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Predictors of Placebo Response to Local (Intra-Articular) Therapy In Osteoarthritis: An Individual Participant Data Meta-Analysis

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Objective. We undertook this study to evaluate potential predictors of placebo response with intra-articular (IA) injections for knee/hip osteoarthritis (OA) using individual participant data (IPD) from existing trials.

Methods. Randomized placebo-controlled trials evaluating IA glucocorticoid or hyaluronic acid published to September 2018 were selected. IPD for disease characteristics and outcome measures were acquired. Potential predictors of placebo response included participant characteristics, pain severity, intervention, and trial design. Placebo response was defined as at least a 20% reduction in baseline pain. Logistic regression models and odds ratios were computed as effect measures to evaluate patient and pain mechanisms and then pooled using a random effects model. Generalized mixed-effect models were applied to intervention and trial characteristics.

Results. Of 56 eligible trials, 6 shared data, and these were combined with the existing 4 OA Trial Bank studies, yielding 10 studies with IPD of 621 placebo participants for analysis. In the total placebo population, at short-term follow-up, the use of local anesthetic and ultrasound guidance were associated with reduced odds of placebo response. At midterm follow-up, mid- to long-term trial duration was associated with increased odds of placebo response, and worse baseline function scores were associated with reduced odds of a placebo response.

Conclusion. The administration of local anesthetics or ultrasound guidance may reduce IA placebo response at short-term follow-up. At midterm follow-up, participants with worse baseline function scores may be less likely to respond to IA placebo, and mid- to long-term trial duration may enhance the placebo response. Further studies are required to corroborate these potential predictors of IA placebo response.

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SIGNIFICANCE & INNOVATIONS

- This is the first individual participant data meta-analysis conducted to identify predictors of placebo response, specifically in intra-articular (IA) injection trials in osteoarthritis (OA).
- Identifying potential predictors of placebo in IA interventions in OA may help to provide guidance and modify the design for future IA clinical trials.
- Severe baseline function scores, administration of local anesthetic, ultrasound-guided injections, or joint fluid aspiration attempts may reduce the odds of an IA placebo response, whereas trial durations of 12 to 24 and longer than 24 months may increase the odds of IA placebo response.

INTRODUCTION

The majority of pharmacological treatments in osteoarthritis (OA) have failed to demonstrate a minimum clinically important difference over placebo. This directly affects the development of prospective pharmacological innovations and their translation to therapeutic options for this progressively disabling condition. The placebo effect is a well-recognized phenomenon in OA treatments, with previous meta-analyses of randomized controlled trials (RCTs) assessing the placebo response across a range of therapies in OA (non-pharmacological, pharmacological, and surgical treatments), confirming that placebo effect size (ES; standardized mean difference [SMD] between baseline and endpoint) for pain in OA (ES 0.51, 95% confidence interval [CI] 0.46–0.55) is greater than no treatment (ES 0.03, 95% CI –0.13 to 0.18) (1). With invasive therapies, participants' expectations and beliefs can lead to increased placebo/contextual effects with pain-relieving effects demonstrated with injections/needles ($\beta = 0.144$, $P = 0.020$) (1). The ES for debridement and lavage was 0.48 (95% CI 0.24–0.71) and from intra-articular (IA) glucocorticoid and hyaluronic acid (HA) data 0.34 (95% CI 0.11–0.56) for single-dose placebo injection and 0.63 (95% CI 0.15–1.12) for multiple injections (1). IA placebo injections have been demonstrated to result in a significant improvement in pain reduction in relation to oral placebo (ES = 0.29, credible interval 0.04–0.54) (2,3). The magnitude of the placebo response in OA clinical trials is significant, with about 75% of the treatment effect being attributable to placebo or contextual effects (4). When considering clinical trial design in IA therapies, the type of placebo, its volume, frequency of injection, concomitant local anesthetic, and radiological guidance use, along with participant disease characteristics, can all be a cause of between-person heterogeneity within a clinical trial. To date, placebo responses are typically measured as a change in outcome from baseline in the placebo treatment group in comparison with the active treatment group. This method is potentially influenced by spontaneous effects, such as the Hawthorne effect (ie, the effect caused by being observed in trials) (5), natural fluctuation of OA disease, and regression to the mean (1,6).

A meta-analysis of OA treatments has shown that the magnitude of placebo response also can vary greatly between individuals (4), but the variations of the treatment or placebo responses across individuals cannot be examined in an aggregate data meta-analysis. Because the placebo response can be attributed to the individual and factors at the treatment or study level, assessment of the placebo response using individual participant data (IPD) meta-analysis will give insight into the different predictors of placebo response both at individual and study levels. IPD meta-analysis is now increasingly used and is considered to provide more robust results, because it facilitates more powerful analyses and the standardization of analyses across different studies and allows derivation of the desired information (7).

The primary aim of this study is to evaluate the potential predictors of placebo response in IA injection trials in OA using IPD from published trials. This IPD meta-analysis will examine the role of potential placebo response modifiers from the participant level to the intervention and trial design level. For the purpose of this analysis, only placebo-controlled studies of IA glucocorticoid and HA were included, because these are the more widely studied IA drugs with fewer methodological concerns and less heterogeneity than other IA therapies (8,9).

PATIENTS AND METHODS

This study was conducted under the umbrella of the OA Trial Bank, an international collaboration endorsed by the Osteoarthritis Research Society International and the European Alliance of Associations for Rheumatology. It brings together IPD data from RCTs (10,11) to identify specific responsive subgroups for the different OA treatments. The research question and study proposal of this study were approved by the steering committee of the OA Trial Bank before the development of the published study protocol (12). The PROSPERO registration number is CRD42018095188.

Types of study and participants. All randomized placebo-controlled trials, including crossover trials, evaluating either IA glucocorticoid or IA HA injections were eligible for inclusion. There were no language restrictions. Participants from the identified RCTs, assigned to the placebo group, had to have a diagnosis of knee and hip OA according to the criteria defined by the American College of Rheumatology and the European Alliance of Associations for Rheumatology evidence-based recommendations for the diagnosis of knee OA (13,14) or on the basis of defined clinical and/or radiographic information, fulfilling the specified diagnostic criteria of OA of the respective trials.

Outcomes. The minimum criterion for inclusion of RCTs was sufficient participant reporting of pain measures in at least

one of the subsequent follow-up time frames: short-term (up to 4 weeks), midterm (closest to 12 weeks) or long-term (closest to 24 weeks). As a minimum, age, sex, and body mass index (BMI) were required. If available, potential placebo response modifier variables were extracted, including disease duration, OA at other joints, radiographic information, stiffness and function scores, signs of effusion and inflammatory features (either by physical examination or by radiographic imaging with ultrasound or magnetic resonance imaging), and intervention and trial design characteristics.

Eligible studies. Literature searches were conducted separately for randomized placebo-controlled trials of IA glucocorticoid and IA HA. Data were searched from June 2012 to September 2018 for RCTs of IA glucocorticoid versus placebo and then combined with the existing studies from the OA Trial Bank reported in an IPD analysis of subgroup effects of glucocorticoid injections with searches from 1995 until June 2012 (10). The search for IA HA versus placebo was conducted from inception to September 2018 because of the potential availability of earlier studies, hence the broadened search time frame. A systematic literature search was conducted using the following databases: PubMed (Medline), EMBASE, Web of Science, and Cochrane Central. Efforts were made to identify unpublished trials through the International Standard Randomised Controlled Trial Number Registry of clinical trials, ClinicalTrials.gov.au, and the Australian New Zealand Clinical Trials Registry. Reference lists were further searched for identification of published work. The search strategy was developed by the reviewers in consultation with the OA Trial Bank.

