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# Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys

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ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends intra-articular (IA) hyaluronic acid (HA) for management of knee osteoarthritis (OA) as second-line treatment in patients who remain symptomatic despite use of non-steroidal anti-inflammatory drugs (NSAIDs). This recommendation is based upon accumulating evidence that IA HA provides a significant benefit in knee OA. There is good evidence that IA HA injections reduce pain and increase function in knee OA, and the benefits are long-lasting as compared with IA corticosteroids. Evidence from real-life studies of repeat courses of IA HA demonstrates an improvement in pain or function lasting up to 40 months (12 months after the last injection cycle), a reduction in use of concomitant analgesia by up to 50%, and suggests that there may be a delay in the need for total knee replacement (TKR) of around 2 years. The clinical benefit of IA HA on knee OA may be 2-fold: (i) mechanical viscosupplementation of the joint (allowing lubrication and shock absorption) and (ii) the re-establishment of joint homeostasis through induction of endogenous HA production, which continues long after the exogenous injection has left the joint. The magnitude of the clinical effect may be different for different HA products, but this has not been proven so far and requires further investigation. IA HA injections are generally considered to be safe, although a slightly higher number of cases of local reactions and post-injection non-septic arthritis has been reported with high molecular weight cross-linked HAs. The use of IA HA in knee OA patients with mild–moderate disease, and for more severe patients wishing to delay TKR surgery, is recommended by the ESCEO task force. Further investigation into the OA patient types most likely to benefit from IA HA is warranted. Viscosupplementation with IA HA is a safe and effective component of the multi-modal management of knee OA.



## Introduction

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends intra-articular (IA) hyaluronic acid (HA) for advanced pharmacological management of knee osteoarthritis (OA) in patients who remain severely symptomatic despite use of non-steroidal anti-inflammatory drugs (NSAIDs) [1]. While there is increasing evidence that HA injections provide a significant benefit in knee OA [2–4], the level of recommendation afforded to HA by international and national societies varies (Table 1) [1,5–7]. The European League Against Rheumatism (EULAR) guidelines recommend IA HA based upon level 1B evidence for both pain reduction and joint functional improvement [5]. Both the American College of Rheumatology (ACR) guidelines and ESCEO algorithm recommend IA HA in patients whose symptoms persist despite prior treatments [1,6]. The 2014 Osteoarthritis Research Society International (OARSI) guidelines give an "uncertain" recommendation to IA HA [7]. This "uncertain" classification "is 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" [7], leading to the prescription of IA HA for specific clinical phenotypes and not for all individuals with knee OA. Besides, surprisingly and against all the evidence from literature and daily clinical practice, OARSI guidelines attributed to IA HA injection a "risk score" superior to the

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**Table 1**
Recommendations for the use of intra-articular hyaluronic acid for knee osteoarthritis

| Guideline committee | Recommendation for IA HA |
|---|---|
| European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) | Recommended for advanced pharmacological management in persistent symptomatic patients if still symptomatic after intermittent or longer cycles of oral NSAIDs. |
| European League Against Rheumatism (EULAR) | Evidence to support efficacy. Limitations: logistic and cost issues. |
| American College of Rheumatology (ACR) | No recommendation in the initial management. Conditionally recommended if no satisfactory response to prior treatments. |
| Osteoarthritis Research Society International (OARSI) | Uncertain but possible for knee OA after physician patient interaction. Not appropriate for multi-joint OA. |

IA HA, intra-articular hyaluronic acid; OA, osteoarthritis; NSAIDs, non-steroidal anti-inflammatory drugs.

"risk score" of IA corticosteroid injection in knee OA patients with co-morbidities.

## Review of the evidence base for efficacy of IA HA

Numerous meta-analyses have investigated the evidence for the efficacy of IA HA in treating the symptoms of knee OA [2–4,8–11]. Table 2 summarizes the meta-analyses published to date and their main characteristics [2–4,8–18]. The Cochrane review of 2006 included 76 trials of a number of different HA products mostly administered at weekly intervals for 3–5 weeks, in comparison with placebo, IA corticosteroids, NSAIDs, and other therapies [8]. The analysis found that viscosupplementation is an effective treatment for OA of the knee. Beneficial effects on pain, function, and patient global assessment at different post-injection time periods were noted, but especially at 5–13 weeks post-injection which showed a percent improvement from baseline of 28–54% for pain and 9–32% for function [8]. It was noted that the magnitude of the clinical effect was different for different products, and considerable heterogeneity of outcomes was found between trials [8].

