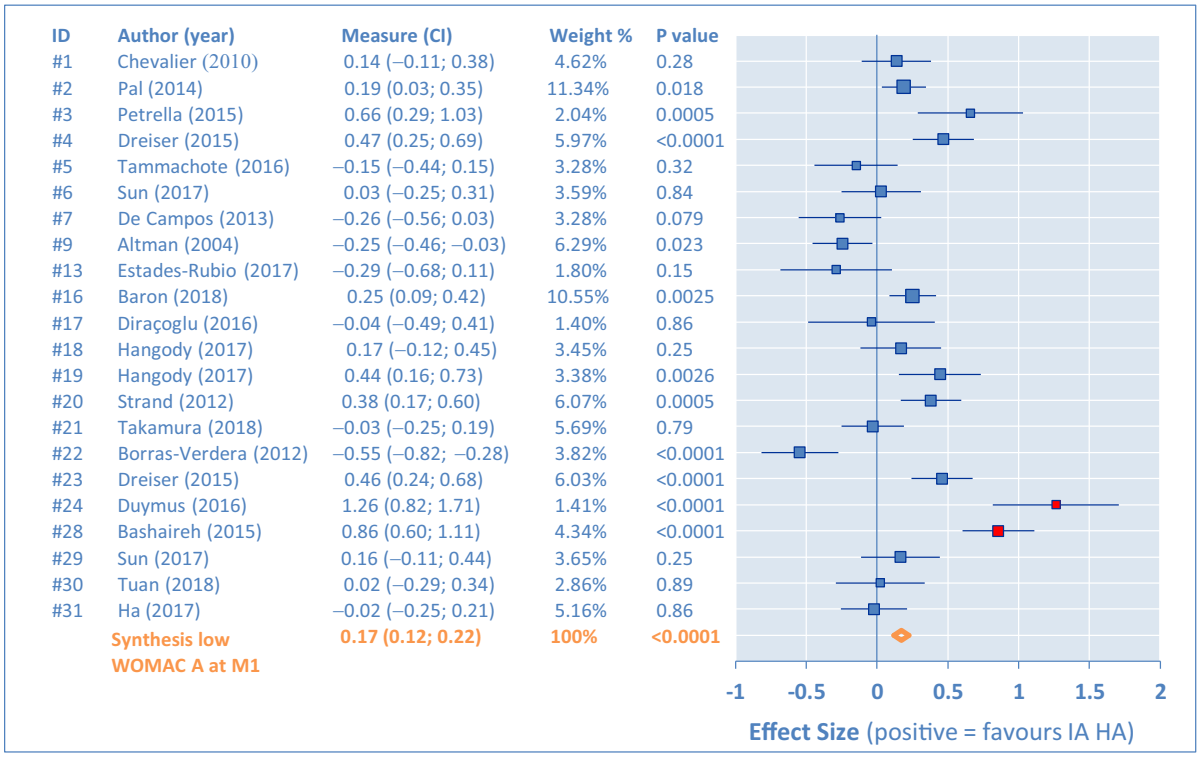


Figure 2. Western Ontario and MacMaster Universities pain subscore (WOMAC A). Comparison of intra-articular hyaluronic acid (IA HA) monoinjection versus intra-articular placebo at 1-month follow-up visit (M1).

- #24: In this alternative treatment study (autologous PRP preparation or IA ozone),[64] Ostenil-Plus (TRB Chemedica Ltd, Geneva, Switzerland) was used as control. After an abnormally strong beneficial effect at M1 and M3, the effect was reduced drastically, becoming insignificant at M6, which was surprising.
- #28: In this well-documented open-label study,[68] a huge placebo effect was seen and, despite being a good match by KL profile, our comparison placebo arm revealed it to be unsuitable. To us, there was no real bias related to the study, but rather a deficit in our available data.

For the restricted analysis, by removing the poorly KL-placebo-matched studies and the lowest populations (<30 patient/arm), we improved heterogeneity between studies, to confirm a strong average result, unchanged from our extended analysis. We assumed the risk of bias to be acceptable, without incidence on this synthetic result.

Table 3
Matching placebo arms to patient Kellgren-Lawrence (KL) profiles.