Two review authors (SPY and LAD) independently selected citations based on titles and abstracts and assessed full articles that met the eligibility criteria independently before consensus was reached. If a consensus was not reached, the OA Trial Bank members (MvM) were consulted for arbitration.

Data collection and transfer. The corresponding authors of eligible trials were approached, and data sharing was enquired via standardized email initially and subsequently by telephone. If the corresponding authors were uncontactable, communication was attempted with the other authors and/or institutions listed. Three attempts were made to contact the corresponding authors, institutes, and/or study sponsors. IPD data were requested per OA Trial Bank protocol, and terms (15) and data transfer license agreements were signed between both parties. With the existing stored IA glucocorticoid trials in the OA Trial Bank, the corresponding authors were contacted to sign a further data transfer agreement for the purpose of this analysis. All anonymous data were kept in their original versions in a secured server at the University of Sydney and the Erasmus University Medical Centre. All data were checked for consistency with the published papers, and data quality was ensured through independent checking and assessing for data entry mistakes and discrepancies by reproducing the main baseline characteristics and reported changes over time for the available outcomes.

Risk and quality assessment. The methodological quality of the studies was assessed using the risk of bias assessment tool for randomized trials recommended by the Cochrane Collaboration (16,17). The domains assessed included randomization of procedure; anonymization of participants, physicians, and treatment allocation; use of intention-to-treat analysis; incomplete outcome data; baseline group similarity; reporting bias; and other sources of biases. The risk of bias was scored as "low," "high," or "unclear." Two review authors assessed the risk of bias (SPY and LAD). Any disagreement between the reviewers was resolved by discussion and, if required, input from a third reviewer from the OA Trial Bank.

Data analysis. The primary outcome of the IPD meta-analysis was change in pain from baseline at short-, mid-, and long-term. Participants were classified as responders if they achieved a clinically important pain reduction, defined as ≥20% reduction in pain score from baseline. This value was chosen to be consistent with the prior study by the OA Trial Bank assessing placebo responders (11) and has been recommended for use in pain and function assessment in rheumatic diseases such as OA (18,19). The value was also used to define the placebo response, which is equivalent to an ES of 0.8 (20), implying a response was unlikely to be caused by spontaneous effects. The outcomes measured on different scales were standardized. The visual analog scale pain score was preferentially used for the analysis. If unavailable, the pain subscales from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcomes Score, or other Likert pain scores were converted to a 0 to 100 scale as per former OA Trial Bank protocols (15). Supplementary analysis was performed using the absolute change in pain score, defined as a ≥20 points reduction in pain score from baseline on the 0 to 100 scale.

Tests of heterogeneity were conducted using Q statistics, which was distributed as a chi-square random variable (assumption of the homogeneity of ESs). The between-study heterogeneity was assessed with τ^2 (estimate of between-study variance) and I^2 (the percentage of total variation due to between-study variance), with interpretation as follows: $I^2 < 25\%$ means no heterogeneity, $I^2 < 50\%$ means low heterogeneity, $I^2 < 75\%$ means moderate heterogeneity, and $I^2 \geq 75\%$ indicates high heterogeneity (21). Only complete case analysis was performed, as the value of missing observations was <5%.

The study sponsor of one trial requested that their data must be analyzed on a specified secure server. Because of participant confidentiality and data sharing agreement stipulations for the other trials, IPD from those trials were unable to be uploaded to

the specified server for a one-stage approach analysis. Consequently, a two-stage approach was used.

The trials were grouped for analysis into a total IA placebo population from all available trials, and, to account for potential heterogeneity in trial design between IA therapies, the placebo groups were also separated into IA glucocorticoid/placebo trials and IA HA/placebo trials. Baseline and follow-up data on outcome measures and putative modifiers from the placebo arm were used to estimate the predictors of the placebo response. The change from baseline pain was determined as the dependent variable, and independent variables were the potential predictors of placebo response. These included patient-level characteristics and pain mechanisms that were chosen a priori, which were recognized risk factors for OA symptoms:

- Participant characteristics: age, sex, BMI, bilateral versus unilateral disease, and disease duration
- Pain mechanisms: peripheral pain mechanisms (signs of inflammation, morning stiffness symptoms, and radiographic findings) and central pain mechanisms (OA pain at other joints and pain severity with severe pain, defined as ≥70 on 0–100 scale)

For the first stage univariate analysis, logistic regression models and odds ratios (ORs) were computed as the effect measure to evaluate patient and pain mechanisms. The second stage involved pooling the results using random effects models with restricted maximum likelihood method of estimation. If more than one potential predictor variable was significant in each IA placebo group, multivariate meta-analysis was planned.

Intervention and trial characteristics were analyzed as follows:

- Intervention characteristics: aspiration attempt, frequency of injection, volume of injection, local anesthetic use, and ultrasound-guided injection
- Trial characteristics: dropout rate, role of funder/sponsor, randomization groups, trial duration (≤12, 12–24, and ≥24 weeks), single-center/multicenter study, or funding/sponsor

A generalized mixed-effects model using a logit link function accounting for the intrastudy correlations was applied; the study by Chevalier et al (22) was omitted in this analysis because of data server security limitations.

OR effect measures and 95% CIs were generated for each outcome measure. $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using Stata version 17 (StataCorp).

RESULTS

Study descriptions. The literature search for IA glucocorticoid RCTs resulted in 418 study abstracts. After screening, 30 publications with full text were evaluated, 14 fulfilled the inclusion criteria, and IPD were sought from these studies (Figure 1). Two authors agreed to participate and contributed data (23,24). The authors/institutions/sponsors of six studies responded positively to the data share request but were subsequently lost to further contact or had data availability/access issues. Contact was unable to be established with six studies.

The literature search for IA HA RCTs resulted in 1,787 abstracts. After screening, 49 studies were evaluated in full text, and 42 studies fulfilled the inclusion criteria and were contacted for IPD for participation (Figure 1). Four studies agreed to participate (22,25–27). The authors/institutions/sponsors of six studies did respond to the data share request but were subsequently lost to further contact or had data availability/access issues. Contact was unable to be established with 31 studies. The full list of studies contacted is available in the "Supplementary list of studies contacted."

The IPD from the six studies (two glucocorticoid and four HA; n = 949) were combined with the existing IPD from the OA Trial Bank (28–31), yielding 10 studies with 1,399 participants. The characteristics of the included studies are presented in Table 1. A total of six studies compared IA glucocorticoid (n = 190) with placebo (n = 181), and five studies compared IA HA (n = 555) with placebo (n = 458); Atchia et al (28) had both IA glucocorticoid and HA versus placebo groups. Data on 621 placebo participants were available for analysis.

The risk of bias scores of the studies are presented in Supplementary Table 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25212). All studies were deemed to be of low bias in relation to randomization, compliance, timing, and selective outcome reporting.

Table 2 details the baseline characteristics of the study participants for all studies and the placebo comparison groups. For the total placebo participants, the average age was 62 years, and 58% were women. Severe pain was reported in 29% of the placebo participants.

