Review article

Title: Use of Intra-Articular Hyaluronic Acid in the Management of Knee Osteoarthritis in Clinical Practice

Running head: Intra-Articular Hyaluronic Acid in the Management of Knee Osteoarthritis

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# Abstract

This review emphasizes the safety profile of intra-articular hyaluronic acid treatment of knee osteoarthritis, as well as its moderate but real efficacy on symptoms, which is in the same range than other pharmacological modalities used in this indication. Effectiveness of intra-articular hyaluronic acid has also been highlighted based on ‘real-life’ data, together with the clinical benefit of systematic repeated treatment cycles, and the influence of the molecular weight of hyaluronic acid on treatment outcome. These aspects should be particularly helpful to clinicians when making personalized care decisions.

Significance & Innovations

* Beside efficacy and safety, this review also addresses less frequently evaluated aspects of the intra-articular use of hyaluronic acid in the management of knee osteoarthritis such as effectiveness and efficiency.
* This is the first time that a group of experts recommends systematic repeated intra-articular hyaluronic acid treatment in knee osteoarthritis patients who had a beneficial response with a previous cycle of treatment.

# 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 non-pharmacological and pharmacological modalities (1) primarily intended to relieve the symptoms of pain and loss of knee function. In clinical practice, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are generally recommended to relieve pain and improve joint function (2-5)(Jordan et al. 2003; McAlindon et al. 2014a; Zhang et al. 2010). However, due to their vascular and gastro-intestinal 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). Intra-articular (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 (9-13).

IA hyaluronic acid (HA) is a local treatment modality devoid of the systemic AEs observed after IA corticosteroid injection or oral administration of analgesics and NSAIDs. Thus, IAHA represents an alternative to analgesics and NSAIDs in patients with co-morbidities, as well as a secondary option in case of inadequate response to first-line pharmacological 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 osteoarthritis (OA) and clinical research methodology. Seven members of this working group (GHB, DU, PR, FR, AM, OB, CC) 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 one‑day meeting in January 2016 that took place 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, fifteen meta-analyses/systematic reviews assessing the symptomatic effects of IAHA on KOA were published to date (16-30). Six of them concluded on a clear efficacy of IAHA (17,20,24,27,29,30), four considered it as a marginally efficacious treatment modality (16,19,25,26), and two meta-analyses found no significant difference in efficacy between IAHA and IA placebo (18,21) (Table 1).

The reported effect sizes (ESs) 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%CI 0.28 to 0.65) that is still observable at 24 weeks (ES 0.21, 95%CI 0.10 to 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, ESs of 0.34 (95%CI 0.02 to 0.67) and 0.20 (95%CI 0.03 to 0.37) in favor of IAHA were obtained at 8 and 24 weeks, respectively (24). These results were confirmed by Richette and colleagues, 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 to 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%CrI 0.04 to 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 ESs *vs* oral placebo at 3 months. IAHA was found to be the most efficacious intervention with an ES of 0.63 (95%CrI 0.39 to 0.88), followed by IA corticosteroids (ES 0.61, 95%CrI 0.32 to 0.89), diclofenac (ES 0.52, 95%CrI 0.34 to 0.69), ibuprofen (ES 0.44, 95%CrI 0.25 to 0.63), naproxen (ES 0.38, 95%CrI 0.27 to 0.49), celecoxib (ES 0.33, 95%CrI 0.25 to 0.42) and IA placebo. With an ES of 0.18 (95%CrI 0.04 to 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 of one or both knees that received two 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 3.7 ± 1.8 points and 5.6 ± 1.7 points on a 10‑point visual analogue scale, respectively. In parallel, distance walked in a 6-minute walk test increased on average by 115 m in this patient group. These improvements in pain and physical function were 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, 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 TKA 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 one-year increase in time to surgery (35,36). The study including only those younger than 65 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 two studies suggested additional benefit from higher molecular weight (MW) HA products (36,37). The consistency of results from the three 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 co-morbidities.