A recent network meta-analysis was performed on 137 studies comprising 33,243 participants using a Bayesian random-effects model to determine the comparative effectiveness of pharmacological interventions for knee OA [4]. For pain, all interventions significantly outperformed oral placebo, with the exception of paracetamol; the most efficacious treatment was found to be IA HA with an effect size (ES) of 0.63 (95% central credible interval [CrI]: 0.39–0.88). The least effective treatment was paracetamol (ES: 0.18, 95% CrI: 0.04–0.33) [4]. For function, all interventions with the exception of IA corticosteroids and paracetamol were significantly superior to oral placebo, and for stiffness most of the treatments did not differ significantly from one another. It was notable that 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 (CrI: 0.26–0.42) was observed for IA HA on pain at 3 months, which is of the magnitude observed in conventional meta-analyses,

**Table 2**
Characteristics and results of the meta-analyses published on intra-articular hyaluronic acid injections in knee OA

| Study/analysis details | Number of articles analyzed | Main outcome | Results/quantification of effect (95% CI) | Conclusion |
|---|---|---|---|---|
| Lo et al. [12] | 22 | Pain change at M1–4 | ES: 0.32 (0.17–0.47) | Intermediate |
| Wang et al. [13] versus placebo | 20 | Pain change | Pooled change + | Positive |
| Arrich et al. [14] versus placebo | 22 | Pain during movement VAS | Mean change: −7 mm at W22–30 | Negative |
| Modawal et al. [15] versus placebo | 11 | Pain VAS | Between group difference: −18 mm at W8–12 | Positive moderate |
| Bellamy et al. [8] versus placebo | 40 | Pain/function (WMD or SMD) | −28% to 54% Reduction in pain at W5–13 | Positive |
| Medina et al. [16] versus placebo | | Pain | — | Positive |
| Low MW versus Hylan G-F20 (Reichenbach et al. [17]) | 13 | Pain at endpoint | ES: on between group difference −0.27 in favor of Hylan, but more post-injection flares | Discourage Hylan use |
| Therapeutic trajectory versus IA corticosteroids (Bannuru et al. [11]) | 7 | Pain change from baseline | ES: 0.22 (−0.05 to 0.49) at W8 in favor of IA HA<br>ES: 0.39 (0.18–0.59) at W26 in favor of IA HA | Positive from W8 |
| Therapeutic trajectory (Bannuru et al. [2]) | 54 | Pain change from baseline | ES: 0.46 (0.28–0.65) at W8<br>0.21 (0.10–0.31) at W24 | Positive |
| Colen et al. [18] versus placebo/HAs | 74 | Pain change from baseline | −30% Pain over IA placebo effect (−10 mm on VAS) | Intermediate |
| Rutjes et al. [3] versus placebo | 71 | Pain difference vs. control at endpoint | ES: −0.37 (−0.46 to −0.28) | Positive but discussed |
| US-approved HAs ($n = 6$) versus placebo (Miller and Block [10]) | 29 | Pain/function at endpoint | SMD: 0.38–0.43 for pain; 0.32–0.34 for function | Positive |
| Bannuru et al. [9] versus NSAIDs | 5 | Pain at endpoint | Hedges's $g$: −0.07 (−0.24 to 0.10) | No difference |
| Bannuru et al. [4] versus placebo/other options | 52 | Pain/function at M3; SMD | ES: IA versus oral placebo 0.29 (0.04–0.54) > paracetamol<br>HA versus IA placebo 0.34 (0.26–0.42) | Positive |

ES, effect size; HA, hyaluronic acid; IA, intra-articular; M, month; MW, molecular weight; SMD, standardized mean difference; VAS, visual analog scale; W, week; WMD; weighted mean difference.

e.g., ES on pain of 0.46 (95% confidence interval [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 [2,3]. A further analysis of trials directly comparing IA HA and NSAIDs suggests that the effect of IA HA is not significantly different from continuous oral NSAIDs in the short term, at 4 and 12 weeks for pain, function, and stiffness in knee OA [9]. Injection site pain was the most common adverse event (AE) reported in the HA group, and gastrointestinal (GI) AEs were more common in the NSAIDs group. Given the favorable safety profile of IA HA over NSAIDs, this result suggests that IA HA might be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced AEs [1].