Placebo response. At short-term follow-up, 45.5% of placebo participants were placebo responders reporting ≥20% pain reduction from baseline, 52.6% were responders at midterm follow-up, and 54.7% were responders at long-term follow-up. Of the 262 nonresponders at short-term follow-up, 107 participants became responders at midterm follow-up and 82 participants at long-term follow-up. Of the 219 responders at short-term follow-up, 53 became nonresponders at midterm follow-up and 32 at long-term follow-up.

The response rate was 56.3% in women and 47.5% in men at short-term ($P = 0.02$), 61.4% in women and 54.7% in men at midterm ($P = 0.10$), and 61.2% in women and 54.7% in men at long-term follow-up ($P = 0.17$).

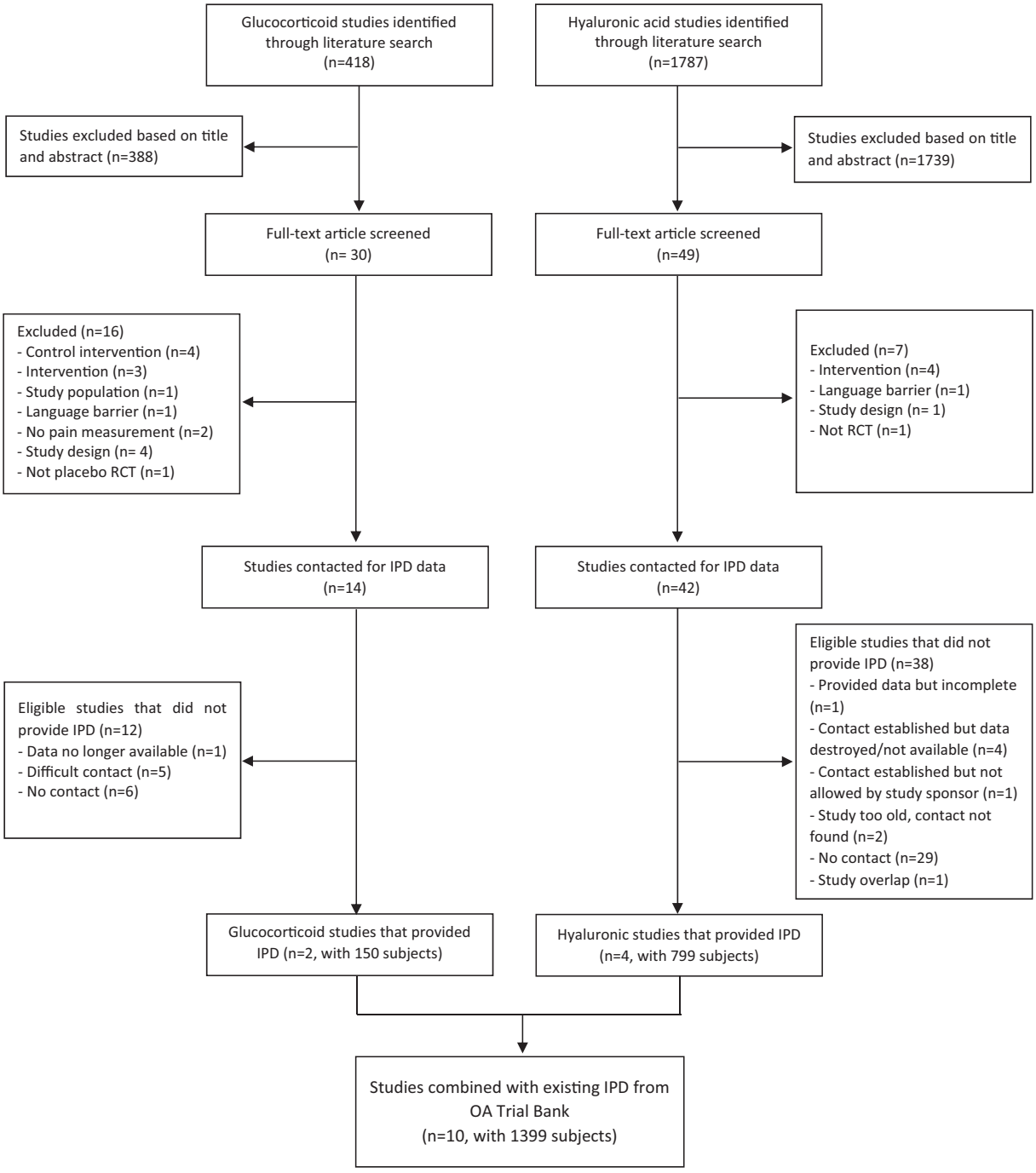

Figure 1. Flow diagram of updated search and included studies. IPD, individual participant data; OA, osteoarthritis.

The mean (±SD) age was 60.8 years (±10.5 years) and the mean (±SD) BMI was 29.2 kg/m^2 (± 4.0 kg/m^2) for responders, and it was 61.3 years (± 8.9 years) with a BMI of 29.0 kg/m^2 (± 4.2 kg/m^2) for nonresponders at short-term follow-up. The mean (±SD) age was 61.3 years (± 10.1 years) with a BMI of 29.0 kg/m^2 (± 3.8 kg/m^2) for responders and 62.0 years (± 11.01 years) with a BMI of 29.2 kg/m^2 (± 4.3 kg/m^2) for nonresponders at midterm follow-up. The mean (±SD) age was 61.3 years (± 10.4 years) with a BMI of 28.9 kg/m^2 (± 3.8 kg/m^2) for responders and 60.9 years (± 11.0 years) with a BMI of 29.4 kg/m^2 (± 4.0 kg/m^2) for nonresponders at long-term follow-up.

Potential predictors of placebo response. There were no associations with placebo response at the short-term follow-up. At the midterm follow-up, participants with a severe baseline pain score (≥70 on a 100-point scale) compared with those with a less severe baseline pain score in the IA glucocorticoid/placebo population had increased odds of a response to placebo