# Safety

Seven meta-analyses of RCTs comparing IAHA to IA placebo evaluated safety of the intervention (17,18,20,21,26,27,29). AEs occurred slightly more often among patients who received an IAHA treatment (RR 1.08, 95%CI 1.01 to 1.15) (18). However, they were usually mild transient local reactions such as pain at the injection site and swelling with a relative risk (RR) of 1.19 (95%CI 1.01 to 1.41) according to Wang *et al.* (17) or 1.34 (95%CI 1.13 to 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 to 2.72) and effusion at the injected knee (RR 1.15, 95%CI 0.38 to 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 and colleagues raised concerns about safety of IAHA. Their meta-analysis emphasized an increased risk of serious AEs (RR 1.41, 95%CI 1.02 to 1.97) and dropouts due to AEs (RR 1.33, 95%CI 1.01 to 1.74). However, these findings have been criticized regarding the methodological rigor with which the serious AEs were analyzed and the biological plausibility of the reported events (38,39).

As shown in a review by Pagnano *et al.* (40), 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 eight-fold increase in the frequency of acute local reactions compared with patients receiving only one course (41).

In addition to the AEs mentioned above, post-marketing 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 pharmacological 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 chapters dealing with 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 ten 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 (AAOS) 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 (NICE) 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 pharmacological treatment modalities, *i.e.*, acetaminophen, symptomatic slow-acting drugs (SYSADOAs) and NSAIDs, as well as in patients with co-morbidities 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 pharmacological therapy. Furthermore, they emphasized its particular interest for patients aged above 75 years, who are not recommended to take oral NSAIDs (4,14). The EULAR considers the use of IAHA for pain relief and knee functional improvement based on level 1B evidence (2).

OARSI guidelines for the non-surgical 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, the 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 physician’s self-analysis of the patient situation; they are designed 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 intra-articularly, 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 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 pharmacological 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 and colleagues (53) highlighted the major role of HA binding to cluster of differentiation 44 (CD44) receptors in this complex mechanism, as numerous of its mediated effects (*e.g.*, inhibition of IL-1β, IL-6 and MMPs expression, reduction in PGE2 synthesis) contribute to the chondroprotection, proteoglycan/glycosaminoglycan synthesis, anti-inflammatory and subchondral effects as observed *in vitro*. Alternative pathways involving HA binding to intercellular adhesion molecule 1 (ICAM-1) and modulation of TRPV1 channel activity (54) have also been described. In addition, the toll-like receptor (TLR) signaling pathway has been suggested to contribute to the anti-inflammatory 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 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 four consecutive cycles (five weekly IA injections) of either non-crosslinked HA of biofermentative origin or placebo. Follow-up 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 OMERACT-OARSI response criteria (57) was significantly higher in the IAHA group than in the control group (80.5% vs 65.8%; RR 1.22, 95%CI 1.07 to 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 one year onwards (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 *vs* biofermentation), mean MW (500-6,000 kDa) and MW distribution, molecular structure (linear, crosslinked, and 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 three MW categories: low- (500-730 kDa), intermediate- (800-2,000 kDa) and high-MW (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, anti-inflammatory, 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 to 3.49; I2 28%) and post-injection flares (RR 2.04, 95%CI 1.18 to 3.53; I2 0%) were observed to be twice higher 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 non-inferiority with respect to symptomatic efficacy between the various HA preparations evaluated (59-64). To our knowledge, only one RCT was able to demonstrate a statistically significant difference between two 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 endpoints 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 nine 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 than other pharmacological treatment modalities (*e.g.*, NSAIDs) used in this indication. 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 co-morbidities, thus restraining 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 pharmacological 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 determining candidates that may take most advantage of IAHA.

References

1. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence [Review]. Osteoarthritis Cartilage. 2007;15:981-1000.

2. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: An evidence based approach to the management of knee osteoarthritis: Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) [Review]. Ann Rheum Dis. 2003;62:1145-55.

3. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis [Review]. Osteoarthritis Cartilage. 2014;22:363-88.

4. Hochberg MC, Altman RD, Toupin April K, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012. Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee [Review]. Arthritis Care Res (Hoboken). 2012;64:465-74.

5. National Institute for Health and Care Excellence. Osteoarthritis: Care and management in adults. NICE clinical guideline 177 [Internet]. London, United Kingdom: National Clinical Guideline Centre; 2014 [cited 2016 Jun 7]. Available from: http://www.nice.org.uk/guidance/cg177.

6. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials [Review]. Lancet. 2013;382:769-79.

7. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: Not as safe as we thought? A systematic literature review of observational studies [Review]. Ann Rheum Dis. 2016;75:552-9.

8. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis [Review]. Best Pract Res Clin Rheumatol. 2014;28:5-15.

9. Axelrod L. Glucocorticoids. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, editors. Textbook of Rheumatology. 4th ed. Philadelphia, PA: W.B. Saunders Company; 1993. p. 779-96.

10. Lazarevic MB, Skosey JL, Djordjevic-Denic G, Swedler WI, Zgradic I, Myones BL. Reduction of cortisol levels after single intra-articular and intramuscular steroid injection. Am J Med. 1995;99:370-3.

11. Wicki J, Droz M, Cirafici L, Vallotton MB. Acute adrenal crisis in a patient treated with intraarticular steroid therapy. J Rheumatol. 2000;27:510-1.

12. Younes M, Neffati F, Touzi M, Hassen-Zrour S, Fendri Y, Bejia I, et al. Systemic effects of epidural and intra-articular glucocorticoid injections in diabetic and non-diabetic patients. Joint Bone Spine. 2007;74:472-6.

13. Choudhry MN, Malik RA, Charalambous CP. Blood glucose levels following intra-articular steroid injections in patients with diabetes: A systematic review [Review]. JBJS Rev. 2016;4.

14. Bruyère O, Cooper C, Pelletier JP, Branco J, Brandi ML, Guillemin F, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) [Review]. Semin Arthritis Rheum. 2014;44:253-63.

15. Treatment of osteoarthritis of the knee. Evidence-based guideline 2nd edition [Internet]. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2013 [cited 2016 Jul 31]. Available from: www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf.

16. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: A meta-analysis [Review]. JAMA. 2003;290:3115-21.

17. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials [Review]. J Bone Joint Surg Am. 2004;86-A:538-45.

18. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Müllner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: Systematic review and meta-analysis [Review]. CMAJ. 2005;172:1039-43.

19. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain [Review]. J Fam Pract. 2005;54:758-67.

20. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee [Review]. Cochrane Database Syst Rev. 2006:CD005321.

21. Medina JM, Thomas A, Denegar CR. Knee osteoarthritis: Should your patient opt for hyaluronic acid injection? [Review]. J Fam Pract. 2006;55:669-75.

22. Reichenbach S, Blank S, Rutjes AW, Shang A, King EA, Dieppe PA, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: A systematic review and meta-analysis [Review]. Arthritis Rheum. 2007;57:1410-8.

23. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis [Review]. Arthritis Rheum. 2009;61:1704-11.

24. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis - meta-analysis [Review]. Osteoarthritis Cartilage. 2011;19:611-9.

25. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: A systematic review and meta-analysis with emphasis on the efficacy of different products [Review]. Biodrugs. 2012;26:257-68.

26. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: A systematic review and meta-analysis [Review]. Ann Intern Med. 2012;157:180-91.

27. Miller LE, Block JE. US-approved intra-articulr hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: Systematic review and meta-analysis of randomized, saline-controlled trials [Review]. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6:57-63.

28. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis [Review]. Semin Arthritis Rheum. 2014;43:593-9.

29. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: A systematic review and network meta-analysis [Review]. Ann Intern Med. 2015;162:46-54.

30. Richette P, Chevalier X, Ea HK, Eymard F, Henrotin Y, Ornetti P, et al. Hyaluronan for knee osteoarthritis: An updated meta-analysis of trials with low risk of bias [Review]. RMD Open. 2015;1:e000071.

