

# Use of Intraarticular Hyaluronic Acid in the Management of Knee Osteoarthritis in Clinical Practice

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## Introduction

Knee osteoarthritis (KOA) is a chronic disorder characterized by joint pain, increasing physical disability, and progressive cartilage degeneration, which can lead to total knee arthroplasty (TKA). Despite extensive research, the complex pathophysiology of KOA remains incompletely understood. As a result, no established disease-modifying treatment exists today, and the management of KOA still relies on a combination of nonpharmacologic and pharmacologic modalities (1) primarily intended to relieve the symptoms of pain and loss of knee function. In clinical practice, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are generally recommended to relieve pain and improve joint function

(2–5). However, due to their vascular and gastrointestinal toxicity (6,7), the risk-benefit ratio of these rapid-acting drugs might not be favorable, particularly for long-course therapies and within the aging population in which KOA is most prevalent (8). Intraarticular (IA) injections of corticosteroids such as triamcinolone hexacetonide and methylprednisolone acetate are also commonly prescribed. As a systemic absorption occurs following IA corticosteroid injection, systemic adverse events (AEs) can be expected and precautions should be observed in patients with concomitant diseases such as hypertension or diabetes mellitus (9–13).

IA hyaluronic acid (HA) is a local treatment modality devoid of the systemic AEs observed after IA corticosteroid

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## Significance & Innovations

- Besides efficacy and safety, this review also addresses less frequently evaluated aspects of the intraarticular use of hyaluronic acid (HA) in the management of knee osteoarthritis (KOA) such as effectiveness and efficiency.
- This is the first time that a group of experts recommends systematic repeated intraarticular HA treatment in KOA patients who had a beneficial response to a previous cycle of treatment.

injection or oral administration of analgesics and NSAIDs. Thus, IAHA represents an alternative to analgesics and NSAIDs in patients with comorbidities, as well as a secondary option in case of inadequate response to first-line pharmacologic KOA treatments (14). Registered as medical devices in the US, IAHA preparations are currently approved for the symptomatic treatment of KOA, one of the most commonly affected joints. Despite being widely employed in the daily management of KOA for almost 20 years in the US (about 30 years in Europe and Japan), controversies persist regarding their efficacy and safety, as highlighted by discrepancies in the guidelines related to the use of IAHA in clinical practice (2–5,15), which largely reflect the divergent conclusions drawn by meta-analyses on the topic (16–30).

For this purpose, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) convened an international task force of experts in OA and clinical research methodology. Seven members of this working group (CC, FR, PR, OB, GH-B, AM, and DU) were entrusted with the task of preparing a review on diverse aspects of the use of IAHA in the management of KOA. Current knowledge on the mode of action, efficacy, effectiveness, safety, and cost-effectiveness of this treatment modality was presented and discussed at a 1-day meeting in January 2016 in Geneva (Switzerland).

The objective of this review is to provide specialists and practicing physicians with clear, concise, and reasoned answers to questions they might have on the use of IAHA in the management of KOA.

### Efficacy

Efficacy of IAHA on pain and joint function has been evaluated in numerous randomized controlled trials (RCTs). Consequently, 15 meta-analyses/systematic reviews assessing the symptomatic effects of IAHA on KOA have been published to date (16–30). Six of them concluded on a clear efficacy of IAHA (17,20,24,27,29,30), 4 considered it as a marginally efficacious treatment modality (16,19,25,26), and 2 meta-analyses found no significant difference in efficacy between IAHA and IA placebo (18,21) (Table 1).