IA HA has a long lasting effect on pain in OA [2,10,11]. A recent analysis of 29 studies ($n = 4866$) of US-approved IA HA injections versus placebo found a large treatment effect from 4 weeks up to 26 weeks for knee pain and function compared to pre-injection values [10]. Compared to saline controls, standardized mean difference (SMD) with IA HA was maintained at 0.38 for knee pain and 0.32 for knee function at weeks 14–26 ($p < 0.0.001$), which equates to a moderate but true effect [10]. A therapeutic trajectory of IA HA versus placebo found that IA HA is efficacious by 4 weeks (ES: 0.31; 95% CI: 0.17–0.45), reaching a peak in effectiveness at 8 weeks (ES: 0.46, 95% CI: 0.28–0.65), and with a residual detectable effect for knee OA pain at 6 months post-intervention (ES: 0.21, 95% CI: 0.10–0.31) [2]. In addition, IA HA induces longer-lasting pain control compared with IA corticosteroids [11]. Analysis of 7 head-to-head randomized clinical trials (RCTs) of 606 participants, found that the pattern of relative efficacy varied over time following injection. From baseline to week 4, IA corticosteroids were relatively more effective for pain than IA HA, but by week 4 the two approaches had equal efficacy, and beyond week 8 up to 26 weeks IA HA had greater efficacy (Table 3) [11].

## Evidence from real-life studies and surveys

HA is not a rapidly acting agent, rather its clinical effect on pain and function shows a carryover effect that extends for a long time after administration. The long-term effects of HA on disease progression over 40 months have been investigated in the Osteo-Arthritis Modifying Effects of Long-term Intra-articular Adant (AMELIA) study [19]. The study followed 306 patients with knee OA who received 4 cycles of 5 injections of IA HA or placebo, for up to a year after the fourth cycle. At the end of the study (40 months), significantly more patients receiving HA responded to treatment compared with placebo according to OARSI 2004 criteria for pain, function, and patient global assessment [80.5% of responders to HA versus 65.8% for placebo; relative risk (RR): 1.22, 95% CI: 1.07–1.41; $p = 0.004$] [19]. The number of responders to HA injections progressively increased after each treatment cycle, while response to placebo remained fairly stable, with a significant difference between groups evident from 1 year onwards ($p <$ 0.05). In other observational studies, IA HA injections in knee OA were highly effective in improving resting and walking pain with duration of symptom control up to 6 months, and a reduction in concomitant analgesia use of 30–50%. Few AEs were reported, mostly limited to mild or moderate local AEs of transient pain and swelling [20–22].

**Table 3**
Comparative effect of intra-articular hyaluronic acid and corticosteroids on pain in knee osteoarthritis over time [11]

| Weeks from injection | Effect size (95% CI) | Favors |
|---|---|---|
| Week 2 | −0.39 (−0.56 to −0.12) | CS > HA |
| Week 4 | −0.01 (−0.23 to 0.21) | CS = HA |
| Week 8 | 0.22 (−0.05 to 0.49) | HA = CS |
| Week 12 | 0.35 (0.03–0.66) | HA > CS |
| Week 26 | 0.39 (0.18–0.59) | HA > CS |

Analysis of 7 clinical trials ($N = 606$; HA, $n = 312$; CS, $n = 298$); CS, corticosteroid; HA, hyaluronic acid; IA, intra-articular.