Table 1. Trial characteristics*

Study	Origin	Joint	OA diagnosis	N in intervention	N in Placebo	Interventions	Injection technique	Outcome	Inflammation	Follow-up	Funding source
Atchia et al (2011) (28)	UK	Hip	Clinical diagnosis of knee OA + radiographic evidence	n = 19 steroid; n = 19 hyaluronic acid	29 (n= 19, placebo; n= 20, standard care [no injection control group])	Methylprednisolone acetate 3 ml/120 mg vs placebo (3 mg saline) vs standard care vs hyaluronic acid (Durolane)	U/S guided; LA used; aspiration attempted	Pain (NRS); WOMAC pain, physical function, stiffness, total	Presence of synovitis >7 mm on ultrasound	1, 4, 8, and 16 weeks	Government institution and funding agency
Chao et al (2010) (29)	USA	Knee	ACR criteria for knee OA (1986) + radiograph within 1 year of enrollment	40	39	Triamcinolone acetonide 40 mg vs placebo (1 ml 0.9% saline)	No U/S guidance; no LA use; aspiration not attempted	Pain (VAS); WOMAC pain and total	Pathologic effusion of ≥5 mm present on ultrasound	4 and 12 weeks	Government institution and funding agency
Chevalier et al (2010) (22)	France	Knee	ACR criteria for knee OA (knee pain for most days of the previous month, and osteophyte(s) at joint margins visible on x-ray and measurable joint space)	124	129	Hylan G-F 20 vs placebo (6 ml, buffered physiological sodium chloride solution)	U/S guided; LA used; aspiration attempted	WOMAC pain, physical function, stiffness; patient global assessment; clinical observer global assessment	Presence of effusion by clinical assessment	1, 4, 8, 12, 18, and 26 weeks	Funding agency
Dahlberg et al (1994) (25)	Sweden	Knee	Cartilage abnormality on arthroscopy (Outerbridge score ≥2 in 1 joint surface)	28	24	Hyaluronan 2.5 ml, 10 mg/ml vs placebo (2.5 ml sodium chloride, dibasic sodium phosphate, sodium dihydrogen, and phosphate dihydrate)	No U/S guidance; LA used; aspiration attempted	Pain (VAS); function (VAS); activity (VAS); mobility (VAS); Lysholm score	-	2, 4, 13, 26, and 52 weeks	Government institution
Hall et al (2014) (24)	UK	Knee	Clinical diagnosis of painful knee OA + KL grade ≥2	25	25	Methylprednisolone 40 mg vs placebo (1 ml, 0.9% saline)	No U/S guidance; LA use – N/A; aspiration attempted	Pain (VAS); WOMAC pain, physical function, stiffness	Presence of effusion/ synovial hypertrophy on ultrasound	1 week	Government institution
Henriksen et al (2015) (23)	Denmark	Knee	ACR criteria for knee OA (1986) + radiographic confirmation	50	50	Methylprednisolone acetate 40 mg + 4 ml lidocaine hydrochloride (10 mg/ml) vs placebo (1 ml isotonic saline + 4 ml lidocaine hydrochloride [10	U/S guided; LA used; aspiration attempted	KOOS pain, ADL, QOL, function in sports or recreation, symptoms	Presence of effusion/ synovitis on MRI imaging	2, 14, and 26 weeks	Government institution

(Continued)

Table 1. (*Cont'd*)

Study	Origin	Joint	OA diagnosis	N in intervention	N in Placebo	Interventions	Injection technique	Outcome	Inflammation	Follow-up	Funding source
						mg/ml]). Followed by 12-week exercise program starting at week 2					
Lambert et al (2007) (31)	Canada	Hip	ACR criteria for hip OA (1991) + radiologic evidence of OA	31	21	Triamcinolone 40 mg + 10 mg bupivacaine vs placebo (10 mg bupivacaine + 2 ml saline)	U/S guided; LA used; aspiration attempted	WOMAC pain, physical function, stiffness, total; global assessment	-	1, 2, 3, and 6 months	Funding agency
Ravaud et al (1999) (30)	France	Knee	ACR criteria for knee OA (1986) + inclusion criteria of KL grade ≥2	25	73 (placebo n = 28; joint lavage plus placebo n = 21; joint lavage plus corti costeroid, n = 24)	Cortivazol 3.75 mg in 1.5 ml vs placebo (1.5 ml 0.9% saline) vs joint lavage plus IA placebo vs joint lavage plus IA steroid	No U/S guidance; no LA used; aspiration not attempted	Pain (VAS); global status (VAS)	Evidence of effusion by clinical assessment (present or not)	1, 4, 12, and 24 weeks	Government institution and funding agency
Strand et al (2012) (27)	USA; Japan	Knee	Pain in affected knee of ≥4 weeks while standing or walking with radiological evidence of OA with KL grade 1-3	251	128	Gel-200 (30 mg in 3.0 ml) vs placebo (3.0 ml, phosphate buffered saline)	No U/S guidance; no LA used; aspiration attempted	Pain (WOMAC pain subscore - VAS); WOMAC total, physical function, stiffness; physician and patient global	Evidence of effusion by clinical assessment (present or not)	1,3, 6, 9, and 19 weeks	Funding agency
Takamura et al (2019) (26)	USA; Japan	Knee	Clinical diagnosis of knee OA with radiological evidence of OA with KL grade 1–3	152	159	Gel-200 (30 mg in 3.0 ml) vs placebo (3.0 ml, phosphate buffered saline)	U/S guided; LA used; aspiration attempted	Pain (WOMAC pain subscore - VAS); WOMAC total, physical function, stiffness; physician and patient global	Evidence of effusion by clinical assessment (present or not)	3, 6, 12, 18, and 26 weeks	Funding agency

* ACR, American College of Rheumatology; ADL, activity of daily living; KL, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; LA, local anesthetic; MRI, magnetic resonance imaging; NRS, Numerical Rating Scale; OA, osteoarthritis; QOL, quality of life; U/S, ultrasound guided; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Baseline characteristics of participant*

Characteristic	Total population, N = 1399	Placebo-only population, n = 621	Placebo only (glucocorticoid trials group), n = 181	Placebo only (hyaluronic acid trials group), n = 458
Age, y, mean (SD)	62.66 (10.57)	62.07 (10.82)	65.08 (10.77)	60.90 (10.65)
Female sex, n (%)	842 (60.1)	361 (58.1)	89 (49.2)	284 (62.0)
BMI, kg/m^2, mean (SD)	28.88 (4.52)†	29.27 (4.54)‡	29.38 (4.56)§	29.03 (4.08)
Duration of symptoms, mean (SD), mon	44.49 (71.66)¶	78.07 (79.59)#	85.29 (106.87)**	66.79 (36.23)††
KL grade, n %				
0	2 (0.1)	1 (0.2)	1 (0.6)	0 (0.0)
1	60 (4.3)	22 (3.5)	4 (2.2)	21 (4.6)
2	513 (36.7)	217 (34.9)	27 (14.9)	194 (42.4)
3	657 (47.0)	283 (45.5)	75 (41.4)	218 (47.6)
4	83 (5.9)	35 (5.6)	34 (18.8)	1 (0.2)
Missing	84 (6.0)	64 (10.3)	40 (22.1)	24 (5.2)
Inflammation, n (%)	481 (51.2)§§	259 (45.2)¶¶	113 (71.97)##	88 (28.9)***
Effusion, n (%)	306 (35.5)†††	168 (30.4)‡‡‡	96 (70.07)§§§	40 (13.9)¶¶¶
Pain (0–100), mean (SD)	60.32 (18.30)	61.85 (17.04)	55.78 (19.86)	65.53 (14.25)
Severe pain (≥70 points on VAS), n (%)	293 (28.1)###	179 (29.0)****	49 (27.53)††††	137 (29.9)
OA other joints, n (%)	373 (58.5)‡‡‡‡	275 (57.9)§§§§	6 (21.43)¶¶¶¶	194 (67.6)####

* BMI, body mass index; KL, Kellgren-Lawrence; OA, osteoarthritis; VAS, visual analog scale.
† N = 1,162 (not available for Lambert and Chao).
‡ N = 561 (not available for Lambert and Chao).
§ N = 121 (not available for Lambert and Chao).
¶ N = 1,223 (not available for Henriksen, Hall, Dahlberg).
# N = 433.
** N = 101.
†† N = 350.
§§ N = 939 (not available for Lambert and Dahlberg and there are only placebo data for inflammation for Strand and Takamura).
¶¶ N = 537.
N = 157.
*** N = 305 (not available for Dahlberg).
††† N = 861 (not available for Lambert and Dahlberg and there are only placebo data for inflammation for Strand and Takamura).
‡‡‡ N = 553.
§§§ N = 137.
¶¶¶ N = 287.
N = 1,043 (only have placebo data for Strand and Takamura).
**** N = 618.
†††† N = 178.
‡‡‡‡ N = 638 (not available for Lambert, Hall, Henriksen, Dahlberg, Chao, or Atchia).
§§§§ N = 444 (not available for Lambert, Hall, Henriksen, Dahlberg, Chao, or Atchia).
¶¶¶¶ N = 28 (not available for Lambert, Hall, Henriksen, Chao, or Atchia).
N = 287.