The reported effect sizes (ES) for pain favored IAHA over IA placebo and ranged from 0.20 (30) to 0.46 (24). Heterogeneity of outcomes between trials was relatively high in several meta-analyses (16,20,24,27). As shown by Bannuru et al, the benefits of IAHA vary over time, with a maximal effect

on pain at 8 weeks (ES 0.46 [95% confidence interval (95% CI) 0.28, 0.65]) that is still observable at 24 weeks (ES 0.21 [95% CI 0.10, 0.31]) (24). This time dependency may partly contribute to the differences in pain estimates that have been observed between meta-analyses. Another possible explanation is the inclusion of clinical trials that widely differ in methodological quality. Thus, when the analysis was restricted to high-quality trials, an ES of 0.34 (95% CI 0.02, 0.67) and of 0.20 (95% CI 0.03, 0.37) in favor of IAHA was obtained at 8 and 24 weeks, respectively (24). These results were confirmed by Richette et al, who examined clinical data obtained from IA placebo controlled trials with a low risk of bias only ( $n = 8$ ) in order to reach the highest level of evidence. Based on an ES of 0.20 (95% CI 0.12, 0.29) for pain at 12 weeks, the authors concluded that IAHA provided a moderate but real effect on pain in patients with KOA (30).

Since the estimates for pain mentioned above were based on the difference between the IA placebo and the IAHA effects, it is worth noting that evidence for a clinically significant response of the IA delivery method itself has recently been demonstrated in a meta-analysis, with an ES of 0.29 (95% credible interval [95% CrI] 0.04, 0.54) in favor of IA placebo compared with oral placebo (29). In the same study, different treatment options of KOA were compared based on their ES versus oral placebo at 3 months. IAHA was found to be the most efficacious intervention with an ES of 0.63 (95% CrI 0.39, 0.88), followed by IA corticosteroids (ES 0.61 [95% CrI 0.32, 0.89]), diclofenac (ES 0.52 [95% CrI 0.34, 0.69]), ibuprofen (ES 0.44 [95% CrI 0.25, 0.63]), naproxen (ES 0.38 [95% CrI 0.27, 0.49]), celecoxib (ES 0.33 [95% CrI 0.25, 0.42]), and IA placebo. With an ES of 0.18 (95% CrI 0.04, 0.33), acetaminophen was considered as not superior to oral placebo in relieving pain (29). In direct comparison, IAHA was shown to be not significantly different from continuous oral NSAID treatment at 4 and 12 weeks regarding pain, function, and stiffness (28), and superior to IA corticosteroids from 8 to 26 weeks regarding pain (23).

### Effectiveness

The extent to which IAHA achieves its intended effect in the “real-life” clinical setting cannot be measured in RCTs, since patients in such studies are not representative of those seen in usual practice. Therefore, observational studies of real practice are better suited in evaluating effectiveness of IAHA.

Petrella and Wakeford retrospectively assessed the effectiveness of IA crosslinked HA (hylan) using the Southwestern Ontario database, a Canadian real-world cohort (31). For this purpose, they identified 1,263 patients with OA in 1 or both knees that received 2 consecutive series of IA hylan injections and no other prescribed OA medications. They compared them to a cohort of 3,318 demographically matched KOA patients who were never treated with IAHA. All patients were evaluated fully between 2006 and 2012. Results showed that in the group of patients who received repeated treatments of IA hylan, pain at rest and pain after a 6-minute walk decreased by mean  $\pm$  SD  $3.7 \pm 1.8$  points and  $5.6 \pm 1.7$  points on a 10-point visual analog scale, respectively. In parallel, the distance walked in a 6-minute walk test increased on average by 115 meters in this patient group. These improvements in pain and physical function were

**Table 1. Meta-analyses evaluating intraarticular hyaluronic acid in the symptomatic treatment of knee osteoarthritis\***

