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Guidelines in Comparison

IAHA Therapy

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International Symposium Intra Articular Treatment

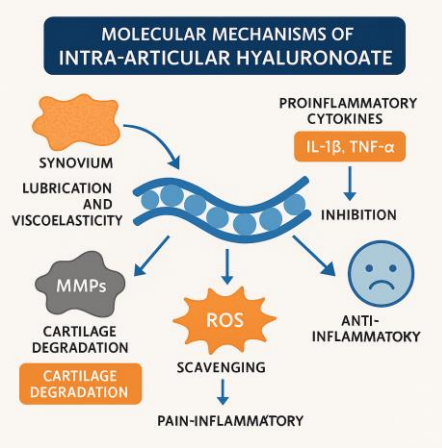
Various orthopedic and rheumatologic associations include or discuss intra-articular hyaluronate (IAHA) as a treatment option for osteoarthritis when nonpharmacological and primary pharmacological therapies are ineffective.

HA injections aim to restore the viscoelastic properties of synovial fluid, relieve pain, improve joint function, and potentially delay surgeries such as total joint arthroplasty (TJA).

The IAHA application guidelines and recommendations are based on updated systematic reviews and clinical practice guidelines.

Mechanism	Key Molecular Interactions	Signaling Pathways Involved	Functional Outcome
Synovial Fluid Viscosity	-HA supplementation increases the concentration and size of HA molecules in the synovial fluid	-Primarily physical effects (no direct signaling)	-Improved joint lubrication, shock absorption, and smoother movement
Chondroprotection	-Formation of HA–aggrecan complexes via linking proteins	-Activation of CD44 leading to MAPK/ERK and PI3K/Akt pathways	-Enhanced ECM synthesis, cartilage repair, and protection against enzymatic degradation
Anti-inflammatory Effects	-HA binding to receptors (CD44, RHAMM, TLRs)	-Inhibition of NF-κB and suppression of TLR-mediated pathways	-Reduced production of proinflammatory cytokines (e.g., IL-1β, TNF-α) and decreased joint inflammation
Antioxidant Activity	-Direct scavenging of reactive oxygen species (ROS) via HA's hydroxyl groups	-Upregulation of antioxidant enzymes via CD44-mediated signaling	-Reduced oxidative stress; protection of chondrocytes and preservation of ECM integrity
Bone Remodeling	-Modulation of osteoblast and osteoclast activities	-Regulation via RANKL/OPG balance and Wnt/β-catenin signaling	-Maintenance of subchondral bone integrity and balanced bone remodeling

HA's molecular mechanisms in OA



Rationale for IAHA underscored in recommendations

Objectives of the Umbrella Review

focused on evaluating the use of IAHA in cases of osteoarthritis (mainly KOA), paying particular attention to the diversity and timeline of guidelines and recommendations for their use.

Glinkowski WM, Tomaszewski W. Intra-Articular Hyaluronic Acid for Knee Osteoarthritis: A Systematic Umbrella Review. J Clin Med. 2025 Feb 14;14(4):1272. doi: 10.3390/jcm14041272.

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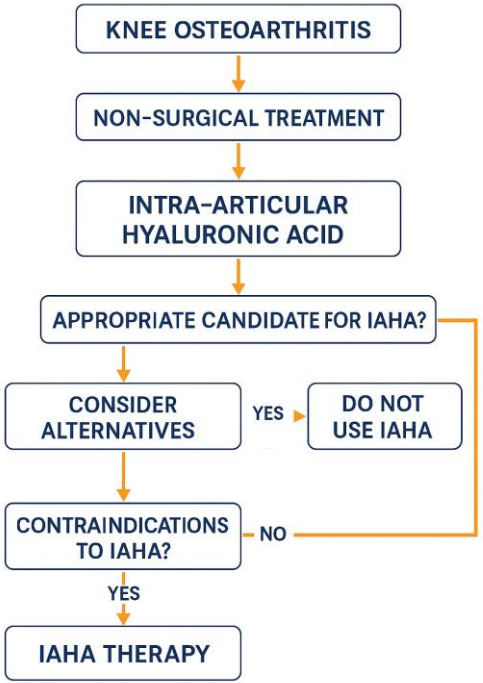
DECISION FLOWCHART FOR IAHA USE



Guidelines
and
Recommendations

- The development of guidelines and recommendations currently uses the GRADE methodology in most cases.
- The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) provides a transparent approach to rating the strength of evidence and certainty in recommendations for any given clinical question.
- GRADE rates the complete body of evidence on a given clinical question.
- An update is mandatory.