31. Petrella RJ, Wakeford C. Pain relief and improved physical function in knee osteoarthritis patients receiving ongoing hylan G-F 20, a high-molecular-weight hyaluronan, versus other treatment options: Data from a large real-world longitudinal cohort in Canada. Drug Des Devel Ther. 2015;9:5633-40.

32. Petrella RJ. Hyaluronic acid for the treatment of knee osteoarthritis: Long-term outcomes from a naturalistic primary care experience. Am J Phys Med Rehabil. 2005;84:278-83.

33. Waddell DD, Bricker DC. Clinical experience with the effectiveness and tolerability of hylan G-F 20 in 1047 patients with osteoarthritis of the knee. J Knee Surg. 2006;19:19-27.

34. Kausch T, Lahne U, Thomas R, Kipshoven C, Schuld M. [The intra-articular treatment of osteoarthritis with hyaluronic acid]. Orthopädische Praxis. 2009;45:258-66. German.

35. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: Evidence from a large U.S. health claims database. PLoS One. 2015;10:e0145776.

36. Ong KL, Anderson AF, Niazi F, Fierlinger AL, Kurtz SM, Altman RD. Hyaluronic acid injections in medicare knee osteoarthritis patients are associated with longer time to knee arthroplasty. J Arthroplasty. 2016;31:1667-73.

37. Altman R, Fredericson M, Bhattacharyya SK, Bisson B, Abbott T, Yadalam S, et al. Association between hyaluronic acid injections and time-to-total knee replacement surgery. J Knee Surg. 2015;29:564-70.

38. McAlindon TE, Bannuru RR. Osteoarthritis: Is viscosupplementation really so unsafe for knee OA? [Review]. Nat Rev Rheumatol. 2012;8:635-6.

39. Cutolo M, Berenbaum F, Hochberg M, Punzi L, Reginster JY. Commentary on recent therapeutic guidelines for osteoarthritis [Review]. Semin Arthritis Rheum. 2015;44:611-7.

40. Pagnano M, Westrich G. Successful nonoperative management of chronic osteoarthritis pain of the knee: Safety and efficacy of retreatment with intra-articular hyaluronans [Review]. Osteoarthritis Cartilage. 2005;13:751-61.

41. Leopold SS, Warme WJ, Pettis PD, Shott S. Increased frequency of acute local reaction to intra-articular hylan GF- 20 (Synvisc) in patients receiving more than one course of treatment. J Bone Joint Surg Am. 2002;84-A:1619-23.

42. Chen AL, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after hylan G-F 20 viscosupplementation of the knee: A report of six cases. J Bone Joint Surg Am. 2002;84-A:1142-7.

43. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee [Review]. Cochrane Database Syst Rev. 2006:CD005328.

44. Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: The AMELIA project. Ann Rheum Dis. 2011;70:1957-62.

45. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines [Review]. Osteoarthritis Cartilage. 2008;16:137-62.

46. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology, Subcommittee on Osteoarthritis Guidelines [Review]. Arthritis Rheum. 2000;43:1905-15.

47. Rosen J, Avram V, Fierlinger A, Niazi F, Sancheti P, Bedi A. Clinicians' perspectives on the use of intra-articular hyaluronic acid as a treatment for knee osteoarthritis: A North American, multidisciplinary survey. Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:21-7.

48. Migliore A, Bizzi E, Herrero-Beaumont J, Petrella RJ, Raman R, Chevalier X. The discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis: Mind the gap! [Review]. Eur Rev Med Pharmacol Sci. 2015;19:1124-9.

49. Bruyère O, Cooper C, Pelletier JP, Maheu E, Rannou F, Branco J, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis - From evidence-based medicine to the real-life setting [Review]. Semin Arthritis Rheum. 2016;45:S3-S11.