Reference	Comparator	Main outcome	ES (95% CI)	General outcome
Lo et al, 2003 (16)	IA placebo	Pain change from BL at M1–4	SMD = 0.32 (0.17, 0.47)	Intermediate
Wang et al, 2004 (17)	IA placebo	Pain on movement	MPD = 7.9 (4.1, 11.7)	Positive
Arrich et al, 2005 (18)	IA placebo	Pain on movement at W2–6	WMD = 3.8 (–1.4, 9.1) I <sup>2</sup> = 81%	Negative (no clinical difference)
		Pain on movement at W10–14	WMD = 4.3 (0.9, 7.6) I <sup>2</sup> = 0%	
		Pain on movement at W22–30	WMD = 7.1 (2.4, 11.8) I <sup>2</sup> = 0%	
Modawal et al, 2005 (19)	IA placebo	Pain change at W5–7	MD = 17.6 (7.5, 28.0)	Intermediate
	Pain change at W8–12	MD = 18.1 (6.3, 29.9)		
	Pain change at W15–22	MD = 4.4 (–15.3, 24.1)		
Bellamy et al, 2006 (20)	IA placebo	Pain/function at W5–13	WMD/SMD variable for different HA products	Positive
Medina et al, 2006 (21)	IA placebo	Pain	MPD = 2.4 (–0.6, 5.5)	Negative (no statistical difference)
		Function	MPD = 2.0 (–0.8, 4.9)	
		Stiffness	MPD = 5.5 (2.2, 8.8)	
Reichenbach et al, 2007 (22)	IA hylan	Pain at end of followup	SMD = –0.27 (–0.55, 0.01) I <sup>2</sup> = 88%	HA > hylan
Bannuru et al, 2009 (23)	IA CS	Pain change from BL at W2	SMD <sup>§</sup> = –0.39 (–0.65, –0.12) I <sup>2</sup> = 47%	Positive (HA > CS from W8 onward)
		Pain change from BL at W4	SMD <sup>§</sup> = –0.01 (–0.23, 0.21) I <sup>2</sup> = 37%	
		Pain change from BL at W8	SMD <sup>§</sup> = 0.22 (–0.05, 0.49) I <sup>2</sup> = 47%	
		Pain change from BL at W12	SMD <sup>§</sup> = 0.35 (0.03, 0.66) I <sup>2</sup> = 49%	
		Pain change from BL at W26	SMD <sup>§</sup> = 0.39 (0.18, 0.59) I <sup>2</sup> = 0%	
Bannuru et al, 2011 (24)	IA placebo	Pain change from BL at W4	SMD <sup>§</sup> = 0.31 (0.17, 0.45) I <sup>2</sup> = 75%	Positive
		Pain change from BL at W8	SMD <sup>§</sup> = 0.46 (0.28, 0.65) I <sup>2</sup> = 75%	
		Pain change from BL at W12	SMD <sup>§</sup> = 0.25 (0.15, 0.36) I <sup>2</sup> = 60%	
		Pain change from BL at W16	SMD <sup>§</sup> = 0.20 (0.11, 0.30) I <sup>2</sup> = 7%	
		Pain change from BL at W24	SMD <sup>§</sup> = 0.21 (0.10, 0.31) I <sup>2</sup> = 32%	
Colen et al, 2012 (25)	IA placebo	Pain change from BL at M3	vs. IA placebo: WMD = 10.2 (4.4, 16.0) I <sup>2</sup> = 92%	Intermediate
			vs hylan SMD = 0.07 (–0.10, 0.24) I <sup>2</sup> = 72%	
Rutjes et al, 2012 (26)	Sham or no intervention	Pain at end of followup	SMD: 0.37 (0.28, 0.46) τ <sup>2</sup> = 0.09	Intermediate
Miller and Block, 2013 (27)	IA placebo	Pain at W4–13	SMD = 0.43 (0.26, 0.60) I <sup>2</sup> = 73%	Positive
		Pain at W14–26	SMD = 0.38 (0.21, 0.55) I <sup>2</sup> = 75%	
		Function at W4–13	SMD = 0.34 (0.16, 0.51) I <sup>2</sup> = 54%	
		Function at W14–26	SMD = 0.32 (0.18, 0.45) I <sup>2</sup> = 69%	
Bannuru et al, 2014 (28)	NSAIDs	Pain change from BL at W4	SMD <sup>§</sup> = –0.01 (–0.18, 0.15) I <sup>2</sup> = 0%	Positive (HA = NSAIDs)
		Pain change from BL at W12	SMD <sup>§</sup> = 0.05 (–0.17, 0.28) I <sup>2</sup> = 30%	
		Pain change from BL at end of followup	SMD <sup>§</sup> = 0.07 (–0.10, 0.24) I <sup>2</sup> = 16%	

(continued)

Table 1. (Cont'd)