Migliore, A.; Bizzi, E.; Herrero-Beaumont, J.; Petrella, R.J.; Raman, R.; Chevalier, X. The discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis: Mind the gap! Eur. Rev. Med. Pharmacol. Sci. 2015, 19, 1124–1129.

The Osteoarthritis Research Society International (OARSI)

- Conditionally recommends IAHA for KOA, especially for patients who do not respond to other treatments such as NSAIDs or physical therapy.
- Part of a multimodal approach when first-line therapy fails.
- Recognizes heterogeneity of clinical responses based on patient phenotype and disease stage.

Bannuru, R.R.; Osani, M.C.; Vaysbrot, E.E.; Arden, N.K.; Bennell, K.; Bierma-Zeinstra, S.M.A.; Kraus, V.B.; Lohmander, L.S.; Abbott, J.H.; Bhandari, M.; et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr. Cartil. 2019, 27, 1578–1589.

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO)

- supports IAHA as a second-line treatment for KOA, mainly when NSAIDs are ineffective or contraindicated.
- for pain relief and functional improvement in OA's early-to-moderate stages.
- **ESCEO** advocates for IAHA as a core part of OA management, particularly in early-to-moderate disease stages.
- ESCEO endorses IAHA because of its dual benefits of symptom relief and chondroprotection.

Bruyère, O.; Honvo, G.; Veronese, N.; Arden, N.K.; Branco, J.; Curtis, E.M.; Al-Daghri, N.M.; Herrero-Beaumont, G.; MartelPelletier, J.; Pelletier, J.P.; et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin. Arthritis Rheum. 2019, 49, 337–350

American Academy of Orthopaedic Surgeons (AAOS)

- AAOS strongly advises against the routine use of IAHA for KOA and HOA due to inconsistent evidence of its benefits.
- However, IAHA may be appropriate for only specific and selected patient populations that do not respond to other treatments.
- Cites limited clinical benefit and stringent thresholds.

Brophy, R.H.; Fillingham, Y.A. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. J. Am. Acad. Orthop. Surg. 2022, 30, e721–e729.

The American College of Rheumatology (ACR) and Arthritis Foundation (A.F.)

- conditionally recommend using IAHA for KOA, citing mixed evidence of its efficacy. Although IAHA may offer benefits, it is often modest and inconsistent, making it less favorable than other corticosteroid treatments
- **ACR** provides conditional recommendations for IAHA use in select patients, particularly those who fail to respond to other non-surgical options such as NSAIDs and physical therapy.
- emphasizes individualized decision making based on patient-specific factors

Kolasinski, S.L.; et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of theHand, Hip, and Knee. Arthritis Care Res. 2020, 72, 149–162.

Canadian evidence-based perspective

- Outcomes - consistent and statistically significant improvements in pain, function, and stiffness up to 26 weeks with IAHA therapy compared with IA placebo or controls, regardless of trial size or quality.
- Overall outcomes based on IAHA show significantly improved pain outcomes for HMW compared with lower MW HAs.
- IAHA therapy is well tolerated with no increased risk of serious adverse events compared with placebo and the full therapeutic effect of IAHA therapy appears to have considerable clinical importance, consisting of the combined IA placebo and HA therapeutic effects.
- IAHA therapy is a well-tolerated and effective option for patients with mild-to-moderate knee OA failing first-line pharmacological therapy.

Bhandari M, Bannuru RR, Babins EM, Martel-Pelletier J, Khan M, Raynauld JP, Frankovich R, Mcleod D, Devji T, Phillips M, Schemitsch EH, Pelletier JP. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. Ther Adv Musculoskelet Dis. 2017 Sep;9(9):231-246. doi: 10.1177/1759720X17729641. Epub 2017 Sep 12. Erratum in: Ther Adv Musculoskelet Dis. 2017 Nov;9(11):295. doi: 10.1177/1759720X17740505. PMID: 28932293; PMCID: PMC5600311.

