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# Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: Results of an extensive critical literature review

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ABSTRACT

*Objectives:* There is a discrepancy between evidence in support of the widespread use of intra-articular hyaluronic acid (IAHA) to treat knee osteoarthritis (OA) in clinical practice, and the often discordant recommendations from multiple international guideline committees, which requires further investigation.
*Methods:* We conducted a literature review to determine the strength of evidence in support of the efficacy and safety of IAHA, from randomized controlled trials and meta-analyses.
*Results:* Our analysis shows that IAHA provides a moderate symptomatic benefit to knee OA patients and without major safety concerns. In fact, IAHA may offer one of the best benefit/risk ratios among pharmacologic options, as measured by improvements in knee OA health outcomes, overall gain in quality-adjusted life years and substantial delays in time to total knee replacement.
*Conclusions:* We advocate for the consideration of recommending IAHA injection as a treatment option in the management of knee OA, tailored by disease stage and patient phenotype. Future research efforts should focus on identification of OA patient subgroups that demonstrate a more robust response to IAHA, determination of long-term effects of repeat IAHA injections on patient-reported outcomes and total knee replacement-sparing effect, further elucidation of disease-modifying effects, and the potential for combination therapy with other pharmacologic and non-pharmacologic therapies to optimize the management of knee OA.


## Introduction

Osteoarthritis (OA) is a degenerative disease of the synovial joints causing joint pain and functional impairment [1]. It occurs frequently in adults over 50 years old and is a major cause of disability worldwide [2,3]. OA is a progressive disorder with different degrees of disease severity that requires long-term management with various treatment options over the course of the disease. In the absence of a cure for OA, there are multiple treatment modalities that can manage the symptoms of OA, however, few may be considered as disease modifying. Paracetamol, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and yet have significant toxicity [4–9]. Analgesics and NSAIDs are particularly poorly tolerated by OA patients because these patients are frequently of advanced age, have comorbidities, and are receiving multiple medications. Thus, intra-articular (IA) therapy is often preferred by OA patients and their physicians [10].

There are multiple international recommendations for the management of knee OA, published by the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), the American Academy of Orthopedic Surgeons (AAOS), the Osteoarthritis Research Society International (OARSI), and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) all of which recommend non-pharmacologic treatments as first line [11–15]. However, to exercise or lose weight requires the patient to be pain-free or at the Patient

*Abbreviations:* IAHA, intra-articular hyaluronic acid; OA, osteoarthritis.

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Acceptable Symptom State (PASS) [16,17], which first necessitates pain reduction. Though data from randomized controlled trials (RCTs) and meta-analyses indicate that intra-articular hyaluronic acid (IAHA) offers the best benefit/risk balance among the various pharmacologic treatments to ameliorate knee OA pain [18–21], there is a lack of agreement among national and international guidelines about the use of IAHA for the medical management of symptomatic knee OA [11–15,22]. Despite the lukewarm recommendations provided in published guidelines, many rheumatologists, orthopedic surgeons and other clinicians worldwide continue to offer this treatment to their patients with good clinical results, facilitating the control of symptoms and even delaying the need for a surgical intervention [10,23].

*What is HA? Mechanism of action*

HA is a glycosaminoglycan molecule found intrinsically within the knee joint where it provides viscoelastic properties to synovial fluid. During the course of OA, the synovial fluid undergoes degradation similar to other tissues of the joint which manifests as a decrease in the amount and the average molecular weight of HA [24], which is correlated with joint pain and functional impairment [25].

Injection of HA into the joint acts to restore IA lubrication, consequently improving joint biomechanics. While it is known that the residence time of IAHA in the joint is only 2–3 days, prolonged effects lasting several weeks post-injection suggest that other mechanisms of action must be at work [24]. IAHA has been found to: stimulate the endogenous synthesis of HA and extracellular matrix components by synovial fibroblasts, promote chondroprotection by mitigating proteoglycan loss in cartilage and apoptosis of chondrocytes, reduce HA degradation by decreasing the production of pro-inflammatory cytokines, and reduce the induction of pain mediators [26]. Evidence of the numerous mechanisms by which HA acts on joint structure and function provides support that IAHA may be clinically beneficial in knee OA not only by providing pain relief but also by delivering potential disease-modifying effects. Though the evidence is promising, confirmation of the disease-modifying effects of IAHA requires further investigation.

*Current controversy on IAHA use in OA*

As an international group of clinicians, we are concerned by the discrepancy between the abundant evidence base attesting to the efficacy of IAHA, confirmed by our own clinical experience, and the published recommendations provided by some treatment guidelines committees. A negative assessment of the utility of IAHA from treatment recommendations may restrict patients' access to this valuable treatment option. Such a restriction is likely to accelerate referrals to orthopedic surgeons and will increase the rate of total knee replacement in many countries, which is very costly and not without risk. We propose to address this discrepancy through careful consideration of the evidence base, so that clinicians worldwide are able to offer all of the most beneficial treatment options throughout the disease course enabling truly patient-centered care in OA.

## Methods

Articles included in this narrative review were identified through a literature search of PubMed using the following MeSH items or free words: "osteoarthritis", "knee", "systematic review", "meta-analysis", "hyaluronic acid", "intra-articular", and "viscosupplementation". The search strategy was limited to studies conducted in humans, publications in English language, and full-length articles published until 31 October 2017. For assessment of the efficacy and safety of IAHA we included meta-analyses of IAHA versus placebo or other OA treatments.