Reference	Comparator	Main outcome	ES (95% CI)	General outcome
Bannuru et al, 2015 (29)	Other options	Pain change from BL at M3	vs IA placebo: SMD <sup>g</sup> = 0.34 (0.26, 0.42)† vs oral placebo: SMD <sup>g</sup> = 0.63 (0.39, 0.88)†	Positive
		Function change from BL at M3	vs IA placebo: SMD <sup>g</sup> = 0.30 (0.20, 0.40)† vs oral placebo: SMD <sup>g</sup> = 0.45 (0.08, 0.84)†	
Richette et al, 2015 (30)	IA placebo	Pain at W12	SMD = 0.20 (0.12, 0.29) I <sup>2</sup> = 32%	Positive
		Function at W12	SMD = 0.12 (0.02, 0.22) I <sup>2</sup> = 0%	

\* Positive effect sizes (ES) favor intraarticular hyaluronic acid, negative ES favor comparator. 95% CI = 95% confidence interval; IA = intraarticular; BL = baseline; M = month; SMD = standardized mean difference; MPD = mean percent difference; W = week; WMD = weighted mean difference; MD = mean difference; HA = hyaluronic acid; hylan = hylan G-F 20; CS = corticosteroid; SMD<sup>g</sup> = standardized mean difference adjusted for small sample size (Hedges' g); NSAIDs = nonsteroidal antiinflammatory drugs.  
† 95% credible interval.

significantly greater than those achieved in KOA-matched patients treated with other prescribed OA medications (intergroup comparison  $P < 0.012$  for pain at rest,  $P < 0.001$  for pain after a 6-minute walk, and  $P < 0.001$  for distance walked in a 6-minute walk test). Previous observational studies already found that IAHA was effective in relieving pain and improving knee function for up to 6 months (32–34). Such pragmatic trials were also adapted in the assessment of longer-term outcomes.

Three recent retrospective studies examined the time from diagnosis of KOA to TKA and whether this time would be influenced by the use of IAHA (35–37). Large populations of insured subjects were screened and about 250,000 TKAs were reviewed after exclusions. In these studies, the median time to arthroplasty from the index time of KOA diagnosis was 114, 86, and 326 days in those not receiving IAHA. The median time from diagnosis to TKA in those receiving IAHA was 484, 585, and 908 days. Two studies including 65-year-old subjects showed a 1-year increase in time to surgery (35,36). The study including only those younger than age 65 years showed an increase in time to surgery of 1.6 years (37). All studies showed increased time to surgery with increased series of IAHA, and 2 studies suggested additional benefit from higher molecular weight (MW) HA products (36,37). The consistency of results from the 3 studies suggests both clinical and economic benefits to IAHA. However, they are insufficient to prove that the observed delay in time to TKA results from the use of IAHA, as treatment was not allocated randomly. Thus, between-group differences might reflect a bias in patient selection.

As the evidence for efficacy of IAHA on knee pain and function is currently established, the ESCEO task force suggests promoting pragmatic trials in order to focus clinical research on the effectiveness of IAHA in real-life conditions, considering the patient situation in terms of individual and disease characteristics, medical history, and comorbidities.

## Safety

Seven meta-analyses of RCTs comparing IAHA to IA placebo evaluated the safety of the intervention (17,18,20,21,26,27,29).

AEs occurred slightly more often among patients who received an IAHA treatment (relative risk [RR] 1.08 [95% CI 1.01, 1.15]) (18). However, they were usually mild transient local reactions such as pain at the injection site and swelling, with an RR of 1.19 (95% CI 1.01, 1.41) according to Wang et al (17) or RR 1.34 (95% CI 1.13, 1.60) according to Rutjes et al (26). The use of IAHA has also been associated with increased risk of flares (RR 1.51 [95% CI 0.84, 2.72]) and effusion at the injected knee (RR 1.15 [95% CI 0.38, 3.54]), which were not statistically significant (26). In contrast, the meta-analysis of US-approved HA products by Miller and Block reported no statistically significant differences between IAHA and IA placebo for any safety outcomes, including serious AEs ( $P = 0.12$ ), treatment-related serious AEs ( $P = 1.0$ ), study withdrawal ( $P = 1.0$ ), and AE-related study withdrawal ( $P = 0.46$ ) (27). Only Rutjes et al raised concerns about the safety of IAHA. Their meta-analysis emphasized an increased risk of serious AEs (RR 1.41 [95% CI 1.02, 1.97]) and dropouts due to AEs (RR 1.33 [95% CI 1.01, 1.74]). However, these findings have been criticized regarding the methodological rigor with which the serious AEs were analyzed and the biologic plausibility of the reported events (38,39).