The impact of HA on further long-term outcomes, namely delay of total knee replacement (TKR) surgery, has not, as yet, been studied in prospective, controlled studies; however, it has been investigated in retrospective works. In a retrospective database analysis [23], patients enrolled in the database from 2007 to 2011 who went on to TKR were identified as having received prior HA injections ($n = 7000$) or no HA injections ($n = 19{,}627$). A propensity scoring method was implemented to adjust for baseline characteristics of patients in HA ($n = 6891$) and non-HA cohorts. The analysis found that each course of HA injections delayed patients' progression to TKR, with each treatment course increasing the median gap by an average 202 days. After 4 or more treatment courses, a delay in TKR of approximately 2.2 years was found in the study population [23]. This is in agreement with a previous 6-year retrospective database study that found a median delay in TKR of 2.1 years with HA treatment in patients with grade IV severe OA [24]. The median times from the initial specialist visit to TKR were 199 and 443 days for non-HA cohort and the HA cohort with 1 episode of HA treatment, respectively. For the HA cohort with 3 and 4 or more treatment episodes, the median times to TKR were 784 (585 days delay) and 1009 days (810 days delay), respectively (Fig. 1) [23]. In another Spanish study which looked at the management of knee OA patients referred to orthopedic surgeons for TKR, the authors reported a mean delay to TKR of 2.2 years among patients who had received treatment with IA HA injections (using a mathematical modelization) [25].

## Does molecular weight of HA matter?

HA is a glycosaminoglycan constituent of synovial fluid and cartilage matrix in normal joints. The properties of the synovial fluid are dependent on the concentration of HA and its molecular weight (MW); in OA, the concentration and MW of HA are decreased [26]. The exogenous HA available for IA viscosupplementation is formulated as different MW preparations: low (range: 500,000–730,000 Da), intermediate (800,000–2,000,000 Da), and high MW (average: 6,000,000 Da) including cross-linked formulations of HA (hylans).

The precise mechanism of action of exogenous HA is unknown. However, the proposed mechanism of HA activity occurs in 2 stages: a mechanical stage and a pharmacological stage [11,27]. During the mechanical stage, OA synovial fluid is replaced by higher concentrations of HA thereby improving viscosity [28]. This also restores the shock-absorbing and lubricating abilities of depleted synovial fluid and maintains a boundary layer around nociceptors, reducing pain induction [29]. The pharmacological stage induces the biosynthesis of endogenous HA and extracellular matrix components [30], which reduces proteoglycan loss in cartilage and apoptosis of chondrocytes [28,31]. It also reduces inflammatory cell activities to reduce HA degradation and acts by reducing induction of pain mediators [28,29].

The endogenous synthesis of HA by synovial fibroblasts is influenced by the concentration and MW of HA in the extracellular environment (Fig. 2) [30]. With low MW HA preparations only weak binding occurs and the biosynthesis of HA may not be sufficiently stimulated. With exogenous HA of intermediate MW, strong binding occurs and because of the high number of receptors stimulated endogenous HA biosynthesis is enhanced. While maximal receptor binding occurs with high MW HA, the large domains

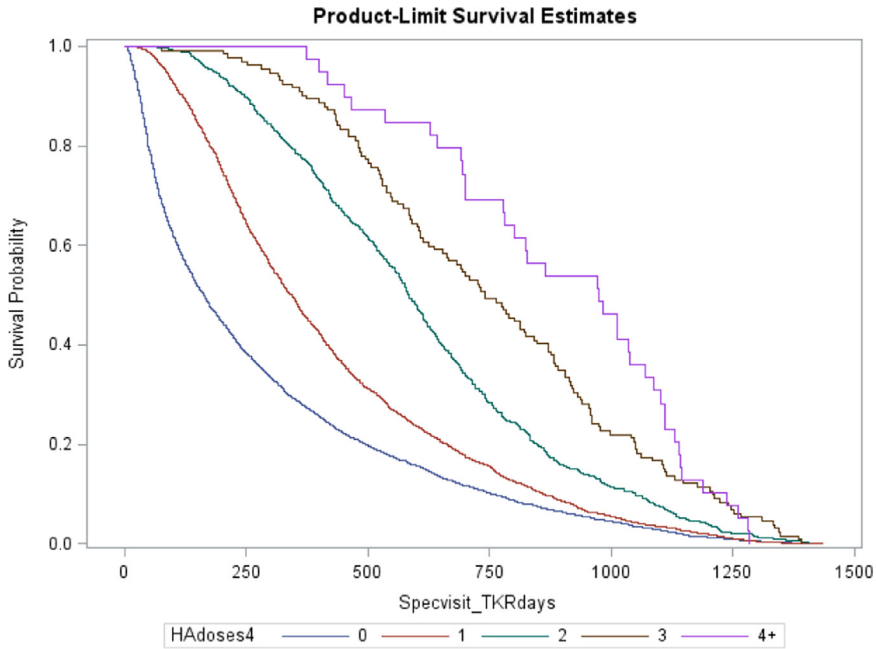


**Fig. 1.** Impact of repeat episodes of intra-articular hyaluronic acid injections on time to total knee replacement (TKR) surgery [23]. (Reproduced with permission from Abbott et al. [23]; copyright permission granted.)