## Efficacy of HA

We identified 17 meta-analyses of RCTs investigating the efficacy of IAHA versus placebo in treating the symptoms of knee OA, of which 13 were positive for a treatment benefit of IAHA [18,21,27–37], 2 showed an intermediate effect [38,39] and 2 were negative [40,41] (summarized in Table 1). Overwhelmingly, the 17 meta-analyses found a positive effect for the use of IAHA versus placebo, with an effect size (ES) of between 0.30 and 0.40 above that of the IA "placebo effect" (Table 1). An ES above 0.20 is considered to be slightly clinically relevant on an individual patient basis in chronic pain conditions such as knee OA, while a medium ES difference of between 0.4 and 0.6 is considered to have clinical importance [42]. An additional 3 meta-analyses compared the efficacy of IAHA against other treatments, and these studies demonstrated that IAHA was as effective as NSAIDs for pain relief [43], and provided a longer-lasting benefit than IA corticosteroids from week 8 onwards, with an ES of 0.22 at week 8 (95% confidence interval [CI]: −0.05–0.49) rising to 0.39 (95% CI: 0.18–0.59) at week 26 in favor of IAHA [44,45] (Table 1). One meta-analysis compared a high molecular weight HA formulation to a low molecular weight HA, and did not identify any differences on efficacy, but reported a higher rate of acute post-injection flare with the high molecular weight HA [46].

A 2006 Cochrane review of 40 placebo-controlled trials of multiple HA products mostly administered at weekly intervals for 3–5 weeks found beneficial effects on pain, function and patient global assessment versus placebo. The benefits were particularly noticeable at 5–13 weeks post-injection with percentage of improvement from baseline ranging from 28 to 54% for pain and from 9 to 32% for function [29]. Bannuru et al. examined the therapeutic trajectory of IAHA, finding that IAHA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks (ES = 0.46; 95% CI: 0.28–0.65) and exerts residual detectable effects up to 24 weeks [31]. Although the meta-analysis of 71 RCTs by Rutjes et al. found a moderate ES for IAHA of 0.37 (95% CI: 0.28–0.46), the authors pooled data from studies with placebo and active comparator arms, which might have biased their results towards the null [32]. Also, the inclusion of studies that incorporated other types of interventions (arthroscopy, ultrasonography, cyclooxygenase-2 [COX-2] inhibitors etc.) or controls (such as appropriate care, treatment of the contralateral knee) will introduce heterogeneity that can obfuscate interpretation. Despite this severe selection bias, it should be noted that an ES of 0.37 (corresponding to a 9 mm change on a 100 mm visual analog scale) was exactly the value of the minimal clinically important difference (MCID) for pain reduction that was pre-determined by the authors to conclude positively regarding efficacy. Since an ES of 0.37 was reported by the authors, their conclusions for the efficacy of IAHA should logically have been positive. Instead, in contradiction to their methodology, the authors concluded that treatment of knee OA with IAHA was associated with a small and clinically irrelevant benefit.

In contrast, a recent systematic review of overlapping meta-analyses performed using PRISMA-compliant methodology found that 12 meta-analyses met the eligibility criteria, and overall the studies demonstrated that IAHA is an effective intervention for knee OA without increased risk of adverse events (AEs) (Fig. 1) [47].

A study that assessed the relative effect of varying routes of administration of placebo (oral, IA, topical, oral + topical) on knee OA pain found that the effect of IAHA was limited by a large placebo effect for IA saline control [48]. This network meta-analysis which included 39,814 participants from 149 RCTs, demonstrated that the use of the IA delivery method itself had a significant effect, with an ES of 0.29 (95% credible interval [CrI]: 0.04–0.54) for IA placebo compared with oral placebo. The statistically significant benefits of IAHA on pain were maintained versus IA placebo with an ES of 0.34 (95% CrI: 0.26–0.42) at 3 months, which is of a comparable magnitude to that observed in other meta-analyses [31,32]. To summarize these