As shown in a review by Pagnano and Westrich (40), the safety of IAHA appears to remain unchanged with multiple courses of treatment, while there might be an increase in AEs after the first hylan injection(s). Leopold et al reported that patients receiving multiple cycles of IA hylan exhibited more than an 8-fold increase in the frequency of acute local reactions compared with patients receiving only 1 course (41).

In addition to the AEs mentioned above, postmarketing device surveillance highlighted the occurrence of rare cases of localized inflammatory reactions such as pseudosepsis/severe acute inflammatory reactions, predominantly reported after avian high-MW crosslinked HA injections (hylan) (42).

In comparison with other pharmacologic interventions for the treatment of KOA, IAHA therapy was shown to exhibit fewer systemic AEs than acetaminophen or oral NSAIDs, but more local reactions (43). These events were reported to be

similar between different IA therapies, i.e., HA and corticosteroids. Withdrawals due to AEs were more common among patients receiving acetaminophen or NSAIDs than IA therapies (29). As a result, after almost 30 years of use, IAHA is usually recognized as a safe treatment modality for KOA.

**Current guidelines**

As shown in the previous sections dealing with the efficacy, effectiveness, and safety of IAHA, there is increasing evidence that the risk-benefit balance is favorable to the use of IAHA in the management of KOA (24,26,27,29,30,44). However, while IAHA was initially clearly recommended by national and international professional societies, such as the Osteoarthritis Research Society International (OARSI) (45), the European League Against Rheumatism (EULAR) (2), and the American College of Rheumatology (ACR) (46), some clinicians, researchers, and decision makers feel that current guidelines are conflicting and less favorable than 10 years ago (47,48). Nevertheless, there is relative general agreement on the place of IAHA in the management of KOA across organizations (Table 2). Apart from the American Academy of Orthopedic Surgeons, which refutes the use of IAHA based on insufficient clinical efficacy compared with IA saline (15), and the National Institute for Health and Care Excellence, which does not assess the modality at all (5), the use of IAHA is recommended as second-line treatment of KOA (Table 2).

Based on the available evidence and guidelines, the ESCEO recommends using IAHA in patients remaining symptomatic despite continuous or intermittent treatment with conventional pharmacologic treatment modalities, i.e., acetaminophen, symptomatic slow-acting drugs, and NSAIDs, as well as in patients with comorbidities precluding the use of NSAIDs. This positioning is clearly highlighted in the ESCEO treatment algorithm for the management of KOA and may help the prescribing physician prioritize interventions (14,49). The ACR guidelines move in the same direction and present IAHA as an alternative to unsatisfactory initial pharmacologic therapy (46). Furthermore, they emphasize its particular interest for patients ages >75 years, who are not recommended to take oral NSAIDs (4,14). EULAR considers the use of IAHA for pain relief and knee functional improvement based on level 1B evidence (2).

OARSI guidelines for the nonsurgical management of KOA probably raise the most considerable amount of misunderstanding. However, as clearly stated in the main part of the article, an “uncertain” classification was “...not intended to be a negative recommendation or preclude use of that therapy. Rather it indicates a role for physician-patient interaction in determining whether this treatment may have merit in the context of its risk: benefit profile and the individual characteristics, co-morbidities, and preferences of the patient” (3). In other words, OARSI privileges the use of IAHA for specific clinical phenotypes, which should be defined by the prescribing physician.