50. Altman RD, Schemitsch E, Bedi A. Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid [Review]. Semin Arthritis Rheum. 2015;45:132-9.

51. Balazs EA. Viscoelastic properties of hyaluronic acid and biological lubrication. Univ of Mich Med Cent J. 1968;33:255-9.

52. Balazs EA, Denlinger JL. Viscosupplementation: A new concept in the treatment of osteoarthritis [Review]. J Rheumatol. 1993;20:3-9.

53. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: A systematic review [Review]. BMC Musculoskelet Disord. 2015;16:321.

54. Caires R, Luis E, Taberner FJ, Fernandez-Ballester G, Ferrer-Montiel A, Balazs EA, et al. Hyaluronan modulates TRPV1 channel opening, reducing peripheral nociceptor activity and pain. Nat Commun. 2015;6:8095.

55. Gomez R, Villalvilla A, Largo R, Gualillo O, Herrero-Beaumont G. TLR4 signalling in osteoarthritis - finding targets for candidate DMOADs [Review]. Nat Rev Rheumatol. 2015;11:159-70.

56. Campo GM, Avenoso A, Campo S, D'Ascola A, Traina P, Calatroni A. Differential effect of molecular size HA in mouse chondrocytes stimulated with PMA. Biochim Biophys Acta. 2009;1790:1353-67.

57. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12:389-99.

58. Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacovelli G, Chevalier X, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis. 2012;71:1454-60.

59. Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 2002;41:1240-8.

60. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthritis Cartilage. 2006;14:154-62.

61. Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, Jordi B, et al. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: A randomized controlled trial. Arthritis Rheum. 2007;56:3610-9.

62. Maheu E, Zaim M, Appelboom T, Jeka S, Trc T, Berenbaum F, et al. Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F 20 in symptomatic osteoarthritis of the knee (KOA). Results of a non inferiority, prospective, randomized, controlled trial. Clin Exp Rheumatol. 2011;29:527-35.

63. Pavelka K, Uebelhart D. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial) vs hylan G-F 20 (Synvisc) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study. Osteoarthritis Cartilage. 2011;19:1294-300.

64. Dreiser RL, Avouac B, Bardin T. A 6 month trial evaluating efficacy of one intraarticular injection of 2 per cent sodium hyaluronate versus Hylan G F 20 in the treatment of painful tibiofemoral osteoarthritis [Abstract]. Ann Rheum Dis. 2015;74(Suppl 2):376.

65. Waddell D, Rein A, Panarites C, Coleman PM, Weiss C. Cost implications of introducing an alternative treatment for patients with osteoarthritis of the knee in a managed care setting. Am J Manag Care. 2001;7:981-91.

66. Torrance GW, Raynauld JP, Walker V, Goldsmith CH, Bellamy N, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): Economic results. Osteoarthritis Cartilage. 2002;10:518-27.

67. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine. 2003;70:276-81.

68. Yen ZS, Lai MS, Wang CT, Chen LS, Chen SC, Chen WJ, et al. Cost-effectiveness of treatment strategies for osteoarthritis of the knee in Taiwan. J Rheumatol. 2004;31:1797-803.

69. Mazières B, Bard H, Ligier M, Bru I, d'Orsay GG, Le Pen C. Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: The MESSAGE study. Joint Bone Spine. 2007;74:453-60.

70. Turajane T. Cost analysis of intra-articular sodium hyaluronate treatment in knee osteoarthritis patients who failed conservative treatment. J Med Assoc Thai. 2007;90:1839-44.

71. Chou CW, Lue KH, Lee HS, Lin RC, Lu KH. Hylan G-F 20 has better pain relief and cost-effectiveness than sodium hyaluronate in treating early osteoarthritic knees in Taiwan. J Formos Med Assoc. 2009;108:663-72.

72. Miller LE, Block JE. An 8-week knee osteoarthritis treatment program of hyaluronic acid injection, deliberate physical rehabilitation, and patient education is cost effective at 2 years follow-up: The OsteoArthritis Centers of America Experience. Clin Med Insights Arthritis Musculoskelet Disord. 2014;7:49-55.