**Table 1**
Meta-analyses of the efficacy of intra-articular hyaluronic acid injections in knee osteoarthritis

| Study: Author (year)/ Analysis details | Number of studies analyzed | Primary outcome | Results: Quantification of effect (95% CI) | Conclusion |
|---|---|---|---|---|
| IAHA versus placebo | | | | |
| Lo GH (2003) [38] | 22 | Pain change at M1−4 SMD | ES: 0.32 (0.17−0.47) | Intermediate (positive effect but concerns over potential publication bias) |
| Wang CT (2004) [27] | 20 | Pain/Function change | Significant improvement in pain and function | Positive |
| Arrich J (2005) vs. placebo [40] | 22 | Pain during movement VAS | Mean change: −7 mm at W22−30 | Negative (did not meet clinically meaningful difference of −15 mm VAS) |
| Modawal A (2005) [28] | 11 | Pain VAS | Between group difference: −18 mm at W8−12 | Positive (considered as a moderate effect over placebo) |
| Bellamy N (2006) [29] | 40 | Pain/Function (WMD or SMD) | −28% to 54% reduction in pain at W5−13 | Positive |
| Strand V (2006) [30] | 5 | Pain/Function (Lesquesne score) | ES: 0.20 | Positive |
| Bannuru RR (2011) Therapeutic trajectory vs. placebo [31] | 54 | Pain change from baseline SMD | ES: 0.46 (0.28−0.65) at W8 0.21 (0.10−0.31) at W24 | Positive |
| Colen S (2012) [39] | 74 | Pain change from baseline | −30% pain over IA placebo effect (WMD −10 mm on VAS) | Intermediate (effect of HA not considered conclusive due to large placebo effect) |
| Rutjes (2012) [32] | 71 | Pain difference vs. control at endpoint SMD | ES: −0.37 (−0.46−−0.28) | Positive (but of moderate benefit and safety issues) |
| Miller LE (2013) [33] | 29 | Pain/Function at endpoint | SMD: 0.38−0.43 for pain; 0.32−0.34 for function | Positive |
| Bannuru RR (2015) (placebo and vs. other treatments) [18] | 52 | Pain/Function at M3; SMD | ES: IA placebo vs. oral placebo 0.29 (0.04−0.54) IAHA vs. IA placebo 0.34 (0.26−0.42) IAHA vs. oral placebo 0.63 (0.39−0.88) | Positive |
| Campbell KA (2015) [34] | 10 | Pain/Function at endpoint | IAHA superior to placebo for pain and function | Positive |
| Jevsevar D (2015) [41] | 19 | Pain/Function at endpoint | Did not meet MCID vs. placebo | Negative |
| Richette P (2015) [35] | 8 | Pain at 3M | SMD: −0.21 (−0.32−−0.10) | Positive |
| Strand V (2015) [36] | 29 | Pain/Function at W4-26 | SMD: 0.38−0.43 for pain and 0.32−0.34 for function vs. placebo | Positive |
| Johansen M (2016) [37] | 71 | Pain at endpoint | ES: −0.39 (−0.47 to−0.31) vs. placebo | Positive |
| Trojian TH (2016) vs. IA placebo (and IA CS) [21] | 11 | OMERACT-OARSI response criteria | 11% greater chance of response vs. IA placebo (15% greater chance of response vs. IA CS) | Positive |
| ***IAHA versus other treatments*** | | | | |
| Bannuru RR (2014) vs. NSAIDs [43] | 5 | Pain at endpoint SMD | Hedges's g: −0.07 (−0.24−0.10) | Non-inferiority of HA vs. NSAIDs |
| Bannuru RR (2009) Therapeutic trajectory vs. IA corticosteroids [44] | 7 | Pain change from baseline SMD | ES: 0.22 (−0.05−0.49) at W8 in favor of IAHA ES: 0.39 (0.18−0.59) at W26 in favor of IAHA | Positive for HA from W8 |
| He WW (2017) vs. IA corticosteroids [45] | 12 | Pain change from baseline | CS > HA at 1 M CS = HA at 3 M HA > CS at 6 M | Positive for HA at 6M |
| Reichenbach S (2007) Low MW vs. Hylan G-F20 [46] = HA vs. HA | 13 | Pain at endpoint SMD | ES: on between group difference −0.27 in favor of Hylan, but more post-injection flares | Positive effect (but discouraged Hylan use for safety reasons) |

Abbreviations: CI confidence interval; CS, corticosteroid; ES, effect size; HA, hyaluronic acid; IA, intra-articular; M, month; OMERACT-OARSI, Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International; MCID, minimal clinically important difference; MW, molecular weight; SMD, standardized mean difference; VAS, visual analog scale; W, week; WMD; weighted mean difference.

| Outcome | Lo 2003 | Wang 2004 | Modawal 2005 | Arrich 2005 | Strand 2006 | Bellamy 2006 | Bannuru 2011 | *Rutjes 2012 | Colen 2012 | Miller 2013 | Richette 2015 | Strand 2015 | Bannuru 2015 | Jevsevar 2015 | †Campbell 2015 | §Johansen 2016 | Trojian 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall pooled effect size | 22 | | | | | | | | | 29 | | | 52 | | | 71 | |
| Lequesne index score (early) | | | | | 5 | 7 | | | | | | | | | | | |
| Lequesne index score (late) | | | | | | 4 | | | | | | | | | | | |
| Knee function (early) | | | | 9 | | 3 | 16 | | | ? | 5 | 14 | | | 8 | | |
| Knee function (late) | | | | 4 | | | | 52 | | ? | | 13 | | | | | |
| Knee stiffness | | | | | | | 15 | | | | | | 19 | 9 | | | 6 |
| Physical function | | | | | | | | | | | | | | | | | |
| Pain with activities (early) | | 20 | | | | 27 | | | | | | | | | | | |
| Pain with activities (late) | | | | | | 3 | | | | | | | | | | | |
| Patient global assessment (early) | | | | | | 6 | | | | | | | | | | | |
| Patient global assessment (late) | | | | | | 2 | | | | | | | | | | | |
| Pain at rest (early) | | | | 8 | | 12 | | | | | | | | | | | |
| Pain at rest (late) | | | | 2 | | | | | | | | | | | | | |
| Knee pain outcomes (early) | | | 5 | | 5 | 7 | 44 | 71 | 18 | ? | 8 | 20 | | 19 | | | |
| Knee pain outcomes (late) | | | 3 | | | | 20 | | | ? | | 15 | | | | | |
| WOMAC pain | | | | | | 7 | | | | | | | 19 | | 10 | | 7 |
| WOMAC physical function | | | | | | 7 | | | | | | | 19 | 11 | | | 7 |
| OMERACT-OARSI response | | | | | | | | | | | | | | | | | 4 |
| Overall adverse events | | ? | | 15 | | 4 | | 25 | | ? | | 21 | 35 | | | 71 | 11 |
| Discontinued due to adverse event | | | | | 5 | 3 | | 40 | | | | 24 | 36 | | | | |
| Overall study withdrawal | | | | | | 5 | | | | | | 25 | | | | | |