IA HA mono-injection						IA comparator					Statistics	
ID#	Author	N	KL I–II	KL III	KL IV	Pooled placebo	N	KL I–II	KL III	KL IV	χ^2	*P* value
1	Chevalier et al[43]	123	63	60	0	C	129	51	78	1	4.42	0.11
2	Pal et al[44]	394	171	223	0	C+S	258	116	141	1	1.72	0.42
3	Petrella et al[45]	32	18	14	0	C+S	258	116	141	1	1.54	0.46
						C+S+A'	368	156	211	1	2.35	0.31
4	Dreiser et al[46]	147	112	35	0	H+T	228	147	81	0	5.74*	0.017
5	Tammachote et al[47]	50	21	22	7	A+C+S	432	155	231	46	1.68	0.43
						A+C+S+A'	541	195	301	46	3.13	0.21
6	Sun et al[48]	59	39	20	0	C+T	289	143	145	1	5.53	0.063
7	De Campos et al[49]	52	21	18	13	A+T	333	131	157	45	5.51	0.064
8	Kearey,et al[50]	115	50	65	0	C+S	258	116	141	1	0.54	0.77
Subgroup Synvisc-One †		972	495	457	20	C+S+H	327	171	155	1	4.74	0.093
9	Altman et al[51]	172	40	92	40	A	174	39	90	45	0.32	0.85
10	Arden et al[52]	108	33	75	0	A'	110	40	70	0	0.83*	0.36
11	Leighton et al[53]	218	71	147	0	C	129	51	78	1	3.40	0.18
						C+A'	239	91	148	1	2.42	0.30
12	Zhang et al[54]	161	94	67	0	C+S+H	327	171	155	1	2.02	0.36
13	Estades-Rubio et al[55]	27	22	5	0	C+T	289	143	145	1	10.1	0.006
14	Louis et al[56]	24	NA	NA	NA	A+C	304	90	168	46	NA	NA
15	Vaquerizo et al[57]	48	18	21	9	A	174	39	90	45	4.60	0.10
Subgroup Durolane ‡		734	278	407	49	A+C+S	432	155	231	46	5.75	0.056
						A+C+S+A'	542	195	301	46	1.68	0.43
16	Baron et al[58]	217	118	99	0	C+S+H+T	486	263	222	1	0.45	0.80
						C+S+H+T+A'	596	303	292	1	1.12	0.57
17	Diraçoglu et al[59]	20	NA	NA	NA	A+C+S	431	155	231	46	NA	NA
18	Hangody et al[60]	150	122	27	1	H	69	55	14	0	0.61	0.74
19	Hangody et al[60]	149	120	29	0	H	69	55	14	0	0.02*	0.89
20	Strand et al[61]	247	115	132	0	S	128	65	63	0	0.60*	0.44
21	Takamura et al[62]	152	85	67	0	T	159	92	67	0	0.12*	0.73
22	Borras-Verdera et al[63]	80	0	80	0	A	174	39	90	45	57.7	< 0.001
						A+A'	284	79	160	45	53.0	< 0.001
23	Dreiser et al[46]	143	98	45	0	H+T	228	147	81	0	0.65*	0.42
24	Duymus et al[64]	34	24	10	0	H	69	55	14	0	1.06*	0.30
25	Lamo-Espinosa et al[65]	10	4	2	4	A	174	39	90	45	3.86	0.14
26	Conrozier et al[66]	40	13	17	10	A	174	39	90	45	1.92	0.38
27	Monet et al[67]	53	20	23	10	A	174	39	90	45	5.06	0.080
28	Bashaireh et al[68]	84	36	47	1	C+S	258	116	141	1	0.78	0.68
						C+S+A'	368	156	211	1	1.33	0.51
29	Sun et al[48]	62	40	22	0	C+T	289	143	145	1	4.74	0.093
30	Tuan et al[69]	46	27	19	0	C+S	258	116	141	1	3.07	0.22
31	Ha et al[70]	137	78	59	0	C+T	289	143	145	1	2.45	0.29
Subgroup other IA HA		1625	900	678	26	C+S+H	327	171	155	1	5.73	0.057
All monoinjections		3360	1673	1542	95	C+S+H+T	486	263	222	1	2.16*	0.14
						C+S+H+T+A'	596	303	292	1	0.02*	0.89

A = Altman et al[51]; A' = Arden et al[52]; c = Chevalier et al[43]; H = Hangody et al[60]; IA HA = intra-articular hyaluronic acid; KL = Kellgren-Lawrence; NA = not applicable; S = Strand et al[61]; T = Takamura et al[62]; df = degree of freedom.

* Mixing KL III + IV (df = 1).

† Sanofi-Aventis, Bridgewater, New Jersey.

‡ Bioventus LLC, Durham, North Carolina.

Table 4
Selected populations and heterogeneity testing.