The International Cartilage Regeneration and Joint Preservation Society (ICRS)

- The ICRS does not explicitly endorse the use of intra-articular hyaluronic acid (IAHA) for early and moderate osteoarthritis (OA) regarding specific claims concerning the maintenance of joint health, slowing cartilage degradation, and delaying surgical interventions.

- The ICRS provides guidance on the use of orthobiology in the treatment of articular cartilage damage.

Chilan Bou Ghosson Leite, Gergo Merkely, Christian Lattermann, Simon Görtz, ICRS virtual convention 2021: Orthoregenerative therapy from basic science to clinical application, Journal of Cartilage & Joint Preservation,
Volume 1, Issue 3, 2021, 100024, ISSN 2667-2545, https://doi.org/10.1016/j.jcjp.2021.100024

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The International Symposium on Intra-Articular Treatment (ISIAT)

- recommends IAHA for mild-to-moderate KOA, highlighting innovative products that significantly and sustainably improve pain, joint function, and quality of life.
- Supports innovation and patient-tailored treatment.
- The ISIAT emphasizes the need for further research on patient selection criteria and treatment protocols to tailor IAHA treatment to individual patients and to optimize outcomes

Migliore A, Maheu E, Saccone L, de Campos GC, Alekseeva L, Chevalier X, Conrozier T, Crimaldi S, Diracoglu D, Herrero-Beaumont G, Iolascon G, Ionescu R, Jerosch J, Laíns J, Makri S, Martusevich N, Matucci Cerinic M, Pavelka K, J Petrella R, Tarantino U, R Bannuru R. What We Should Expect from an Innovative Intra-Articular Hyaluronic Acid Product: Expert Opinion Based on a Comprehensive Review of the Literature. J Clin Med. 2023 Nov 30;12(23):7422. doi: 10.3390/jcm12237422. PMID: 38068476; PMCID: PMC10707195

The European League Against Rheumatism (EULAR)

- Does not explicitly endorse or reject IAHA.
- Promotes individualized care and careful patient selection, noting the variability in treatment responses.
- Provides general guidance on intraarticular therapies but does not explicitly endorse or reject IAHA for KOA.

Uson, J.; Rodriguez-García, S.C.; Castellanos-Moreira, R.; O'Neill, T.W.; Doherty, M.; Boesen, M.; Pandit, H.; Möller Parera, I.; Vardanyan, V.; Terslev, L.; et al. EULAR recommendations for intra-articular therapies. Ann. Rheum. Dis. 2021, 80, 1299–1305.

The American Medical Society for Sports Medicine (AMSSM)

- Supports IAHA for active patients and athletes.
- Highlights use to manage symptoms and delay surgery.

Trojian, T.H.; Concoff, A.L.; Joy, S.M.; Hatzenbuehler, J.R.; Saulsberry, W.J.; Coleman, C.I. AMSSM Scientific Statement Concerning Viscosupplementation Injections for Knee Osteoarthritis: Importance for Individual Patient Outcomes. Clin. J. Sport Med. 2016, 26, 1–11

The Italian Society of Orthopaedic Surgery (SIOT)

- Supports IAHA, especially in combination with PRP.
- Recognizes long-term safety profile and potential benefits in delaying surgical intervention

Pesare, E.; Vicenti, G.; Kon, E.; Berruto, M.; Caporali, R.; Moretti, B.; Randelli, P.S. Italian Orthopaedic and Traumatology Society (SIOT) position statement on the non-surgical management of knee osteoarthritis. J. Orthop. Traumatol. 2023, 24, 47.