Finally, as recently highlighted by Altman et al (50), clinical practice guidelines, and a fortiori recommendations for the use of IAHA in the management of KOA, are not intended to create uniformity and suppress treating physicians’ self-analysis of the patient situation; they are designed

**Table 2. Recommendations for the use of intraarticular hyaluronic acid in the management of knee osteoarthritis\***

Organization (issue date)	Recommendation
AAOS (2013)	Recommends not using it (recommendation 9 based on lack of evidence for efficacy, and not on potential harm) (15).
ACR (2012)	Does not recommend it in the initial management of the disease. Conditionally recommends it in patients with no satisfactory response to prior recommended treatments (4).
ESCEO (2014)	Recommends it in patients who are severely symptomatic or still symptomatic despite the use of NSAIDs, or in case of contraindications to NSAIDs (step 2) (14).
EULAR (2003)	Recommends it for pain reduction and functional improvement (2).
NICE (2014)	Recommends not offering it (5).
OARSI (2014)	Recommends it only after physician-patient interaction for determining whether it can have merit in the context of their individual characteristics, comorbidities, and preferences (based on an uncertain appropriateness) (3).

\* AAOS = American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; NSAIDs = nonsteroidal anti-inflammatory drugs; ESCEO = European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; EULAR = European League Against Rheumatism; NICE = National Institute for Health and Care Excellence; OARSI = Osteoarthritis Research Society International.

to provide the best evidence-based information available to help physicians in making a treatment decision.

**Mode of action**

In the US, from a purely regulatory point of view, the symptomatic effects of most of the IAHA preparations are considered to primarily result from the unique properties of HA in solution; when injected intraarticularly, exogenous HA is able to compensate for the drop in HA concentration and chain length that has been observed during the progression of OA, thus restoring the elastic and viscous properties of the synovial fluid, which are responsible for its resistance to compression and its lubricating effect, respectively (51,52). However, these direct mechanical effects of exogenous HA cannot account for its long-term benefits observed in clinical trials (24), as it is cleared from the joint within a few days, depending on the IAHA preparation. Over the past 30 years, several possible pharmacologic mechanisms of action explaining how the clinical effects of IAHA could persist for several months have been proposed. A recent review of the preclinical basic science literature performed by Altman et al (53) highlighted the major role of HA binding to cluster of differentiation 44 receptors in this complex mechanism, as numerous of its mediated effects (e.g., inhibition of

**Table 3. Pharmacoeconomic studies evaluating the cost-effectiveness of IAHA in the symptomatic treatment of knee osteoarthritis\***

Reference	Source of data	Country	Duration	Product vs. comparator	Cost-effectiveness	ICER
Waddell et al, 2001 (65)	Cohort†	US	3 years	Synvisc + AC vs. AC	NA	Dominant
Torrance et al, 2002 (66)	RCT (74)	Canada	12 months	Synvisc + AC vs. AC	NA	\$10,000 Canadian per QALY
Kahan et al, 2003 (67)	RCT (67)	France	9 months	Synvisc vs. CC	€829 for 32% improvement in Lequesne index	Dominant
Yen et al, 2004 (68)	Cohort†	Taiwan	6 months	Artz vs. naproxen	\$1,538 US per QALY	\$42,000 US per QALY
Mazières et al, 2007 (69)	Cohort (69)	France	6 months	Suplasyn vs. CC (BL)	€528 for 27% improvement in Lequesne index	Dominant
Turajane et al, 2007 (70)	Retrospective (75)	Thailand	2 years	Hyalgan + AC vs. AC	NA	NA
Chou et al, 2009 (71)	Cohort (71)	Taiwan	6 months	Synvisc vs. CC (BL)	\$299,456 NT per QALY‡	NA
				Artz vs. CC (BL)	\$394,021 NT per QALY	NA
Miller and Block 2014 (72)	Cohort (76)	US	2 years	Registered IAHA vs. CC†	\$12,800 US per QALY	< \$23,400 US per QALY
Hatoum et al, 2014 (73)	RCTs (77,78)	US	12 months	Euflexxa vs. CC (BL)	\$21,281 US per QALY	Dominant
Hatoum et al, 2014 (73)	RCTs (74,77,78)	US	12 months	Euflexxa vs. AC	\$8,816 US per QALY	\$38,741 US per QALY