(OR 2.98, 95% CI 1.01–8.82). The absolute pain reduction using SMD was 3.84 (95% CI −5.57 to 13.25). When analyzed using absolute change in pain, increased odds of placebo response was not demonstrated (Supplementary Table 2).

Worse baseline function score (WOMAC) at midterm follow-up was significantly associated with a reduction in placebo response in the total placebo population (OR 0.98, 95% CI 0.96–1.00) with SMD 0.05 (95% CI −0.11 to 0.22) and in the IA HA/placebo group (OR 0.98, 95% CI 0.96–0.99) with SMD 0.03 (95% CI −0.14 to 0.20). With absolute change analysis, the OR was 0.99 (95% CI 0.97–1.00) in the total placebo population and 0.98 (95% CI 0.97–1.00) in the IA HA/placebo group.

There was no difference in placebo response at mid- or long-term follow-up according to age, sex, BMI, disease duration, baseline pain level, OA in other joints, radiographic severity, signs of inflammation (with or without imaging detection), or symptoms of stiffness (WOMAC) (Table 3).

The analysis of the intervention and trial characteristics at short-term follow-up (Table 4) for the total placebo population revealed that participants who had ultrasound-guided injections were significantly less likely to respond to placebo (OR 0.42, 95% CI 0.23–0.76; SMD −10.03, 95% CI −19.88 to −0.19). Those who received local anesthetics compared with those who did not receive local anesthetics were less likely to respond to

Table 3. Predictors of placebo response: participant and disease characteristics at short-, mid-, and long-term*

Potential predictors	Short-term																	
	Placebo-only population, n = 621 in ten studies						Placebo only (glucocorticoid trials group), n = 181 in six studies						Placebo only (hyaluronic acid trials group), n = 458 in five studies					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Age	609	0.991 (0.97–1.01)	0.346	6.19 (0.721)	0.0	0.000	174	0.992 (0.95–1.03)	0.694	5.62 (0.345)	11.0	0.000	453	0.989 (0.97–1.01)	0.280	1.96 (0.743)	0.0	0.000
Sex	609	1.075 (0.61–1.91)	0.806	15.46 (0.051)	48.2	0.316	174	0.855 (0.25–2.91)	0.801	8.98 (0.062)	55.5	1.060	453	1.024 (0.53–1.98)	0.945	8.72 (0.068)	54.2	0.274
BMI	554	1.004 (0.96–1.05)	0.884	8.49 (0.291)	17.6	0.001	120	1.056 (0.96–1.56)	0.257	3.32 (0.345)	9.6	0.001	452	0.992 (0.95–1.04)	0.747	4.28 (0.369)	6.6	0.000
Disease duration	427	0.999 (0.99–1.00)	0.721	4.97 (0.548)	0.0	0.000	98	1.000 (0.99–1.01)	0.912	3.47 (0.325)	13.5	0.000	347	1.001 (1.00–1.01)	0.825	5.32 (0.150)	43.6	0.000
OA other joints	439	0.824 (0.41–1.64)	0.582	7.47 (0.058)	59.8	0.280	–	N/A	–	–	–	–	411	0.752 (0.35–1.62)	0.466	6.68 (0.035)	70.1	0.323
Pain at baseline	609	1.007 (0.99–1.02)	0.329	11.44 (0.247)	21.3	0.000	174	1.010 (0.99–1.03)	0.299	3.49 (0.625)	0.0	0.000	453	1.006 (0.98–1.03)	0.618	7.72 (0.103)	48.2	0.000
Severe pain (≥70)	609	0.987 (0.66–1.47)	0.947	6.37 (0.606)	0.0	0.000	168	1.072 (0.40–2.87)	0.891	4.93 (0.295)	18.9	0.241	453	0.913 (0.59–1.41)	0.685	2.15 (0.707)	0.0	0.000
KL grade	551	1.054 (0.79–1.40)	0.718	6.24 (0.512)	0.0	0.000	140	1.117 (0.64–1.94)	0.693	4.55 (0.337)	12.0	0.049	428	0.954 (0.66–1.38)	0.804	3.46 (0.326)	13.4	0.020
Patient global	437	1.003 (0.99–1.01)	0.549	2.89 (0.409)	0.0	0.000	–	–	–	–	–	–	409	1.002 (0.99–1.02)	0.740	2.84 (0.242)	29.6	0.000
Effusion	511	0.712 (0.45–1.13)	0.151	3.86 (0.696)	0.0	0.000	133	0.512 (0.19–1.36)	0.178	1.58 (0.664)	0.0	0.000	411	0.785 (0.46–1.33)	0.367	1.71 (0.425)	0.0	0.000
Inflammation	530	0.893 (0.60–1.33)	0.575	5.59 (0.470)	0.0	0.000	153	0.420 (0.16–1.14)	0.088	2.24 (0.524)	0.0	0.000	429	1.160 (0.75–1.79)	0.502	1.83 (0.401)	0.0	0.000
Inflammation detected by imaging	153	0.388 (0.10–1.53)	0.177	2.22 (0.329)	10.0	0.150	153	0.388 (0.10–1.53)	0.177	2.22 (0.329)	10.0	0.150	–	–	–	–	–	–

(Continued)

Table 3. (*Cont'd*)