of these molecules limit the number of sites that can be occupied on the cell surface, and HA biosynthesis may not be strongly stimulated by such a configuration [30]. There is also some evidence that low MW HA could have proinflammatory activity on chondrocytes, while intermediate MW preparations would be neutral in *in vitro* models [32]. However, whether these *in vitro* data translate into clinical evidence is as yet uncertain. It has been suggested by Aviad and Houp [33] that the concentration of HA injections may be more important than the MW of HA regarding the clinical effect.

Most head-to-head clinical trials performed to date have found non-inferiority with respect to symptomatic efficacy between the HA preparations of various MWs tested [34–38]. In a head-to-head clinical trial of 3-weekly injections of intermediate MW HA (GO-ON®) versus low MW HA (Hyalgan) in over 400 knee OA patients, the intermediate MW HA preparation was statistically superior for the primary endpoint of Western Ontario and McMaster Universities (WOMAC) pain subscale score at 6 months after the end of treatment; mean WOMAC pain score decreased by 22.9 $\pm$ 1.4 mm with intermediate MW HA and 18.4 $\pm$ 1.5 mm with low MW HA after 6 months ($p = 0.021$) (Fig. 3) [26]. At 6 months although both groups exhibited a high proportion of responders, there were significantly more OARSI/OMERACT responders in the intermediate MW HA group compared with the low MW HA group (73% versus 58%; $p = 0.001$) [26]. A meta-analysis found no clinically relevant difference in benefit of hylan compared with lower MW HA preparations (1 low MW and 1 intermediate MW) but with an increased safety risk for hylan [17]. Therefore, overall, the current evidence available does not support a superiority of one kind of MW HA preparation over another, perhaps with the exception of a slightly lower efficacy for low MW preparations versus intermediate and high MW HA shown in a single trial which requires further investigation.

## Which patients are likely to respond best to IA HA?

This is a major issue. Unfortunately, little evidence can be found in the available literature, either from clinical trials, or surveys of long-term HA use [39]. Summarizing this limited evidence leads to the following suggestions; IA HA injections seem to be more effective if the patient:

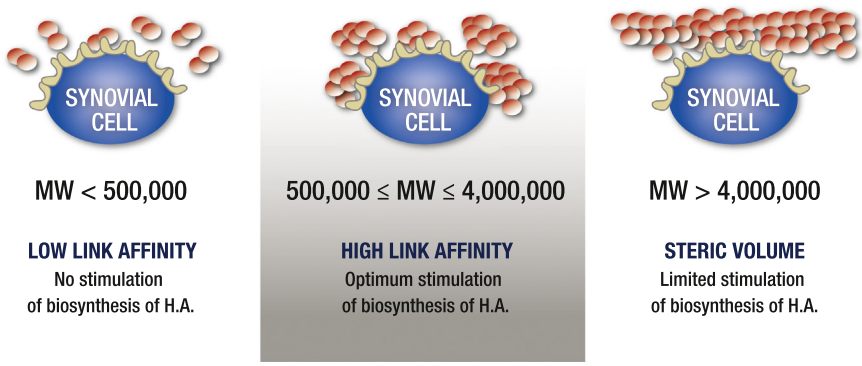


**Fig. 2.** Model of hyaluronic acid binding to receptors on the surface of synovial fibroblasts [30]. HA, hyaluronic acid; MW, molecular weight. (Adapted from Smith and Ghosh [30].)