**Fig. 1.** Outcomes of 17 meta-analyses of intra-articular hyaluronic acid versus placebo in knee osteoarthritis.

Green squares indicate positive results for hyaluronic acids. Blue squares indicate no difference, Red squares indicate a difference favoring placebo. Numbers indicate the number of randomized controlled trials (RCTs) included in the meta-analysis, with the exception of:

†Campbell 2015 for which the numbers listed are for meta-analyses and not RCTs;

*Rutjes 2012 includes 71 trials for the pain analysis, of which 68 were sham-controlled;

§Johansen 2016 includes 85 comparisons reported in 71 randomized trials either vs. placebo or non-intervention;

OMERACT–OARSI, Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. [Adapted from Xing et al. 2016 [47] with additional studies included].

results in a clinical context, the IA placebo effect alone is 1.6 times more than the effect of paracetamol, suggesting an inherent benefit in using IA treatments by virtue of their placebo effects, or that IA saline is not a true placebo. This is an important consideration, both in the interpretation of clinical trial data and in clinical practice [48,49].

Another recent network meta-analysis has investigated the potential for an individual to improve when given IAHA treatment versus another treatment using OMERACT–OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials–Osteoarthritis Research Society International) response criteria, rather than average change in pain or functional outcomes across treatment groups [21]. This analysis found that subjects receiving IAHA were 15% and 11% more likely to respond to treatment by OMERACT–OARSI criteria than those receiving either IA corticosteroid or IA placebo ($p < 0.05$ for both) at 12–26 weeks post-injection.

Some of the differences in the results of meta-analyses can be explained by the different methodologies employed in the assessments. Usually clinicians would like to identify the most effective treatment among a range of alternatives. Traditional pair-wise meta-analysis provides only a limited view of the existing evidence without addressing the relative merits of all available options. RCTs often do not include all available comparator interventions of interest. A network meta-analysis synthesizes all available evidence within a consistent framework, fully preserving the randomization within each trial [50–52]. This method considers all trials simultaneously and enables integration of direct evidence from head-to-head trials (when they exist) with indirect evidence (through a common comparator) [53–55]. The advantages of network meta-analysis include: (1) the ability to compare treatments that have never been compared in any trial, (2) improvement in precision for the estimated effect sizes, and (3) comparing and ranking multiple treatments in a principled statistical analysis [56,57]. In this way, network meta-analysis provides useful evidence for judiciously selecting the best choice(s) of treatment. The network meta-analysis approach applied by Bannuru et al. to the efficacy and safety of pharmacologic interventions for knee OA demonstrates that IAHA is the most efficacious treatment for pain relief, with a very low incidence of AEs [18,58].

In addition to the published meta-analytic data, we analyzed data from 3 published randomized non-inferiority clinical trials [59–61] and one trial presented as an abstract at the EULAR 2016 congress [62] that assessed the efficacy of various IAHA preparations compared in face-to-face non-inferiority studies as measured by the OMERACT–OARSI response criteria, for which 981 out of 1322 OA patients could be classified as responders. The calculated overall response rate to IAHA by these response criteria was 74% (95% CI: 66%–81%).

## Safety of HA

IAHA is generally considered to be a safer alternative to oral NSAIDs and opioids for knee OA. A detailed exploration of the safety of IAHA was undertaken in a recent systematic review and network meta-analysis of 74 studies of 18 HA products involving 13,042 patients aged 45–75 years which found a very low incidence of AEs (Table 2) [58]. The most commonly reported AEs were transient local reactions such as pain, swelling and arthralgia (incidence 8.5%), which subsided rapidly. None of the HA products were statistically significantly different from placebo, nor from each other with regard to incidence of AEs. The rate of withdrawals due to AEs in patients receiving IAHA was reported to be low across 37 trials that

**Table 2**
Estimates of odds ratios for total adverse events from a network meta-analysis of randomized controlled trials of various hyaluronic acid products versus placebo