The French Rheumatology Society

- recommends IAHA for OA, particularly for symptom relief, without expecting chondroprotective effects.
- IAHA is appropriate in patients with symptomatic KOA with no or minimal effusion

Sellam, J.; Courties, A.; Eymard, F.; Ferrero, S.; Latourte, A.; Ornetti, P.; Bannwarth, B.; Baumann, L.; Berenbaum, F.; Chevalier, X.; et al. Recommandations de la Société française de rhumatologie sur la prise en charge pharmacologique de la gonarthrose. Rev.Du Rhum. 2020, 87, 439–446.

The Chinese Guidelines for Osteoarthritis

- Recommends IAHA for persistent/moderate-severe KOA pain.
- Aims to improve symptoms and delay arthroplasty.

Zhang Z, Huang C, Jiang Q, Zheng Y, Liu Y, Liu S, Chen Y, Mei Y, Ding C, Chen M, Gu X, Xing D, Gao M, He L, Ye Z, Wu L, Xu J, Yang P, Zhang X, Zhang Y, Chen J, Lin J, Zhao L, Li M, Yang W, Zhou Y, Jiang Q, Chu CQ, Chen Y, Zhang W, Tsai WC, Lei G, He D, Liu W, Fang Y, Wu D, Lin J, Wei CC, Lin HY, Zeng X. Guidelines for the diagnosis and treatment of osteoarthritis in China (2019 edition). Ann Transl Med. 2020 Oct;8(19):1213. doi: 10.21037/atm-20-4665. PMID: 33178745; PMCID: PMC7607097.

The South African Rheumatism and Arthritis Association (SARAA)

- supports VS, particularly UHMW HA formulations, for KOA in patients requiring sustained relief
- and
- aiming to delay surgical interventions

Rangiah, S.; Govender, I.; Badat, Z. A primary care approach to the management of Arthritis. S. Afr. Fam. Pract. 2020, 62, e1–e7.

The Brazilian Society of Orthopaedics and Traumatology (SBOT)(Brazil)

- advocates using UHMW HAs for extended joint lubrication and pain relief in patients with OA

Eyles, J.P.; Sharma, S.; Telles, R.W.; Namane, M.; Hunter, D.J.; Bowden, J.L. Implementation of Best-Evidence Osteoarthritis Care: Perspectives on Challenges for, and Opportunities From, Low and Middle-Income Countries. *Front. Rehabil. Sci.* **2021**, *2*, 826765

Korean Guidelines

- Support conditional use when other interventions fail.

Park, J.G.; Sim, J.; Han, S.B. Association between intra-articular hyaluronic acid injections in delaying total knee arthroplasty and safety evaluation in primary knee osteoarthritis: Analysis based on Health Insurance Review and Assessment Service (HIRA) claim database in Republic of Korea. BMC Musculoskelet. Disord. 2024, 25, 706.

Spanish Society of Rheumatology

- Recommends VS with preference for UHMW HAs.
- Emphasizes long-term symptom relief and QoL.

Basallote, S.G.; Pulido Morillo, F.J.; Trigueros Carrero, J.A. Atención Primaria de Calidad Guía de Buena Práctica Clínica en Artrosis 2ª EDICIÓN Actualizada, 2nd ed.; International Marketing & Communication, S.A.: Madrid, Spain, 2019; p. 88.

The Indian Rheumatology Association

- Supports IAHA use, recommends UHMW HA for sustained relief.

Misra, R.; Sharma, B.L.; Gupta, R.; Pandya, S.; Agarwal, S.; Agarwal, P.; Grover, S.; Sarma, P.; Wangjam, K. Indian Rheumatology Association consensus statement on the management of adults with rheumatoid arthritis. *Indian J. Rheumatol.* **2008**, *3*, S1–S16

Swiss Society of Rheumatology

- Cautious about routine IAHA use.
- Calls for individualized assessment and better evidence.

Ettlin, L.; Nast, I.; Huber, E.O.; Niedermann, K. Does the Conservative Non-pharmacological Management of Knee Osteoarthritis in Switzerland Reflect the Clinical Guidelines? A Survey Among General Practitioners, Rheumatologists, and Orthopaedic Surgeons. *Front. Rehabil. Sci.* **2021**, *2*, 658831.