Potential predictors	Placebo-only population, n = 621 in ten studies						Placebo only (glucocorticoid trials group), n = 181 in six studies						Placebo only (hyaluronic acid trials group), n = 458 in five studies					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Short-term																		
Stiffness	476	0.992 (0.98–1.00)	0.186	4.37 (0.498)	0.0	0.000	65	0.985 (0.96–1.01)	0.287	0.65 (0.723)	0.0	0.000	429	0.993 (0.98–1.01)	0.331	4.07 (0.254)	26.2	0.000
Function	476	0.990 (0.98–1.00)	0.150	3.65 (0.601)	0.0	0.000	65	1.008 (0.97–1.04)	0.660	2.07 (0.355)	3.4	0.000	429	0.987 (0.97–1.00)	0.087	0.47 (0.925)	0.0	0.000
Midterm																		
	Placebo-only population, n = 545						Placebo only (Glucocorticoid trials group), n = 129						Placebo only (Hyaluronic acid trials group), n = 434					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Age	545	0.997 (0.98–1.02)	0.773	7.63 (0.470)	0.0	0.000	129	1.013 (0.96–1.07)	0.625	5.99 (0.200)	33.2	0.001	434	0.994 (0.97–1.02)	0.582	1.22 (0.747)	0.0	0.000
Sex	545	1.163 (0.70–1.93)	0.558	10.14 (0.181)	31.0	0.149	129	2.446 (0.98–6.08)	0.054	1.97 (0.579)	0.0	0.000	434	0.903 (0.54–1.51)	0.697	4.25 (0.236)	29.3	0.080
BMI	498	0.997 (0.95–1.04)	0.882	2.53 (0.865)	0.0	0.000	83	0.992 (0.95–1.03)	0.694	5.62 (0.345)	11.0	0.000	433	0.997 (0.95–1.04)	0.906	1.96 (0.744)	0.0	0.000
Disease duration	394	1.001 (1.00–1.01)	0.762	6.37 (0.383)	5.8	0.000	82	0.998 (0.99–1.01)	0.570	3.09 (0.379)	2.8	0.000	330	1.001 (1.00–1.01)	0.564	2.70 (0.440)	0.0	0.000
OA other joints	412	0.809 (0.46–1.42)	0.461	4.74 (0.192)	36.7	0.118	–	–	–	–	–	–	393	0.848 (0.46–1.58)	0.603	4.21 (0.122)	52.5	0.159
Pain at baseline	545	1.006 (0.98–1.03)	0.595	16.35 (0.038)	51.1	0.001	129	1.019 (0.98–1.06)	0.382	7.86 (0.097)	49.1	0.001	434	0.998 (0.97–1.03)	0.895	7.17 (0.067)	58.2	0.000
Severe pain (>70)	545	0.987 (0.61–1.60)	0.957	8.15 (0.320)	14.1	0.069	129	2.980 (1.01–8.82)	0.049	0.12 (0.989)	0.0	0.000	434	0.752 (0.48–1.18)	0.214	2.74 (0.433)	0.0	0.000
KL grade	492	0.863 (0.63–1.18)	0.357	2.76 (0.737)	0.0	0.000	99	0.709 (0.34–1.46)	0.352	2.25 (0.325)	11.1	0.046	410	0.911 (0.64–1.30)	0.606	0.08 (0.962)	0.0	0.000
Patient global	411	0.998 (0.98–1.02)	0.855	7.06 (0.070)	57.5	0.000	–	–	–	–	–	–	392	0.993 (0.98–1.01)	0.234	2.24 (0.326)	10.7	0.000

(Continued)

Table 3. (*Cont'd*)

	Midterm																	
	Placebo-only population, n = 545						Placebo only (Glucocorticoid trials group), n = 129						Placebo only (Hyaluronic acid trials group), n = 434					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Effusion	486	0.904 (0.55–1.49)	0.693	2.06 (0.841)	0.0	0.000	93	0.573 (0.16–2.00)	0.383	0.83 (0.661)	0.0	0.000	393	1.010 (0.99–1.03)	0.420	0.37 (0.830)	0.0	0.000
Inflammation	505	0.930 (0.52–1.66)	0.804	7.57 (0.181)	34.0	0.163	112	0.573 (0.16–2.00)	0.383	0.83 (0.661)	0.0	0.000	411	1.033 (0.48–2.24)	0.934	5.92 (0.052)	66.2	0.309
Inflammation detected by imaging	112	0.462 (0.09–2.48)	0.367	0.68 (0.408)	0.0	0.000	112	0.462 (0.09–2.48)	0.367	0.68 (0.408)	0.0	0.000	–	–	–	–	–	–
Stiffness	429	0.991 (0.98–1.00)	0.161	4.18 (0.382)	4.4	0.000	36	0.967 (0.92–1.02)	0.210	0.12 (0.726)	0.0	0.000	411	0.992 (0.98–1.01)	0.320	3.94 (0.268)	23.9	0.000
Function	429	0.979 (0.96–1.00)	0.010	3.86 (0.425)	0.0	0.000	36	0.974 (0.85–1.12)	0.706	1.98 (0.159)	49.5	0.006	411	0.978 (0.96–0.99)	0.006	1.15 (0.564)	0.0	0.000
	Long-term																	
	Placebo-only population, n = 349						Placebo only (glucocorticoid trials group), n = 72						Placebo only (hyaluronic acid trials group), n = 277					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Age	349	1.021 (0.98–1.06)	0.271	8.32 (0.140)	39.9	0.001	72	1.037 (0.95–1.13)	0.408	3.91 (0.141)	48.9	0.003	277	0.997 (0.97–1.02)	0.807	1.54 (0.462)	0.0	0.000
Sex	349	1.408 (0.82–2.42)	0.214	0.42 (0.981)	0.0	0.000	72	1.484 (0.54–4.09)	0.446	0.19 (0.908)	0.0	0.000	277	1.140 (0.70–1.87)	0.604	1.09 (0.581)	0.0	0.000
BMI	337	0.980 (0.93–1.03)	0.429	2.16 (0.706)	0.0	0.000	60	0.996 (0.82–1.21)	0.969	1.53 (0.217)	34.5	0.007	277	0.977 (0.93–1.03)	0.395	0.54 (0.764)	0.0	0.000
Disease duration	283	0.999 (1.00–1.01)	0.672	0.12 (0.989)	0.0	0.000	29	1.001 (0.99–1.02)	0.866	0.05 (0.828)	0.0	0.000	254	0.999 (0.99–1.00)	0.636	0.00 (0.997)	0.0	0.000
OA other joints	272	0.896 (0.54–1.50)	0.678	1.12 (0.570)	0.0	0.000	–	–	–	–	–	–	255	0.896 (0.54–1.50)	0.678	1.12 (0.570)	0.0	0.000
Pain at baseline	349	1.007 (0.99–1.03)	0.441	5.19 (0.393)	3.6	0.000	72	1.018 (0.98–1.06)	0.375	2.56 (0.277)	22.0	0.000	277	1.004 (0.98–1.03)	0.759	2.29 (0.318)	12.6	0.000

(Continued)

Table 3. (*Cont'd*)

	Long-term																	
	Placebo-only population, n = 349						Placebo only (glucocorticoid trials group), n = 72						Placebo only (hyaluronic acid trials group), n = 277					
	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2	n	OR (95% CI)	*P*-value	Cochran's Q (*P*-value)	I^2, %	τ^2
Severe pain (>70)	349	0.889 (0.44–1.79)	0.741	6.55 (0.257)	23.6	0.179	72	1.275 (0.24–6.69)	0.774	3.51 (0.173)	43.0	0.926	277	0.755 (0.36–1.58)	0.456	2.50 (0.287)	19.9	0.095
KL grade	327	0.873 (0.52–1.46)	0.603	5.20 (0.268)	23.0	0.079	72	0.793 (0.24–2.61)	0.702	4.08 (0.130)	50.9	0.567	255	0.947 (0.58–1.56)	0.830	0.79 (0.373)	0.0	0.000
Patient global	272	1.00 (0.98–1.02)	0.879	3.76 (0.153)	46.8	0.000	–	–	–	–	–	–	255	0.992 (0.98–1.01)	0.331	0.91 (0.340)	0.0	0.000
Effusion	315	0.593 (0.21–1.66)	0.321	3.81 (0.149)	47.5	0.390	–	–	–	–	–	–	255	0.881 (0.44–1.76)	0.720	0.54 (0.461)	0.0	0.000
Inflammation	315	0.854 (0.30–2.42)	0.766	5.60 (0.061)	64.3	0.504	–	–	–	–	–	–	255	1.295 (0.74–2.26)	0.364	0.94 (0.333)	0.0	0.000
Inflammation detected by imaging	–	N/A	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Stiffness	267	0.990 (0.97–1.01)	0.310	2.51 (0.286)	20.2	0.000	–	–	–	–	–	–	255	0.993 (0.98–1.01)	0.380	0.58 (0.447)	0.0	0.000
Function	267	0.978 (0.95–1.01)	0.194	3.59 (0.166)	44.2	0.000	–	–	–	–	–	–	255	0.981 (0.94–1.03)	0.402	3.44 (0.064)	70.9	0.001

* Participant and disease characteristics were adjusted for age, sex, and BMI. BMI, body mass index; CI, confidence interval; KL, Kellgren-Lawrence; N/A, not available; OA, osteoarthritis; OR, odds ratio.