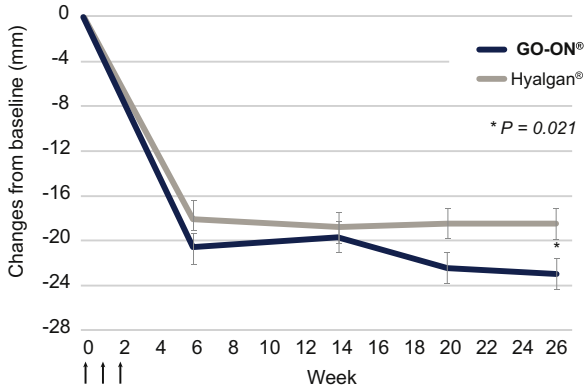


**Fig. 3.** WOMAC pain subscale score change for intermediate MW HA (GO-ON®) ($n = 217$) versus low MW HA (Hyalgan®) ($n = 209$), ITT mean (and SE) change from baseline [WOMAC pain subscale index score (0–100 scale): 47.5 ± 14.3 for the GO-ON group and 48.8 ± 14.9 for the Hyalgan group] [26]. The arrows indicate the intra-articular injections. (Reproduced with permission from Berenbaum et al. [26]; copyright permission granted.)

1. has moderate, radiologically-advanced OA (at a Kellgren–Lawrence grade 2, rather than 3) [39],
2. is not too old [34], and
3. has a high level of symptoms. Karlsson et al. [34] showed that patients with a Lequesne index of at least 10 had a better response.

In addition, the presence of crystals in the joint does not preclude the use of HA injections, and does not reduce the level of response [40,41]. Furthermore, a certain level of physical activity seems to be associated with better results (unpublished data from the Berenbaum trial) [26].

## Safety of IA HA

IA HA injections are widely reported to be relatively safe, and a meta-analysis of US-approved HA products on knee OA found no statistically significant difference between IA HA and saline controls for any safety outcome [10]. Furthermore, the serious AE risk was similar between IA HA and saline (risk difference: 0.7%; 95% CI: −0.2% to −1.5%; $p = 0.12$) [10]. The safety record of IA HA has recently been questioned by a meta-analysis that reported an increased risk of side effects (serious AEs and local AEs) with HA that barely reached significance, and was limited to a small select fraction of trials (8 out of 71) [3]. It is important to note that the considered studies were of poor methodological and reporting quality, rendering the findings questionable [42]. Pseudoseptic reactions have been reported in a small number of cases, occurring more often with cross-linked formulations of the highest MW [43]. A meta-analysis on safety found that high MW, cross-linked formulations of HA (hylans) are twice as likely to cause local adverse reactions (RR: 1.91; 95% CI: 1.04–3.49; $I^2 = 28\%$) and post-injection flares (RR: 2.04; 95% CI: 1.18–3.53; $I^2 = 0\%$) compared with intermediate or low MW HA [17].

## Conclusions

There is good evidence for the efficacy of IA HA in reducing pain and increasing function in knee OA as demonstrated in RCTs. While IA corticosteroids show early relief of symptoms, IA HA demonstrates a greater effect beyond 12 weeks after injection, and with longer lasting benefits up to 6 months. Evidence from a real-life study of repeat courses of IA HA demonstrates an improvement in pain or function lasting up to 40 months (12 months after the last treatment cycle). Other observational studies suggest a reduction in use of concomitant analgesia by up to 50%, and a delay in the need for TKR surgery of around 2 years. This particular outcome should be further studied in prospective long-term controlled trials or surveys.

The clinical benefits of IA HA on knee OA may be considered to be 2-fold: (i) mechanical viscosupplementation of the joint allowing lubrication and shock absorption and (ii) the re-establishment of joint homeostasis through induction of endogenous HA production, which continues long after the exogenous injection has left the joint. The magnitude of the clinical effect for different HA products may vary, and this also requires further prospective controlled investigations to be established. IA HA injections are generally considered to be safe, with only mild to moderate transient local AEs reported on the whole, although a slightly higher occurrence of local reactions and flares has been reported with hylans.

Further investigation into the OA patient phenotypes most likely to benefit from IA HA is warranted. However, the ESCEO recommends the use of IA HA in knee OA patients with mild to moderate disease, and for more severe patients who are either contraindicated to TKR surgery or wishing to delay the surgical procedure. Viscosupplementation with IA HA appears to be a safe and effective treatment and should be kept as a component of the multi-modal management of knee OA.

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