\* ICER = incremental cost-effectiveness ratio; AC = appropriate care (e.g., nonpharmacologic therapy, nonsteroidal antiinflammatory drugs [NSAIDs], analgesics, corticosteroids, total knee arthroplasty); NA = not available; RCT = randomized controlled trial; QALY = quality-adjusted life year; CC = conventional care (i.e., nonpharmacologic therapy, NSAIDs, analgesics); BL = baseline.  
† Hypothetical.  
‡ \$1 NT = \$0.0315 US (2008 exchange).

interleukin [IL]-1 $\beta$ , IL-6, and matrix metalloproteinase [MMP] expression, and reduction in prostaglandin E<sub>2</sub> synthesis) contribute to the chondroprotection, proteoglycan/glycosaminoglycan synthesis, antiinflammatory, and subchondral effects as observed in vitro. Alternative pathways involving HA binding to intercellular adhesion molecule 1 and modulation of transient receptor potential vanilloid channel 1 activity (54) have also been described. In addition, the toll-like receptor (TLR) signaling pathway has been suggested to contribute to the antiinflammatory and anti-catabolic (inhibition of inflammation-induced activation of MMPs) effects of IAHA in joint tissues (55,56). Indeed, there is evidence that HA fragments that are highly expressed in the OA joint can transduce inflammatory signals through TLR2, TLR4, or both. When exogenous HA is injected in the joint, the proportion of these fragments is reduced, thus modulating TLR-mediated innate immune responses.

The ESCEO group is not convinced that one mode of action is sufficient to explain the therapeutic trajectory of IAHA and privilege the hypothesis that several mechanisms overlap and interact to relieve OA pain. Furthermore, in vitro results obtained on chondrocytes may not be the same as what happens clinically (i.e., in an anaerobic medium).

### Systematically repeated treatment

Is it useful and acceptable to propose to re-inject patients with a low level of pain? This very relevant issue in daily

clinical practice has been addressed in the AMELIA (Osteoarthritis Modifying Effects of Long-Term Intra-Articular Adant) study (44), a long-term, randomized, placebo-controlled trial carried out in 306 patients with symptomatic KOA who received 4 consecutive cycles (5 weekly IA injections) of either noncrosslinked HA of biofermentative origin or placebo. Followup visits were conducted at 6 months after the first and second cycles and at 12 months after the third and fourth cycles, resulting in a total study duration of 40 months. At the end of the study, the responder rate according to the Outcome Measures in Rheumatology/OARSI response criteria (57) was significantly higher in the IAHA group than in the control group (80.5% versus 65.8%; RR 1.22 [95% CI 1.07, 1.41],  $P = 0.004$ ). More interestingly, the number of responders to IAHA progressively increased after each treatment cycle, while response to IA placebo remained fairly stable, with a statistically significant between-group difference from 1 year onward ( $P < 0.05$ ). No increase in AEs occurred with repeated cycles of IAHA.

Based on these results, the ESCEO task force encourages the use of repeated cycles of IAHA in patients who responded to the first injection, starting a new treatment cycle as soon as the first symptoms appear.

### Molecular weight

There are more than 80 marketed IAHA preparations worldwide. They differ in many characteristics, including origin

(animal versus biofermentation), mean MW (500–6,000 kDa) and MW distribution, molecular structure (linear, crosslinked, and a mix of both), method of crosslinking, concentration (0.8–30 mg/ml), volume of injection (0.5–6.0 ml), and posology. Some of the preparations include different concentrations of additives, such as mannitol, sorbitol, or chondroitin sulfate. While each of these parameters may theoretically have an impact on the effect of the IAHA treatment, research has mostly focused on the potential differences resulting from the size of HA. For this purpose, the exogenous HA available for IA injections are divided into 3 MW categories: low (500–730 kDa), intermediate (800–2,000 kDa), and high (2,000–6,000 kDa), including crosslinked formulations of HA (58). The rationale for an influence of the MW results from research on the mode of action of IAHA. Indeed, as summarized in the review by Altman et al (53), basic preclinical science showed that higher MW HAs may provide superior chondroprotective, proteoglycan/glycosaminoglycan synthesis, antiinflammatory, mechanical, and analgesic effects. Whether these differences observed *in vitro* translate into clinical evidence is not clearly established yet.