73. Hatoum HT, Fierlinger AL, Lin SJ, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ. 2014;17:326-37.

74. Raynauld JP, Torrance GW, Band PA, Goldsmith CH, Tugwell P, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): Clinical results. Osteoarthritis Cartilage. 2002;10:506-17.

75. Turajane T. Outcomes of intra-articular injection of sodium hyaluronate for the treatment of osteoarthritis of the knee. J Med Assoc Thai. 2007;90:1845-52.

76. Miller LE, Block JE. An 8-week multimodal treatment program improves symptoms of knee osteoarthritis: A real-world multicenter experience. Pragmatic Observational Res. 2013;4:39-44.

77. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum. 2009;39:1-9.

78. Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label extension Study of the FLEXX Trial. Osteoarthritis Cartilage. 2011;19:1169-75.

**Table 1 Meta-analyses evaluating intra-articular 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 to 0.47) | Intermediate |
| Wang *et al.* 2004 (17) | IA placebo | Pain on movement | MPD = 7.9 (4.1 to 11.7) | Positive |
| Arrich *et al.* 2005 (18) | IA placebo | Pain on move-ment at W2-6 | WMD = 3.8 (-1.4 to 9.1)I2 = 81% | Negative(no clinical difference) |
| at W10-14 | WMD = 4.3 (0.9 to 7.6)I2 = 0% |
| at W22–30 | WMD = 7.1 (2.4 to 11.8)I2 = 0% |
| Modawal *et al.* 2005 (19) | IA placebo | Pain change at W5-7 | MD = 17.6 (7.5 to 28.0) | Intermediate |
| at W8-12 | MD = 18.1 (6.3 to 29.9) |
| at W15-22 | MD = 4.4 (-15.3 to 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 to 5.5) | Negative(no statistical difference) |
| Function | MPD = 2.0 (-0.8 to 4.9) |
| Stiffness | MPD = 5.5 (2.2 to 8.8) |
| Reichenbach *et al.* 2007 (22) | IA hylan | Pain at end of follow-up | SMD = -0.27 (-0.55 to 0.01)I2 = 88% | HA > hylan |
| Bannuru *et al.* 2009 (23) | IA CS | Pain change from BL at W2 | SMDg = -0.39 (-0.65 to -0.12)I2 = 47% | Positive(HA > CS from W8 onwards) |
| at W4 | SMDg = -0.01 (-0.23 to 0.21)I2 = 37% |
| at W8 | SMDg = 0.22 (-0.05 to 0.49)I2 = 47% |
| at W12 | SMDg = 0.35 (0.03 to 0.66)I2 = 49% |
| at W26 | SMDg = 0.39 (0.18 to 0.59)I2 = 0% |
| Bannuru *et al.* 2011 (24) | IA placebo | Pain change from BL at W4 | SMDg = 0.31 (0.17 to 0.45)I2 = 75% | Positive |
| at W8 | SMDg = 0.46 (0.28 to 0.65)I2 = 75% |
| at W12 | SMDg = 0.25 (0.15 to 0.36)I2 = 60% |
| at W16 | SMDg = 0.20 (0.11 to 0.30)I2 = 7% |
| at W24 | SMDg = 0.21 (0.10 to 0.31)I2 = 32% |
| Colen *et al.* 2012 (25) | IA placebo | Pain change from BL at M3 | *vs* IA placebo:WMD = 10.2 (4.4 to 16.0)I2 = 92% | Intermediate |
| *vs* hylanSMD = 0.07 (-0.10 to 0.24)I2 = 72% |
| Rutjes *et al.* 2012 (26) | Sham or no intervention | Pain at end of follow-up | SMD: 0.37 (0.28 to 0.46)τ2 = 0.09 | Intermediate |
| Miller *et al.* 2013 (27) | IA placebo | Pain at W4-13 | SMD = 0.43 (0.26 to 0.60)I2 = 73% | Positive |
| at W14-26 | SMD = 0.38 (0.21 to 0.55)I2 = 75% |
| Function at W4-13 | SMD = 0.34 (0.16 to 0.51)I2 = 54% |
| at W14-26 | SMD = 0.32 (0.18 to 0.45)I2 = 69% |
| Bannuru *et al.* 2014 (28) | NSAIDs | Pain change from BL at W4 | SMDg = -0.01 (-0.18 to 0.15)I2 = 0% | Positive(HA = NSAIDs) |
| at W12 | SMDg = 0.05 (-0.17 to 0.28)I2 = 30% |
| at end of follow-up | SMDg = 0.07 (-0.10 to 0.24)I2 = 16% |
| Bannuru *et al.* 2015 (29) | Other options | Pain change from BL at M3 | *vs* IA placebo:SMDg = 0.34 (0.26 to 0.42)\* | Positive |
| *vs* oral placebo:SMDg = 0.63 (0.39 to 0.88)\* |
| Function change from BL at M3 | *vs* IA placebo:SMDg = 0.30 (0.20 to 0.40)\* |
| *vs* oral placebo:SMDg = 0.45 (0.08 to 0.84)\* |
| Richette *et al.* 2015 (30) | IA placebo | Pain at W12 | SMD = 0.20 (0.12 to 0.29)I2 = 32% | Positive |
| Function at W12 | SMD = 0.12 (0.02 to 0.22)I2 = 0% |