Time	N*	Difference of variation to baseline		Effect size (95% CI)	Statistics		
		Mean	SD		*P* value	I^2, (%)	τ^2
Extended analysis (all studies)							
M1	2502	3.18	19.7	0.17 (0.12–0.22)	<0.0001	87	0.13
M2	1887	4.27	21.0	0.21 (0.15–0.28)	<0.0001	85	0.11
M3	3014	6.56	22.2	0.30 (0.25–0.35)	<0.0001	84	0.11
M6	2728	8.41	21.3	0.39 (0.33–0.44)	<0.0001	88	0.18
Limited analysis (less #15, #24, #28)							
M1	2384	2.13	19.7	0.12 (0.07–0.18)	0.0001	81	0.09
M2	1803	3.11	21.1	0.16 (0.10–0.23)	<0.0001	76	0.06
M3	2896	5.76	22.2	0.27 (0.22–0.32)	<0.0001	80	0.09
M6	2562	8.27	21.4	0.39 (0.33–0.44)	<0.0001	81	0.11
Restricted analysis (less #4, #13, #14, #15, #17, #22, #24, #25, #28)							
M1	2127	2.65	19.8	0.14 (0.08–0.20)	<0.0001	75	0.06
M2	1698	3.86	21.5	0.19 (0.12–0.26)	<0.0001	71	0.05
M3	2605	6.36	22.4	0.29 (0.23–0.34)	<0.0001	74	0.06
M6	2296	8.59	21.5	0.40 (0.34–0.45)	<0.0001	78	0.09

* Intra-articular hyaluronic acid group.

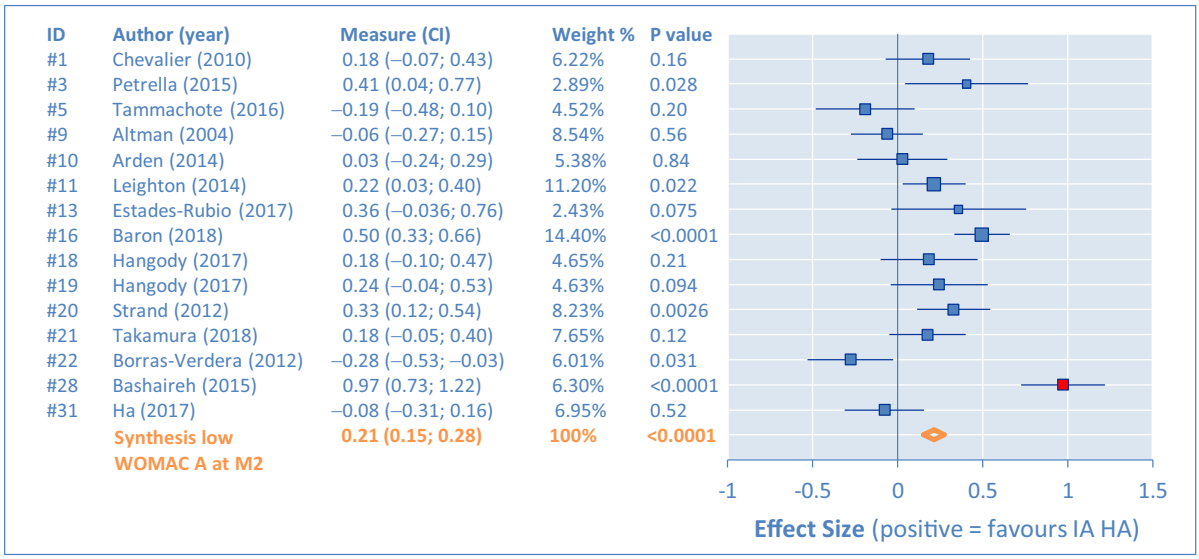


Figure 3. Western Ontario and MacMaster Universities pain subscore (WOMAC A). Comparison of intra-articular hyaluronic acid (IA HA) monoinjection versus intra-articular placebo at 2-month follow-up visit (M2).