| Placebo | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.21 (0.66, 2.35) | **Adant** | | | | | | | | | | | | | | | | | | | | | | |
| 0.97 (0.71, 1.38) | 0.79 (0.39, 1.63) | **Artzal** | | | | | | | | | | | | | | | | | | | | | |
| 0.87 (0.60, 1.30) | 0.72 (0.33, 1.48) | 0.90 (0.57, 1.37) | **Durolane** | | | | | | | | | | | | | | | | | | | | |
| 1.08 (0.75, 1.54) | 0.89 (0.42, 1.78) | 1.12 (0.67, 1.77) | 1.24 (0.73, 2.02) | **Euflexxa** | | | | | | | | | | | | | | | | | | | |
| 0.64 (0.26, 1.42) | 0.51 (0.17, 1.37) | 0.66 (0.25, 1.53) | 0.72 (0.27, 1.72) | 0.58 (0.22, 1.40) | **Fermathron** | | | | | | | | | | | | | | | | | | |
| 0.77 (0.43, 1.45) | 0.63 (0.25, 1.46) | 0.78 (0.39, 1.66) | 0.87 (0.42, 1.86) | 0.71 (0.36, 1.47) | 1.23 (0.44, 3.59) | **Gel_200** | | | | | | | | | | | | | | | | | |
| 0.92 (0.49, 1.64) | 0.75 (0.30, 1.82) | 0.95 (0.45, 1.78) | 1.05 (0.49, 2.06) | 0.85 (0.42, 1.64) | 1.44 (0.55, 4.09) | 1.20 (0.49, 2.65) | **Go_on** | | | | | | | | | | | | | | | | |
| 0.63 (0.33, 1.29) | 0.51 (0.21, 1.31) | 0.65 (0.30, 1.41) | 0.74 (0.33, 1.64) | 0.59 (0.28, 1.29) | 1.03 (0.34, 3.18) | 0.84 (0.33, 2.06) | 0.70 (0.30, 1.72) | **Hyaject** | | | | | | | | | | | | | | | |
| 0.75 (0.15, 3.06) | 0.62 (0.11, 2.73) | 0.78 (0.15, 3.17) | 0.89 (0.17, 3.57) | 0.72 (0.13, 2.94) | 1.18 (0.19, 6.51) | 0.99 (0.17, 4.44) | 0.81 (0.15, 4.01) | 1.19 (0.21, 6.26) | **Hyajoint** | | | | | | | | | | | | | | |
| 0.84 (0.62, 1.11) | 0.69 (0.33, 1.36) | 0.87 (0.55, 1.31) | 0.97 (0.58, 1.52) | 0.78 (0.49, 1.19) | 1.34 (0.57, 3.28) | 1.09 (0.54, 2.12) | 0.92 (0.54, 1.57) | 1.31 (0.62, 2.67) | 1.11 (0.28, 5.27) | **Hyalgan** | | | | | | | | | | | | | |
| 0.70 (0.19, 2.52) | 0.58 (0.14, 2.31) | 0.72 (0.20, 2.60) | 0.81 (0.22, 3.07) | 0.65 (0.18, 2.41) | 1.14 (0.26, 5.28) | 0.93 (0.21, 3.77) | 0.76 (0.20, 3.17) | 1.12 (0.27, 4.47) | 0.91 (0.16, 7.30) | 0.82 (0.23, 3.02) | **Hydros** | | | | | | | | | | | | |
| 0.87 (0.57, 1.40) | 0.72 (0.33, 1.57) | 0.90 (0.53, 1.60) | 1.00 (0.56, 1.82) | 0.81 (0.47, 1.45) | 1.40 (0.56, 3.74) | 1.16 (0.53, 2.44) | 0.96 (0.47, 2.11) | 1.37 (0.63, 3.11) | 1.16 (0.28, 6.28) | 1.04 (0.66, 1.86) | 1.27 (0.34, 4.58) | **Orthovisc** | | | | | | | | | | |
| 0.79 (0.31, 1.86) | 0.64 (0.21, 1.85) | 0.81 (0.30, 1.95) | 0.90 (0.32, 2.29) | 0.73 (0.27, 1.75) | 1.22 (0.38, 4.47) | 1.02 (0.34, 2.95) | 0.86 (0.29, 2.48) | 1.23 (0.39, 3.62) | 1.03 (0.18, 6.66) | 0.92 (0.36, 2.29) | 1.14 (0.23, 5.28) | 0.90 (0.32, 2.25) | **Structovial** | | | | | | | | | |
| 1.03 (0.52, 2.13) | 0.85 (0.32, 2.17) | 1.07 (0.49, 2.29) | 1.18 (0.54, 2.59) | 0.94 (0.43, 2.16) | 1.62 (0.57, 5.12) | 1.33 (0.54, 3.52) | 1.13 (0.46, 2.96) | 1.61 (0.61, 4.51) | 1.36 (0.27, 7.98) | 1.21 (0.57, 2.72) | 1.46 (0.34, 6.26) | 1.16 (0.52, 2.70) | 1.30 (0.44, 4.22) | **Suvenyl** | | | | | | | | |
| 0.89 (0.65, 1.21) | 0.73 (0.35, 1.48) | 0.92 (0.61, 1.35) | 1.03 (0.64, 1.59) | 0.83 (0.55, 1.23) | 1.40 (0.60, 3.59) | 1.17 (0.57, 2.22) | 0.96 (0.53, 1.87) | 1.40 (0.67, 2.88) | 1.18 (0.28, 6.05) | 1.06 (0.74, 1.57) | 1.27 (0.37, 4.43) | 1.02 (0.59, 1.65) | 1.13 (0.51, 2.70) | 0.86 (0.39, 1.88) | **Synvisc** | | | | | | | |

Column headings represent the control group and the row headings represent the intervention group for each comparison. Odds ratios less than 1 indicate a harmful effect of the intervention group.
[Reprinted from: Osteoarthritis and Cartilage 2016; 24(12), Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: a systematic review and network meta-analysis. Pages 2022–41. [Copyright (2016), with permission from Elsevier.]

investigated 13 products versus placebo ($n$ = 5550 patients). Fourteen of 900 patients who received Hyalgan, 6 of 135 patients receiving Hya-lect and 5 of 281 patients receiving Durolane withdrew from treatment due to AEs. For other products the number of patients who withdrew due to AEs was either 1 or none [58].

However, a systematic review published in 2012 raised concerns about the safety profile of IAHA [32]. Pooled AE data from 14 trials ($n$ = 3667 patients) found an increased risk of serious AEs (SAEs) associated with IAHA (relative risk 1.41; 95% CI: 1.02–1.97). The most frequent SAEs were disorders related to the gastrointestinal (GI) system (2 events with IAHA vs. 8 among controls), cardiovascular (CV) system (5 vs. 2 events), cancer (6 vs. 0 events), and musculoskeletal system (4vs. 2 events). Even so, a causal relationship between the SAEs and IAHA seems biologically unlikely [63], and it must be emphasized that most of the SAEs described occurred during the course of a single clinical trial, which was only published as an abstract at the time that the paper by Rutjes et al. was written [64]. This trial was subsequently published by Strand et al. and the authors confirmed that there was no relationship between IAHA injections and the SAEs described [65]. Conversely, in the network meta-analysis of IAHA safety conducted by Bannuru et al. only 3 treatment-related SAEs were reported among 9214 participants (septic arthritis, a pseudoseptic reaction and an episode of anaphylactic shock shortly after injection) [58].