Table 4. Potential predictors of response: intervention and trial characteristics*

	Potential predictors of response	Placebo-only population, n = 492 (exclude Chevalier trial)			Placebo only (glucocorticoid trials group), n = 181			Placebo only (hyaluronic acid trials group), n = 329 (exclude Chevalier trial)		
		OR	*P*-value	95% CI	OR	*P*-value	95% CI	OR	*P*-value	95% CI
Short-term	Volume of injection	0.877	0.314	0.68–1.13	0.909	0.447	0.71–1.16	0.921	0.391	0.12–7.04
	Ultrasound-guided injection	0.415	0.004	0.23–0.76	0.690	0.363	0.31–1.53	0.376	0.076	0.13–1.11
	Local anesthetics	0.539	0.021	0.32–0.91	0.699	0.480	0.26–1.89	0.648	0.221	0.32–1.30
	Aspiration attempted	0.645	0.029	0.44–0.96	N/A	–	–	0.791	0.345	0.49–1.29
	Injection frequency	1.165	0.290	0.89–1.55	1.460	0.457	0.54–3.96	1.010	0.937	0.78–1.30
	Randomization groups	1.431	0.224	0.80–2.55	0.683	0.504	0.22–2.09	1.276	0.326	0.78–2.07
	Single/multicenter	0.620	0.046	0.39–0.99	0.825	0.694	0.32–2.15	0.648	0.221	0.32–1.30
	Dropout rate	0.979	0.585	0.91–1.06	0.976	0.591	0.89–1.07	0.969	0.439	0.89–1.05
	Trial duration	1.870	0.130	0.83–4.21	–	–	–	2.552	0.082	0.88–7.34
	Potential predictors of response	Placebo-only population, n = 422 (exclude Chevalier trial)			Placebo only (glucocorticoid trials group), n = 129			Placebo only (hyaluronic acid trials group), n = 311 (exclude Chevalier trial)		
Midterm	Volume of injection	1.378	0.136	0.90–2.11	1.537	0.163	0.84–2.81	0.522	0.788	0.01–59.57
	Ultrasound-guided injection	0.630	0.442	0.19–2.04	1.037	0.979	0.07–14.83	0.047	0.003	0.01–0.36
	Local anesthetics	0.696	0.492	0.25–1.95	1.037	0.979	0.07–14.83	0.279	0.001	0.13–0.60
	Aspiration attempted	0.685	0.193	0.39–1.21	–	–	–	0.529	0.013	0.32–0.87
	Injection frequency	1.016	0.940	0.68–1.52	–	–	–	1.085	0.788	0.60–1.96
	Randomization groups	1.003	0.990	0.33–1.61	0.101	0.015	0.02–1.03	1.028	0.913	0.63–1.68
	Single/multicenter	0.696	0.492	0.25–1.95	1.037	0.979	0.07–14.83	0.279	0.001	0.13–0.60
	Dropout rate	1.027	0.814	0.82–1.28	1.419	0.355	0.68–2.98	1.057	0.779	0.72–1.55
	Trial duration	10.33	0.003	2.25–47.35	–	–	–	10.68	0.002	2.32–49.25
	Potential predictors of response	Placebo-only population, n = 232			Placebo only (glucocorticoid trials group), n = 72			Placebo only (hyaluronic acid trials group), n = 160 (exclude Chevalier trial)		
Long-term	Volume of injection	1.301	0.109	0.94–1.80	1.388	0.123	0.91–2.10	0.625	0.705	0.06–7.11
	Ultrasound-guided injection	1.853	0.131	0.83–4.13	3.15	0.123	0.73–13.52	–	–	–
	Local anesthetics	2.137	0.038	1.04–4.37	3.15	0.123	0.73–13.52	1.264	0.705	0.37–4.26
	Aspiration attempted	1.190	0.564	0.66–2.16	–	–	–	0.815	0.656	0.33–2.01
	Injection frequency	1.178	0.243	0.89–1.55	–	–	–	1.061	0.704	0.78–1.44
	Randomization groups	–	–	–	–	–	–	–	–	–
	Single/multicenter	2.137	0.038	1.04–4.37	3.15	0.123	0.73–13.52	1.264	0.705	0.37–4.26
	Dropout rate	0.815	0.060	0.66–1.01	0.564	0.123	0.27–1.17	–	–	–
	Trial duration	–	–	–	–	–	–	–	–	–

* Trial characteristics were adjusted for age, sex, and body mass index. CI, confidence interval; N/A, not available; OR, odds ratio.

placebo (OR 0.54, 95% CI 0.32–0.91; SMD –8.84, 95% CI –18.45 to 0.77). Similarly, participants who had joint fluid aspiration attempted compared with those those who did not have aspiration attempt were less likely to respond to placebo (OR 0.65, 95% CI 0.44–0.96; SMD –3.32, 95% CI –9.33 to 2.69). Participants of trials done at single centers compared with those who were in multicenter trials were less likely to respond to placebo (OR 0.62, 95% CI 0.39–0.99; SMD –8.75, 95% CI –16.94 to –0.57). Of the trials included in this study, all the single-center trials (n = 6) were government funded, and the multicenter trials (n = 4) were commercially funded; thus, further analysis of funding sources was not conducted. With absolute change analysis, only ultrasound-guided injections (OR 2.4, 95% CI 0.11–0.53) and local anesthetics administration (OR 0.40, 95% CI 0.17–0.94) were associated with reduced odds of placeo response (Supplementary Table 3).

At midterm follow-up, comparable findings were seen in participants who received local anesthetics, received ultrasound-guided injections, had joint aspiration attempted, were in single-center studies, or were seen in the IA HA/placebo group with reduced odds of placebo response. Trial duration of 12 to 24 weeks and ≥24 weeks in both the total placebo population and the IA HA/placebo comparison group were associated with increased odds of placebo response OR 10.33 (95% CI 2.25–47.35), OR 10.29 (95% CI 2.29–46.31, $P = 0.002$) respectively for 12 to 24 weeks and OR 10.68 (95% CI 2.32–49.27), OR 10.40 (95% CI 2.29–47.24, $P = 0.002$), respectively for ≥24 weeks. When analyzed using absolute change, these intervention and trial characteristics were still significantly associated with reduced/increased odds of placebo response.

There was no association of placebo response with volume of injection, randomization ratio, or dropout rate. No significant associations were seen at long-term follow-up.

DISCUSSION

To our knowledge, this is the first IPD meta-analysis conducted to identify predictors of placebo response, specifically in IA injection trials in OA.