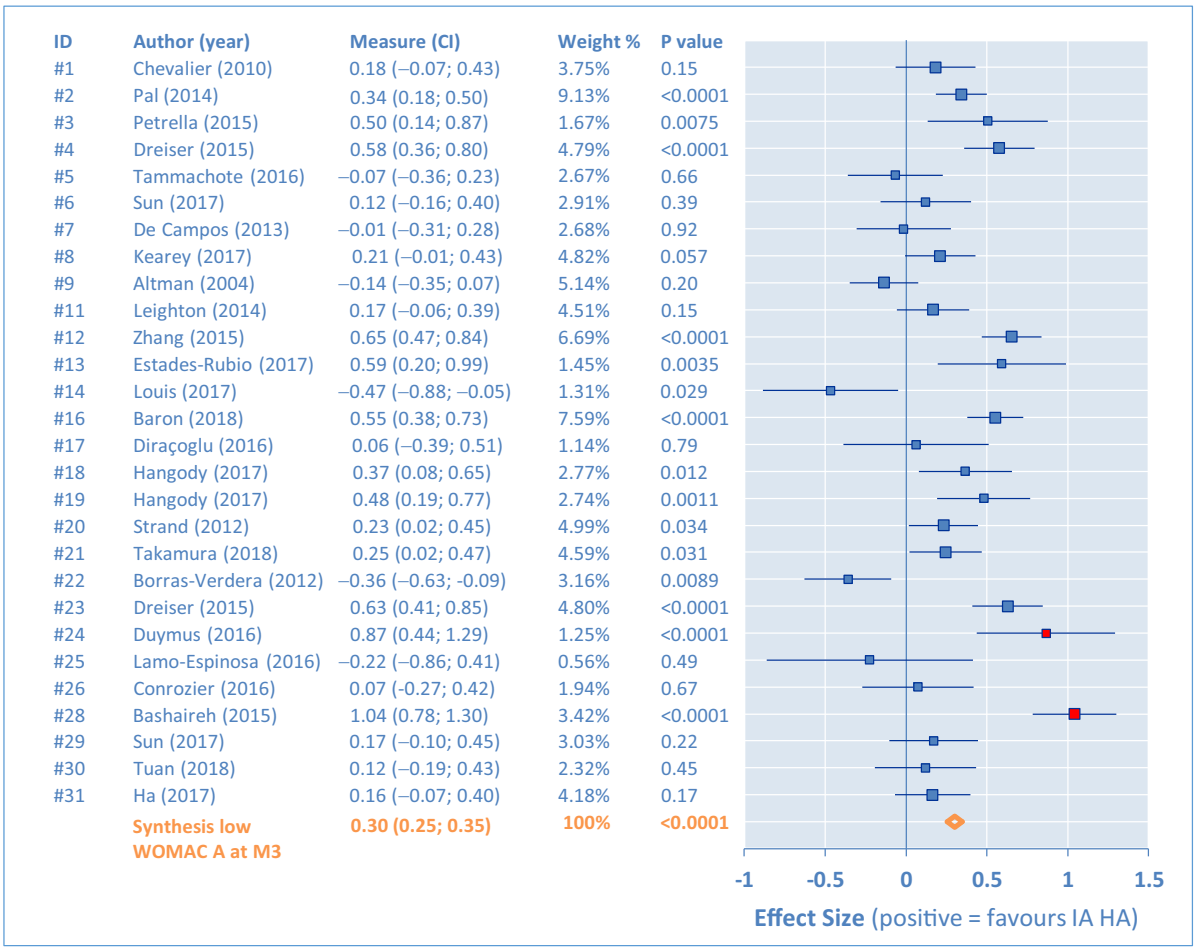


Figure 4. Western Ontario and MacMaster Universities pain subscore (WOMAC A). Comparison of intra-articular hyaluronic acid (IA HA) monoinjection versus intra-articular placebo at 3-month follow-up visit (M3).

Subgroup analyses

Subgroup results are described in Table 5. ES obtained at M3 and M6 for the subgroups Synvisc-One and Durolane are close to those described in the limited analysis presented in Table 4. Synvisc-One was supported by 8 trial arms and Durolane by 5 trial arms, after removal of #15. As shown in the forest plots in Figures 2 through 5, there are differences between trials results inside each subgroup. This synthesis per subgroup allows us to conclude that these 2 products seem to perform similarly, without 1