The safety of repeated courses of IAHA injections is also reported from a post-marketing registry of Supartz HA formulation [66]. Of the 7404 patients with knee OA who received IA Supartz, nearly half (49%; $n$ = 3614) received more than 1 treatment course (of 3–5 injections). IAHA was well tolerated in this population, with only 37 (0.5%) reporting 58 AEs. The majority (95%) of patients who reported an AE did so during the first injection-series, of which 85% were injections site reactions. None of the AEs was serious, and most resolved spontaneously without medical intervention. The overall AE rate after repeat injection courses was 0.008 (95% CI: 0.001–0.055).

## How does HA compare to other treatment options for knee OA?

Guidelines from the ESCEO and ACR recommend IAHA for knee OA in patients for whom symptoms persist despite prior treatment with paracetamol, NSAIDs, and symptomatic slow-acting drugs for OA (SYSADOAs), or other analgesics [12,15]. Paracetamol is widely prescribed as a first-line therapy for OA even though the measured ES of paracetamol on pain is small (0.14; 95% CI: 0.05–0.22) and with no effect on physical function and stiffness in knee OA patients [67,68]. Recent concerns over the safety profile of paracetamol raise questions over routine, chronic use of the drug at the upper end of standard analgesic doses (>3 g/day), because it has been associated with upper GI events, liver toxicity, and renal and cardiovascular AEs [4,69,70].

To determine the comparative effectiveness of pharmacologic interventions for knee OA on the main outcomes of pain and function, a recent network meta-analysis was performed on 137 studies comprising 33,243 participants using a Bayesian random-effects model [18]. For pain, all interventions significantly outperformed oral placebo, and the most efficacious treatment was IAHA with an ES of 0.63 (95% CrI: 0.39–0.88), while the least effective treatment was paracetamol (ES = 0.18; 95% CrI: 0.04–0.33). For function, all interventions apart from IA corticosteroids and paracetamol were significantly superior to oral placebo. The use of the IA delivery method itself was found to have a significant effect, with an ES of 0.29 (95% CrI: 0.04–0.54) for IA placebo compared with oral placebo. Nonetheless, when compared with IA placebo, a statistically significant ES of 0.34 (95% CrI: 0.26–0.42) was observed for IAHA on pain at 3 months (Table 3), which is of the magnitude observed in other meta-analyses e.g., ES on pain of 0.46 (95% CI: 0.28–0.65) at week 8 in the Bannuru meta-analysis, and ES of 0.37 (95% CI: 0.46–0.28) in the Rutjes meta-analysis [31,32].

**Table 3**
Effect size of treatments in knee osteoarthritis versus oral placebo and intra-articular (IA) placebo

| Treatment | Effect size vs. oral placebo (95% CrI) | Effect size vs. IA placebo (95% CrI) |
|---|---|---|
| Paracetamol | 0.18 (0.04–0.33) | −0.11 (−0.38–0.17) |
| IA placebo | 0.29 (0.04–0.54) | – |
| Celecoxib | 0.33 (0.25–0.42) | 0.04 (−0.21–0.30) |
| Naproxen | 0.38 (0.27–0.49) | 0.09 (−0.15–0.34) |
| Diclofenac | 0.52 (0.34–0.69) | 0.23 (−0.03–0.49) |
| IA corticosteroids | 0.61 (0.32–0.89) | 0.32 (0.16–0.47) |
| IA hyaluronic acid | 0.63 (0.39–0.88) | 0.34 (0.26–0.42) |

CrI, credible interval; [Adapted from Bannuru et al. 2015 [18]].

Collectively, oral NSAIDs are reported to have a moderate ES on pain (0.29; 95% CI: 0.22–0.35) [67], and a recent network meta-analysis comparing different NSAIDs found that diclofenac 150 mg/day was the most effective for improving pain (ES = 0.57; 95%CrI: 0.69–0.46) [71]. Regardless of their effectiveness, all oral NSAIDs whether selective or non-selective have the potential to increase the risk of GI and CV events. Both COX-2 inhibitors (selective NSAIDs) and diclofenac are associated with higher CV risk [8,9] and renal failure [72]. All of the safety risks of NSAIDs are increased with age, which is a concern when treating OA patients who are mostly aged [73]. A meta-analysis found that IAHA was not significantly different from continuous oral NSAIDs at 4 and 12 weeks in terms of outcomes for pain, function, and stiffness [43]. Given the favorable safety profile of IAHA over NSAIDs, IAHA might be a preferable alternative to oral NSAIDs for knee OA, especially for older patients at greater risk for systemic AEs [43]. Topical NSAIDs have a moderate effect on pain relief, with a potentially similar efficacy to that of oral NSAIDs, and the advantage of fewer AEs due to a lower systemic absorption [74,75].

Opioid analgesics are recommended to treat moderate to severe OA that does not respond to first line treatments. Opioids significantly decrease pain intensity (ES = 0.79; 95% CI: 0.98–0.59) in the short-term (mean duration 13 weeks) and have small benefits on function compared with placebo in patients with OA [76]. In spite of their efficacy, the potential for opioids to cause AEs is high, and these treatments pose a risk for addiction and could lead to serious withdrawal symptoms once they are discontinued [76]. Opioids are associated with higher risks of CV events, fractures, and safety events requiring hospitalization vs. NSAIDs in OA patients with a mean age of 80 years [77]. Given the significant benefits of IAHA over oral NSAIDs, it is clear that IAHA could similarly prove to be a safer alternative for OA patients who are receiving opioids.