Two meta-analyses comparing different IAHA preparations have been published to date (Table 1). The first one compared hylan with lower-MW IAHA and found no clinically relevant benefits in terms of efficacy of either type of preparation. However, the risks for local AEs (RR 1.91 [95% CI 1.04, 3.49];  $I^2 = 28\%$ ) and postinjection flares (RR 2.04 [95% CI 1.18, 3.53];  $I^2 = 0\%$ ) were observed to be twice as high with hylan than with low- or intermediate-MW HA (22). In addition, a higher number of pseudosepsis cases were reported with hylan than with other IAHA preparations, whose risk might increase with subsequent courses (40). In the second meta-analysis, comparing different commercially available IAHA products, the authors were not able to conclude that one brand had a better efficacy than another due to the heterogeneity of the studies and outcomes (25).

In addition, most head-to-head RCTs performed to date have found noninferiority with respect to symptomatic efficacy between the various HA preparations evaluated (59–64). To our knowledge, only 1 RCT was able to demonstrate a statistically significant difference between 2 IAHA preparations varying in MW regarding symptomatic efficacy. Indeed, this study conducted in 400 patients with KOA showed that an intermediate-MW HA provided statistically superior pain relief at 6 months than a low-MW HA. Secondary end points confirmed the primary finding (58).

Based on the above, the ESCEO task force considers that there is currently no clinical evidence supporting an advantage in efficacy of one product over another. Furthermore, if certain intrinsic properties (e.g., MW) of particular IAHA preparations provide beneficial results in comparison with other IAHA products, characteristics related to the patient are likely to prevail.

### Efficiency

Only 9 pharmacoeconomic studies evaluating the cost-effectiveness of IAHA have been published to date (Table 3) (65–73). Most of them were conducted in patients with KOA who received IA injections of hylan (65–67,71).

Although pharmacoeconomic data are overall in favor of IAHA, only a few evaluations included sensitivity analyses or were performed based on RCTs. Furthermore, some costs were not included, such as those associated with potential AEs. Therefore, the ESCEO task force recommends investigating more in the identification, measurement, and comparison of the costs, risks, and benefits of IAHA in the management of KOA.

### Conclusion

This review addresses major aspects related to the use of IAHA in the management of KOA. It emphasizes its good safety profile and its moderate but real efficacy on symptoms, which is in the same range as other pharmacologic treatment modalities (e.g., NSAIDs) used in this indication. The effectiveness of IAHA has also been highlighted based on real-life clinical data and should therefore be helpful to clinicians when making care decisions tailored to individual patient needs.

The ESCEO working group is aware that IAHA is not a panacea for treating a heterogeneous disease such as KOA. However, KOA is known to mostly affect the elderly and individuals with significant comorbidities, thereby constraining the use of several conventional therapeutic options such as acetaminophen, NSAIDs, opioids, duloxetine, or TKA. Therefore, the experts convened by the ESCEO feel that the medical community cannot afford to neglect the use of IAHA, particularly now that systematic repetitive treatment cycles have been shown to yield positive results in terms of both efficacy and safety. Indeed, they consider that IAHA is a reasonable alternative in patients with KOA who have not sufficiently responded to previous pharmacologic treatments, and a key weapon in the therapeutic armamentarium for managing KOA in patients with contraindications to conventional interventions.

The ESCEO task force calls for additional well-conducted clinical trials (RCTs, cohort studies) to define the predictive factors (i.e., patient phenotypes, treatment characteristics) associated with an optimal risk-benefit ratio. Such research may further help in determining candidates that may take most advantage of IAHA.

### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Cooper 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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**Acquisition of data.** Cooper, Rannou, Richette, Bruyère, Herrero-Beaumont, Migliore, Uebelhart, Reginster.

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### ADDITIONAL DISCLOSURE

Author Collaud Basset is an employee of TRB Chemedica International SA.

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