German Orthopaedic Society (DGOU)

present cautious recommendations for IAHA, indicating potential benefits but emphasizing the need for more robust clinical trials to establish efficacy

Ossendorff, R.; Thimm, D.; Wirtz, D.C.; Schildberg, F.A. Methods of Conservative Intra-Articular Treatment for Osteoarthritis of the Hip and Knee. Dtsch. Arztebl. Int. 2023, 120, 575–581.

National Institute for Health and Care Excellence (NICE)

does not recommend VS as a routine treatment for OA due to a lack of apparent efficacy and cost-effectiveness data.

(NICE), National Institute for Health and Care Excellence. Osteoarthritis in over 16s: Diagnosis and Management. Available online

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2025 updates: IAHA evidence & practice

Umbrella review (J Clin Med 2025): IAHA shows moderate pain/function benefit mainly in early-to-moderate OA; safety favorable; guidelines remain split; call for harmonized methods and phenotype-based selection.

Network meta-analysis (Biomedicines 2025): High/ultra-high molecular weight HA ranks best for pain reduction at 4–6 months; low-MW performs similar to placebo-level.

EUROVISCO 2025 consensus: Scenario-based use; consensus in 18/30 cases; poorer response with obesity and advanced radiographic OA; consider symptoms, comorbidities, and alternatives.

Hip OA 2025 review (Current Pain & Headache Reports): IA injections (CS, HA, PRP, MSC) promising adjuncts; CS strongly supported for flares; HA as part of multimodal non-surgical strategy; evidence still evolving.

Key 2025 references

Migliorini F, Maffulli N, et al. Comparison of Different Molecular Weights of IA HA for Knee OA: Level I Bayesian Network Meta-Analysis. Biomedicines. 2025;13:175.

Monfort J, Henrotin Y, et al. EUROVISCO Good Medical Practice Recommendations for Viscosupplementation in KOA. Cartilage. 2025; DOI:10.1177/19476035241286578.

Li L, Dou X, et al. Current Status and Future Prospects of IA Injection Therapy for Hip OA. Curr Pain Headache Rep. 2025;29:64.

Glinkowski WM, Tomaszewski W. Intra-Articular Hyaluronic Acid for Knee Osteoarthritis: A Systematic Umbrella Review. J Clin Med. 2025;14:1272.

Patient phenotypes: IAHA candidate profiles

Phenotype / Clinical profile	IAHA: Favorable use	IAHA: Not recommended
Early–moderate KOA, pain not controlled by NSAIDs, contraindications to CS	✓ Good candidate	
High BMI, advanced radiographic OA		✗ Poor response
Inflammatory phenotype with effusion/synovitis	✓ Sometimes responsive, but less predictable	✗ If recurrent major effusion
Elderly with polypharmacy, NSAID intolerance	✓ Safe alternative	
Hip OA (adjunct, multimodal)	✓ Possible, evidence emerging	✗ Limited robust RCT support

Guideline positions on IAHA for OA

Guideline	Recommendation	Key notes / Conditions	Level of endorsement
AAOS (2021)	Do not recommend routine IAHA	Insufficient benefit vs cost	Strong against
NICE (UK, 2022)	Not recommended	Evidence not cost-effective	Strong against
OARSI (2019)	Conditional recommendation	Second-line if NSAIDs fail or contraindicated	Conditional
ESCEO (2019)	Recommended in specific patients	When topical/oral therapies inadequate or not tolerated	Conditional/positive
ACR (2019)	Conditional recommendation	Symptomatic KOA, limited options	Conditional
EUROVISCO (2025)	Scenario-based good practice	Consensus in 18/30 scenarios, avoid in obesity/advanced OA	Expert consensus

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IAHA in OA – Summary

Key Consensus:

IAHA is safe, best for early–moderate KOA
Use when NSAIDs/physio are insufficient or contraindicated
Patient selection is crucial (phenotypes matter)

Key Divergence:

AAOS/NICE: strong against routine use
OARSI/ESCEO/ACR: conditional recommendation
EUROVISCO: pragmatic, scenario-based consensus

Research Gaps:

Need standardized outcomes and harmonized trials
Clarify formulation/dose-response (HMW vs LMW)
Define responder phenotypes and biomarkers

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Thank you for your kind attention