IA corticosteroid is a common treatment option for knee OA especially where there is evidence of joint effusion [78]. A Cochrane review of 27 trials of 1767 participants has found only low-grade evidence that IA corticosteroids are more beneficial for pain and function than control [79]. Current evidence suggests that IA corticosteroid may offer only a short-term effect on pain in comparison to IAHA. A meta-analysis found that while IA corticosteroids had an early effect on pain and were relatively more effective than IAHA up to 4 weeks, by week 4 the two treatments had equal efficacy, and from week 8 up to 26 weeks IAHA had greater efficacy [44]. The results of this study were recently corroborated by a meta-analysis reporting that IAHA is more effective than IA corticosteroid in the long term (up to 6 months) [45]. A clinical trial published in 2017 by McAlindon et al. assessed the safety and efficacy of triamcinolone acetonide versus placebo over a two-year period [80]. No significant difference in pain reduction was observed between placebo and the active treatment when measured at 3 months after each injection, which is not surprising given the usual short-term efficacy of IA corticosteroid therapy (4–8 weeks). It must be emphasized that a systematically-repeated corticosteroid injection regimen does not work and is probably not the best way to use IA corticosteroids in knee OA. The group receiving IA corticosteroids showed greater cartilage volume loss of about 2% per year compared with placebo, although this cartilage loss was not associated with worsening of symptoms [80]. Besides, the clinical significance of such cartilage loss is currently not established. Studies on the long-term effects of IAHA are limited; however, it is shown that 80% of patients respond to repeat courses of IAHA injections over 3 years [81] and multiple courses of IAHA are found to be safe in post-marketing surveillance studies [66]. These findings suggest that IA corticosteroid may offer only a short-term effect on pain in comparison to IAHA and that IAHA may be more desirable as a long-term treatment option, for both efficacy and safety reasons.

Although recommended as first-line treatment for knee OA alongside rescue analgesia with paracetamol, the efficacy of SYSADOAs as a class meets with controversy due to the diversity of the agents and inconsistencies in their regulatory status and labeling worldwide. The data for prescription crystalline glucosamine sulfate (pCGS) have shown an efficacy on pain relief (ES = 0.27; 95% CI: 0.12–0.43) [82,83], and pCGS has a long-term safety profile comparable to that of placebo [84]. Similarly, pharmaceutical-grade chondroitin sulfate has also shown a beneficial effect on OA pain, functional outcomes, and, possibly, radiologic progression in RCTs and meta-analyses [85–87]. There is clinical evidence that avocado soybean unsaponifiables (ASU) reduce pain, stiffness, and physical function in studies of patients with hip and knee OA over 3–6 months [88–90], and that these treatments may have an effect on structure modification in hip OA [91].

## Discussion

As illustrated by our review, numerous meta-analyses have been conducted to determine the safety and efficacy of IAHA. Although there are some discrepancies between the studies, the majority are overwhelmingly positive for the use of IAHA as a treatment option in knee OA.

The question then remains as to why IAHA is disregarded in some papers [92], and only cautiously considered in some treatment guidelines [12,14], while it is simultaneously recommended and widely used by rheumatologists and other healthcare professionals. The variability in treatment recommendations for IAHA may be due to a lack of methodological consistency with regard to evidence inclusion and assessment, recommendation formulation, and working group composition [22]. The modest effect size for IAHA found in RCTs may also contribute to the negative recommendations found in clinical guidelines. Reasons for the modest effect of IAHA may relate to the complexity of studying IA therapies within the framework of RCTs. It has been demonstrated that IA saline solution exerts a higher placebo effect than that of oral or topical therapies. Thus, the overall efficacy of HA could be the sum of the effect demonstrated in RCTs plus the effect attributed to an active placebo [49]. This overall efficacy could explain the positive benefit perceived by patients and doctors in everyday clinical practice. Despite the modest effect size for IAHA recorded in RCTs, a lack of valid alternative treatments for OA, especially for patients that cannot tolerate other drugs, makes IAHA a highly valuable treatment option. The modest effect of IAHA on symptoms may also be relevant when a patient requires rehabilitation therapy, as a decrease in pain will allow an easier approach to physical therapy and rehabilitation exercises.

Our findings, supporting the efficacy and safety of IAHA, are in agreement with recent assessments of other international expert groups. A multidisciplinary group of Canadian OA experts reviewed the available evidence from 8 meta-analyses concluding that IAHA therapy was a well-tolerated and effective option for patients with mild to moderate knee OA failing first-line pharmacologic therapy [93]. A recent European task force reached a consensus on recommending IAHA as an effective and well tolerated treatment for mild to moderate knee OA and concluding that its use should not be

limited only to patients who have failed to respond to analgesics and NSAIDs [19]. Another task force of experts from the ESCEO reached the same conclusion [94]. A study commissioned by the American Medical Society for Sports Medicine (AMSSM) led the society to recommend IAHA for Kellgren–Lawrence grade II-III knee OA in patients aged >60 years based on high quality evidence demonstrating benefit using OMERACT–OARSI responder rates; the recommendation was downgraded for those aged <60 years due to only moderate quality evidence in this age group, further studies in this age group being needed [21].