The finding of this IPD meta-analysis demonstrated that participants with severe baseline pain may be more likely to respond to IA placebo in the IA glucocorticoid/placebo group at midterm follow-up. However, this association was not demonstrated in the other placebo comparison groups at any other follow-up time frame, and supplementary analysis using absolute change to avoid small changes from a smaller baseline value did not reveal any significance. Increased placebo ES and response have been associated with higher baseline pain scores (1,3), but one study has negated this (4). This can potentially reflect regression to the mean, and this analysis did not find overall baseline pain to be a predictor of placebo response.

It was shown that participants with decreased baseline function may be less likely to respond to placebo in both the whole placebo population and the IA HA/placebo group at midterm follow-up. It is likely that participants who have heightened functional limitations may have more severe disease and are thus less prone to placebo response, especially at longer follow-up time points.

Other participant-related factors were not shown to be predictors of response at any time frame in this study. This may be in part because of the nature of the RCTs included with adequate randomization of participants in the placebo arm, leading to a wide spread of participant characteristics. A recent study assessing proportional contextual effects (PCEs) in RCTs across different conditions and treatments found that blinded outcome assessor, allocation concealment, lower mean age, higher proportion of women, larger placebo effect, and nonchronic condition trials led to increased PCEs (32). But the sensitivity analysis revealed outcome assessor blinding being the only significant factor. Although this factor was not assessed, our study findings of no association with participant baseline characteristics is concordant with the sensitivity analysis. A crucial difference between this study and the PCE study is that this is an IPD analysis assessing a specific pharmacological intervention in a single disease condition using pain as the primary outcome. Both studies are in accordance that some important contextual factors are unable to be measured, including participants' conceptual beliefs in the intervention, physician characteristics, and attitude and participant–physician interactions—all of which could impact the ability to define predictors of placebo response (33).

We have assessed to what extent specific treatment and trial characteristics affect the placebo response and demonstrated that, at short-term follow-up, participants in the total placebo population who had local anesthetic, aspiration attempt, ultrasound guidance or enrollment in single-center trials were less likely to demonstrate a placebo response. The significance of the characteristics of ultrasound guidance and use of local anesthetic were substantiated using the absolute change analysis. Participant beliefs and knowledge of high-tech equipment has been reported to influence placebo response (34). Based on studies comparing sonograph-guided injections with blinded knee injections with active therapies, participants who had sonograph-guided injections reported increased improvements in pain (35,36). Therefore, there is the expectation that ultrasound-guided placebo injection will lead to increased placebo response, but our study showed the inverse of this. One hypothetical rationale would be that ultrasound guidedance leads to more localization of the placebo injected and therefore can minimize any potential systemic effect of the placebo itself.

There has been no literature in relation to local anesthetic and placebo response in OA. Given the analgesic effect of local anesthetic, there is the assumption that it can impact the placebo

response. However, given their short duration of action, the rebound in pain may lead to less placebo response.

Pain and poor function have been related to synovitis in OA (37,38), and there is the hypothesis that aspiration of synovial fluid before injection may reduce the pro-inflammatory cytokines in the joint, leading to a heightened placebo effect (3,39). Conversely, in patients with OA who have sufficient synovial fluid to aspirate, baseline synovial inflammation volume may be elevated, thus the reduction in cytokines due to aspiration may be transient and the synovial fluid could re-accumulate, possibly leading to reduced placebo response over time. In this study, the aspiration attempt was specified as part of the intervention protocol with each study, but there were limited data on whether synovial fluid was aspirated or the volume.

At midterm follow-up, in the IA HA/placebo group, the same trial characteristics were demonstrated to have reduced odds of placebo response, but this was not seen in the total placebo or IA glucocorticoid/placebo groups. Even though absolute change analysis demonstrated significance, these findings may reflect multiplicity and need to be interpreted with care. Compared with meta-analyses of placebo-controlled HA trials (40,41), only a very limited number of trials were obtained for this analysis. From the prior meta-analyses, viscosupplementation compared with placebo did not reach the minimum clinically important between-group difference, and in the subgroup analysis characteristics in which the SMD favored that of placebo or had clinical equivalence smaller than the minimal clinically important difference included large trial size (≥100), >3 injections (40), trials of 3 to 6 months and >6 months duration, and nonindustry sponsorship (40,41). In our relative change analysis, participants in the single-center, government-funded trials had reduced odds of placebo response. Studies have shown that sample size was associated with the placebo response (1,4,42). Clinical trials with large participant numbers are commonly multicenter trials and can result in larger placebo effects because of the challenges of ensuring homogeneity between centers with outcome assessments (42).

At midterm follow-up, participants in trials of moderate-to-long duration had increased odds of placebo response. Studies analyzing predictors of placebo response in various diseases have found variable associations with study duration (32,43). With the added number of responders at mid- to long-term follow-up, the placebo effect may relate to regression to the mean or symptom fluctuation with the natural history of OA.

This IPD meta-analysis showed that the placebo response persisted well into long-term follow-up, with more than 50% of participants being responders, which is concordant with recent meta-analyses of IA saline placebo injections with therapeutic benefits seen beyond 6 months (39,44,45). This raises the ongoing debate of whether IA saline should be considered as a "pure" placebo, having potential biomechanical effects, leading to a therapeutic effect because of a possible dilutional effect on the inflammatory elements in the joint (39,44). This IPD meta-analysis showed no influence in relation to the frequency or volume of the injections on the placebo response to support this hypothesis. Given the clinical impact of saline placebo injections, further studies are required to explore this issue, and the significant placebo effect should be taken into consideration when planning for new IA therapy trials.

The use of IPD meta-analysis allowed for an increased study sample size, thus reducing the issues with inadequate power often seen in subgroup analyses of traditional meta-analysis. However, there are several limitations to the study. Overall, the authors of 56 potentially eligible IA glucocorticoid and HA publications were approached, and only the IPD of 6 studies were obtained and combined with existing OA Trial Bank studies for a total of 10 studies. Only a subset of eligible studies was analyzed; therefore, this analysis may be subject to selection bias and data availability bias.

The potential predictors of placebo response, including participant characteristics, pain mechanisms, treatment, and trial characteristics were chosen theoretically by the authors; thus, the analysis of potential predictors should be considered as investigative. There were some deviations from the study protocol because of the data availability of factors including unilateral/bilateral disease, comorbidities, morning stiffness (total WOMAC stiffness scores were available), aspirate volume, and IA injection approach (lateral vs medial).

To harmonize the data, participant outcome scores were standardized from their original scores to a 0 to 100 scale, despite potentially having different measurement sensitivities. This reflects the evolution of outcome measures use over time and the introduction of recommended Osteoarthritis Research Society International and Outcome Measures in Rheumatology core outcome measures. The inconsistencies across different trials with outcome measures and clinical signs call for more rigorous outcome measure recommendations by governing associations and measurement groups to enable higher precision in meta-analysis.

In summary, this study demonstrated that participants who are administered local anesthetics or have ultrasound guidance may be less likely to respond to IA placebo at short-term follow-up. At midterm follow-up, participants with worse baseline function scores may be less likely to respond to IA placebo, and those in trials of moderate-to-long duration are more likely to respond to IA placebo. These findings need to be corroborated by further studies before they can be identified as true contextual factors predictive of IA placebo response.

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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 puslished. Dr. Yu 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.

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