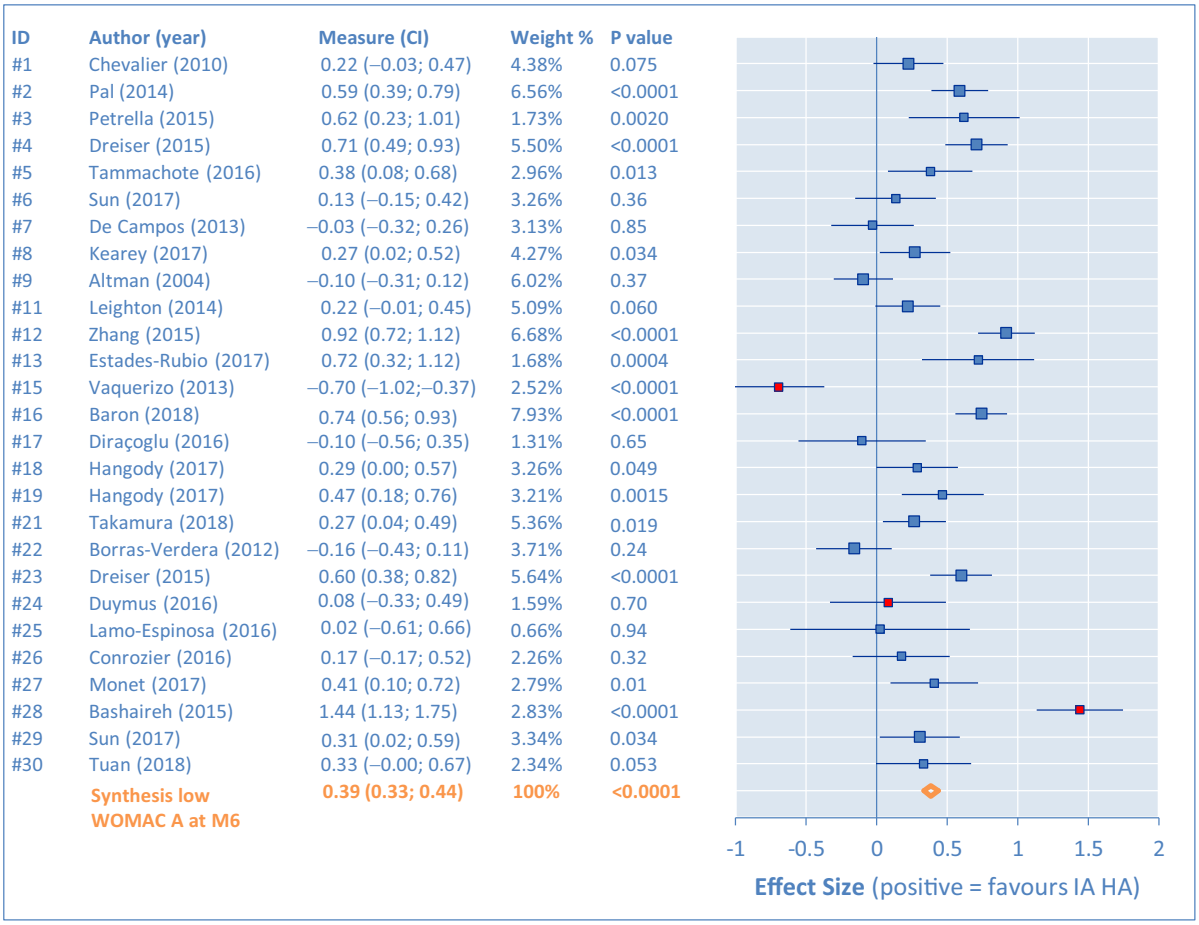


Figure 5. Western Ontario and MacMaster Universities pain subscore (WOMAC A). Comparison of intra-articular hyaluronic acid (IA HA) monoinjection versus intra-articular placebo at 6-month follow-up visit (M6).

Table 5
Subgroup analysis and heterogeneity testing.

Time	N*	Difference of variation to baseline		Effect size (95% CI)	Statistics		
		Mean	SD		*P* value	I^2, %	τ^2
Subgroup Synvisc-One†							
M1	843	3.10	19.5	0.16 (0.07 to 0.25)	0.0007	79	0.07
M2	206	1.97	20.5	0.10 (–0.07 to 0.26)	0.26	72	0.08
M3	962	5.71	22.2	0.26 (0.17 to 0.34)	<0.0001	68	0.04
M6	959	8.17	20.8	0.39 (0.30 to 0.48)	<0.0001	74	0.07
Subgroup Durolane‡ (less #15)							
M1	199	–4.48	18.8	–0.24 (–0.43 to –0.05)	0.013	NS	NS
M2	525	1.87	22.0	0.09 (–0.04 to 0.21)	0.17	55	0.03
M3	569	5.46	22.1	0.25 (0.14 to 0.36)	<0.0001	91	0.22
M6	531	9.34	21.6	0.43 (0.31 to 0.55)	<0.0001	93	0.32
Subgroup other IA HA (less #24, #28)							
M1	1342	2.72	20.0	0.14 (0.06 to 0.21)	0.0004	81	0.10
M2	1072	4.04	21.0	0.19 (0.11 to 0.28)	<0.0001	84	0.09
M3	1365	5.94	22.4	0.27 (0.19 to 0.34)	<0.0001	79	0.10
M6	1072	7.82	21.8	0.36 (0.28 to 0.44)	<0.0001	78	0.09

HA = hyaluronic acid; IA = intra-articular; NS = not significant.
* IA HA group.
† Sanofi-Aventis, Bridgewater, New Jersey.
‡ Bioventus LLC, Durham, North Carolina.