The variability of IAHA effect among different patient phenotypes has not been well understood. Thus, further investigation of patient characteristics associated with a better response to IAHA treatment is warranted. Limited available evidence suggests that IAHA injections tend to be more effective if the patient [20]:

- has moderate, radiologically-advanced OA (at a Kellgren–Lawrence grade II, rather than grade III) [95],
- is not too old, i.e.,<60 years of age (from clinical trials evidence) [96]; in clinical practice IAHA is a good option for older patients receiving poly-pharmacy due to the low potential for AEs and drug-drug interactions with IAHA,
- has a high level of symptoms. Karlsson et al. showed that patients with a Lequesne index of at least 10 had a better response [96], and
- has no effusion [95].

In addition, the presence of crystals in the joint does not appear to influence the efficacy of IAHA [97,98].

A working group of multidisciplinary clinical experts has developed an Appropriate Use Criteria (AUC) for the use of IAHA in knee OA, to determine which types of patients in real-world clinical scenarios are most appropriate to receive IAHA [99]. In line with above considerations, the group determined that IAHA treatment was most appropriate in patients with mild or moderate OA with clinically and radiologically confirmed disease who either had not received other therapies for the knee, had failed other nonpharmacologic or pharmacologic therapies for the knee, or had an incomplete response to other therapies for the knee. In other clinical scenarios, the use of IAHA was considered as uncertain due to a lack of supporting evidence; these patient groups included those with severe OA, and those with mild to moderate OA who have a high risk of AEs, and are intolerant to, or contraindicated to pharmacologic agents for the knee. IAHA injection was considered contra-indicated among symptomatic adults with OA and active local (peri-articular) or IA infection of the knee. The group supports the need for further research to identify specific patient populations, including differentiating among grades of IA severity that may derive greatest benefit from IAHA injections for knee OA [99].

Studies on the long-term effects of IAHA are limited; however, it is shown that IAHA therapy remains efficacious over several years of treatment; 80% of patients respond to repeat courses of IAHA injections over 3 years [81]. Multiple courses of IAHA are shown to be safe over 6–18 months, with an overall AE rate of 0.008 (95% CI: 0.001–0.055) [66]. Evidence for the impact of IAHA on long-term outcomes is provided by retrospective database analyses demonstrating a delay in need for total knee replacement (TKR) surgery of 0.6–2.2 years, and up to 3.6 years with 5 or more courses of IAHA [23,100–103]. Although a cohort study found no significant difference in the risk of any surgical intervention among HA users compared to non-use and corticosteroid use among patients who ultimately had knee surgery, a lower risk of surgery was found with IAHA (hazard ratio = 0.87; 95% CI: 0.79–0.95) [104]. Pharmacoeconomic data on the use of IAHA in the management of knee OA is scarce, although there is some evidence that IAHA is associated with functional improvement of knee OA and quality of life along with a gain in quality-adjusted life years (QALYs) and reduced need for other OA treatments, resulting in an improved benefit/risk ratio [105–107]. A recent study demonstrates that IAHA treatment reduces the use of other pain medications such as NSAIDs, corticosteroids and opioids among patients with knee OA [108].

## Conclusions

The data presented above attests to the efficacy and safety of IAHA as demonstrated in multiple RCTs and meta-analyses. Thus, we conclude that IAHA is a valuable tool in the treatment armamentarium alongside other pharmacologic and non-pharmacologic treatment options and should not be disregarded. International and national recommendations for the management of knee OA should advocate for the use of IAHA injection in the management of symptomatic knee OA, at certain disease stages, and in certain phenotypes of patients. There is, without a doubt, room for such a treatment as IAHA, given its moderate but true symptomatic effect making it better than paracetamol or even NSAIDs for knee pain, and likely offering the best benefit/risk ratio among pharmacologic options for knee OA treatment.

## Research agenda

- Further investigation of mechanisms of action of HA to elucidate the potential disease modification properties of this treatment approach.
- Identification of prospective patient characteristics predictive of response to IAHA.
- High quality studies to determine the clinical benefit of IAHA in those aged 40 – 60 years.
- Further studies of the effect of repeat IAHA injections over a longer period than 6 months.
- Study of the additional symptomatic effect of IAHA, combined with other therapeutic options such as physiotherapy and non-pharmacologic management.
- Further, well-designed studies of the total knee replacement-sparing effect of IAHA injections.

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## Author contributions

All authors contributed equally to researching data for the article, and made substantial contributions to discussion of the content, writing and reviewing/editing of the manuscript before submission.

EM led the group.

RB added his expertise in evidence-based medicine.

GHB added his expertise on HA mechanism of action.

AM, HB and FA added their expertise on clinical use, proofs and evidence of good benefit/risk balance, and additional research questions requiring further investigations.

## Declaration of competing interests

EM reports personal fees from Expanscience during the conduct of the study, and personal fees from FIDIA, IBSA-Genevrier, LCA (France), TRB Chemedica, Rottapharm/Meda, and Expanscience, outside of the submitted work.

RRB reports personal fees from Expanscience during the conduct of the study, and personal fees from Fidia outside of the submitted work.

GHB reports personal fees from Expanscience during the conduct of the study, and is conducting an experimental study treating knee OA in rabbits with HA.

FA reports personal fees from Expanscience during the conduct of the study, and personal fees from Sothema outside of the submitted work.

HB reports personal fees from Sanofi-Aventis, LABRHA, Expanscience, TRB Chemedica, and Abbvie outside of the submitted work.

AM reports personal fees from Expanscience during the conduct of the study, and personal fees from IBSA, Fidia, Guna, ABIOGEN, and LABRHA outside of the submitted work.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2018.06.002.

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