Positive effect sizes favor IAHA, negative effect sizes favor comparator.

\* 95% credible interval (CrI)
BL = baseline; CI = confidence interval; CS = corticosteroid; ES = effect size; HA = hyaluronic acid; hylan = hylan G‑F 20, IA = intra-articular; M = month; MD = mean difference; MPD = mean percent difference; MW = molecular weight; SMD = standardized mean difference; SMDg = standardized mean difference adjusted for small sample size (Hedges’ g); VAS = visual analogue scale; W = week; WMD = weighted mean difference

**Table 2 Recommendations for the use of intra-articular hyaluronic acid in the management of knee osteoarthritis**

|  |  |
| --- | --- |
| **Organisation(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 severly 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, co-morbidities and preferences (based on an uncertain appropriateness)(3). |

AAOS = American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; 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

**Table 3 Pharmacoeconomic studies evaluating the cost-effectiveness of intra-articular hyaluronic acid 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\* | USA | 3 years | Synvisc® +AC *vs* AC | NA | Dominant |
| Torrance *et al.* 2002 (66) | RCT (74) | Canada | 12 months | Synvisc® +AC *vs* AC | NA | CAN$10,000 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 | US$1538 per QALY | US$42,000 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) | Retrospec-tive (75) | Thailand | 2 years | Hyalgan® +AC *vs* AC | NA | NA |
| Chou *et al.* 2009 (71)  | Cohort (71) | Taiwan | 6 months | Synvisc®*vs* CC (BL) | NT$299,456 per QALY | NA |
| Artz®*vs* CC (BL) | NT$394,021 per QALY | NA |
| Miller & Block 2014 (72) | Cohort (76) | USA | 2 years | Registered IA-HA*vs* CC\* | US$12,800 per QALY | <US$23,400 per QALY |
| Hatoum *et al.* 2014 (73) | RCTs (77,78) | USA | 12 months | Euflexxa®*vs* CC (BL) | US$21,281 per QALY | Dominant |
| Hatoum *et al.* 2014 (73) | RCTs (74,77,78) | USA | 12 months | Euflexxa®*vs* AC | US$8,816 per QALY | US$38,741 per QALY |

NT$1 = US$0.0315 (2008 change)

\* hypothetical

AC = appropriate care (*e.g.*, non-pharmacological therapy, NSAIDs, analgesics, corticosteroids, total knee arthroplasty); BL = baseline; CC = conventional care (*i.e.*, non-pharmacological therapy, NSAIDs, analgesics); ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life year; RCT = randomized controlled trial