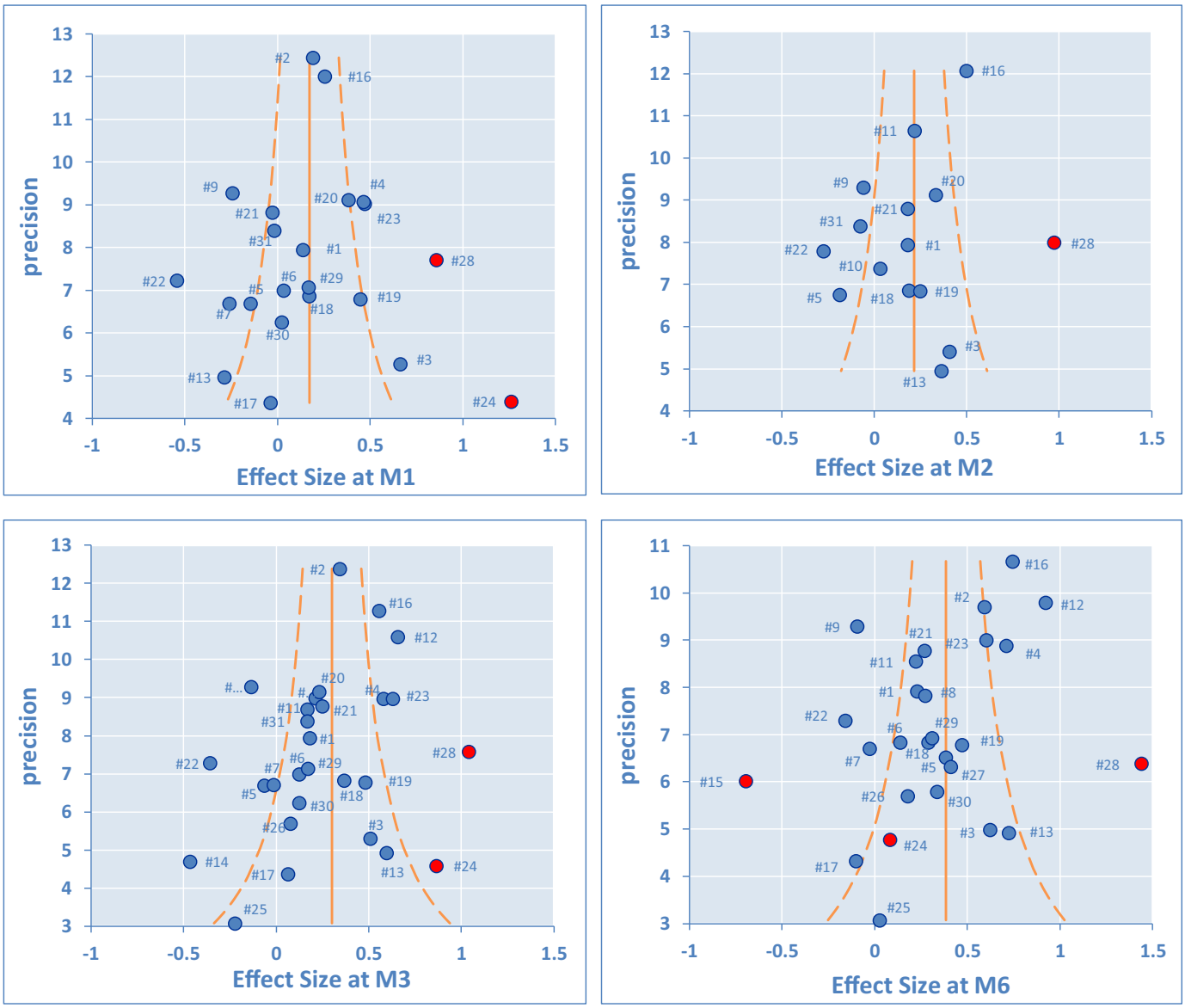


Figure 6. Funnel plots.

being better than the other. At M1 and M2, results are less consistent due to reduced populations and more difficulties finding ideal placebo comparators.

There was some improvement for heterogeneity indicators I^2 and τ^2, with the subgroup Synvisc-One, but none with the subgroup Durolane.

Discussion

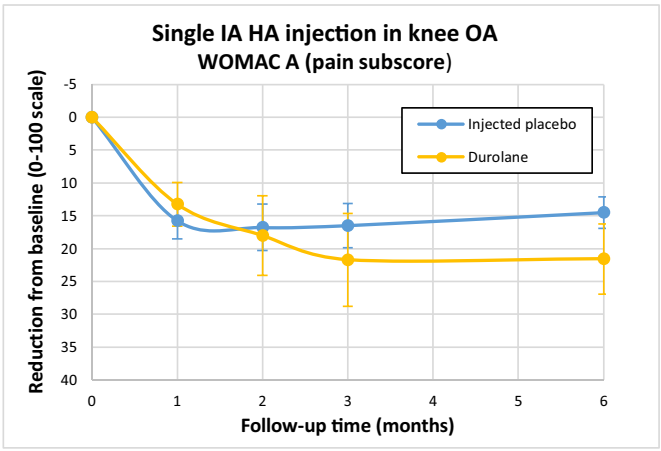
Crossing methods

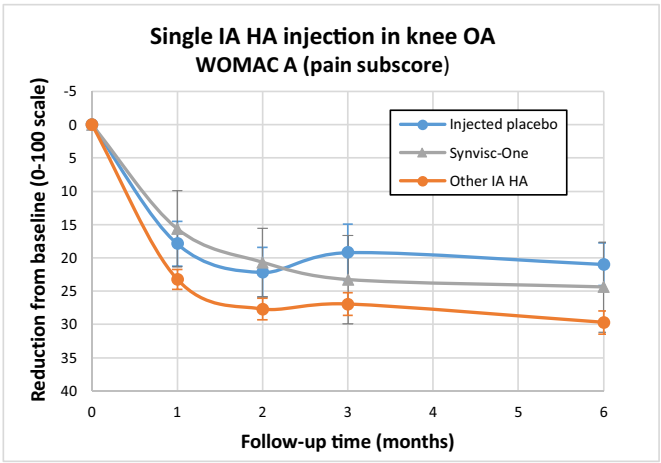
Two approaches were used to reach the final synthetic result of an ES versus injected placebo for the IA HA administrated in monoinjection.

With the first approach, we had to evaluate ES (95% CI) for each trial and select a suitable placebo arm to match the KL profiles. In a second step, the meta-analysis was performed with MIX 2.0, giving results in ES (95% CI), a forest plot representation, and a synthesis based on the fixed effect method.

With the second global approach, we first pooled the variations from baseline for each subgroup, weighing population size for each trial. Then, after selection of the pooled placebo comparator with matching KL profile, we evaluated ES (95% CI). Although it gave no individual study result for ES, this method allowed us to represent the WOMAC A variations from baseline, graphically as a function of time (Figure 7), comparing each subgroup with its placebo. The differences were always significantly in favor of IA HA at any time, from M1 to M6. One can see the importance of the IA placebo effect and its contribution to patient improvement, which has been pointed out by Altman et al,[10] and Bannuru et al.[6,9,11]

Finally, as illustrated with Figure 8, differences were not so great between these methods, leading to ES from 0.37 to 0.39 (maximum at M6) in the comparison versus IA placebo. In terms of differences in score variations (MD) for the populations (Table 4), we reached MD = 8.27 to 8.59 mm on the 0 to 100 mm scale. This is clinically relevant, being greater than both the minimal clinically important difference (7.5 mm for improvement) and the smallest detectable difference (8.1 mm), as defined by Angst et al.[71]





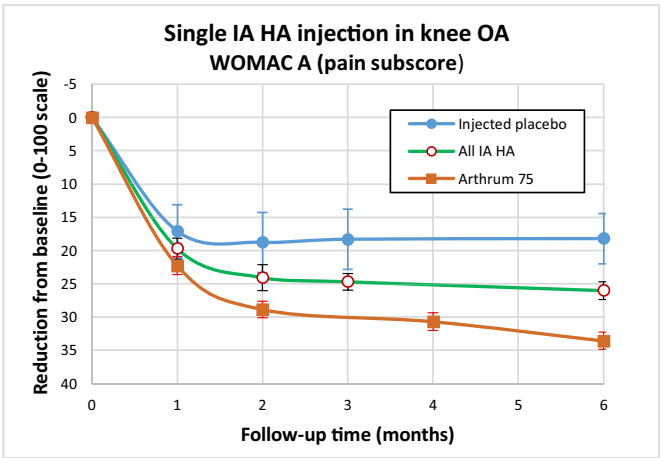


Figure 7. Variation to baseline per subgroup and group. IA HA = intra-articular hyaluronic acid; OA = osteoarthritis. Synvisc-One (Sanofi-Aventis, Bridgewater, New Jersey). Arthrum 75 (Wellchem Pharmaceuticals, Singapore.).

Summary of evidence

From an evidence-based medicine point of view, our meta-analysis cannot reach level I or II because all study designs have been accepted, from double-blind RCTs to observational open-label studies. Our objective was to query the largest database and be close to real-world evidence. We believe it was a success to have >4000 patients for this meta-analysis, and therefore a good representation of monoinjection IA HA.

To answer the question about the relative efficacy of IA HA monoinjection compared with multi-injections, we compared our

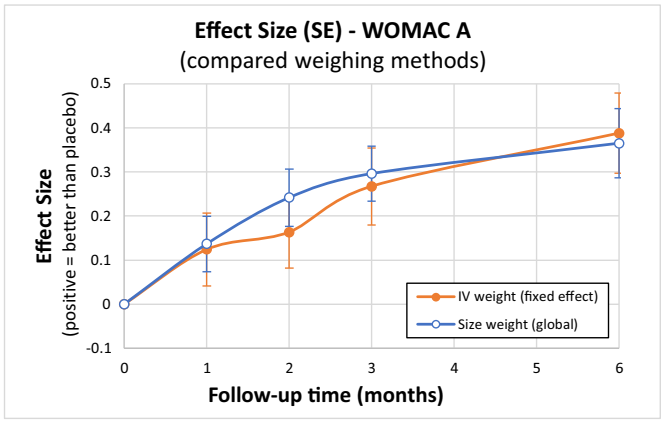


Figure 8. Effect size as time function: Compared weighing methods. IV = inverse variance; WOMAC A = Western Ontario and MacMaster Universities pain subscore; SE = standard error.

results with those obtained for pain (WOMAC A or/and visual analog scale for pain) in other meta-analyses,[2–6] where most data were obtained from multi-injection regimens:

- Bannuru et al[2] found ES = 0.46 (95% CI, 0.28–0.65) with I^2=75% at M2, and ES = 0.25 (95% CI, 0.15–0.36) with I^2 = 60% at M3.
- Rutjes et al[3] found ES = 0.37 (95% CI, 0.28–0.46) with τ^2 = 0.09.
- Colen et al[4] found MD = 10.20 mm (95% CI, 4.42–15.97 mm) with I^2 = 92%.
- Miller and Block[5] found SMD = 0.43 (95% CI, 0.36; 0.60) with I^2 = 73% at 4 to 13 weeks and SMD = 0.38 (95% CI, 0.21–0.55) with I^2 = 75% at 14 to 26 weeks.
- Bannuru et al[6] found ES = 0.34 (95% CI, 0.26–0.42).

In terms of ES or SMD, all these results are very close to ours and heterogeneity seems present at a similar level. Differences between products have been studied by Colen et al,[4] but these results are limited to a few multi-injection products. More recently, Altman et al[8] assessed ES depending on molecular weight (Mw) and found ES = 0.52 (95% CI, 0.48–0.56) for high Mw (>3 MDa (MegaDalton (= 1 million Dalton))) and ES = 0.31 (95% CI, 0.20–0.42) for moderate Mw (1.5–3 MDa). Our results in Table 5 are roughly comparable: a bit smaller with Synvisc-One and Durolane subgroups for the high Mw, and a bit higher with the other IA HA subgroup for the moderate Mw. In other words, we found less difference between high and moderate Mw IA HA products.

In the symptomatic treatment of knee OA with IA HA, the results of monoinjections demonstrate an efficacy similar to the multi-injections in terms of MD, ES (or SMD), and *P* value, when compared with the IA placebo.

Limitations

There are many limitations to our analysis, including making post-hoc IA placebo comparisons when no placebo control was available. Data were obtained from multiple studies done in many different countries, with different patient populations and doctors. This creates possibilities for differences unrelated to treatments used, with a risk of bias, especially for individual trials; however, for each synthesis per subgroup or group, each with large population sizes, the results were properly compared and confirmed using multiple different statistical approaches and weighing methods.

Conclusions

Results of this meta-analysis suggest that the effects of monoinjections of HA produce results similar to multi-injections of IA HA in terms of pain relief in the treatment of knee OA.

Acknowledgments

The author thanks Thierry Thomas, MD, Department Rheumatology, Centre Hospitalier Universitaire (French equivalent of University Hospital) (CHU), St Etienne, France, for providing valuable advice in the conception of this meta-analysis, the interpretation of the results, and the writing of this article. The author also thanks Jo-Ann Elicia West, MSc, an independent contractor in Cartigny L'Epinay, France, for providing editorial support, which was funded by LCA Pharmaceutical, Chartres, France, in accordance with Good Publication Practice guidelines.

Conflicts of Interest

This meta-analysis was entirely sponsored by LCA Pharmaceutical, Chartres, France. P. Vincent is an employee and shareholder of LCA Pharmaceutical. The author has indicated that he has no other conflicts of interest regarding the content of this article.

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