SOCIETÀ ITALIANA
G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE
DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

Alberto Migliore Reumatologo ROMA

The definition of an innovative intra-articular product for OA

Centro Congressi Unione Industriali
TORINO 11-13 MAGGIO 2023

testo

Disclosure

Pfizer
IBSA
ABIOGEN PHARMA
Bristol Myers Squibb
AMGEN
Biogen
Lilly
NOVARTIS
abbvie
ALFASIGMA
SANDOZ
MSD
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Therapeutics and Clinical Risk Management

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EXPERT OPINION

It Is the Time to Think About a Treat-to-Target Strategy for Knee Osteoarthritis

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Abstract: Osteoarthritis (OA) is a rheumatic disea
patient, compromises physical and mental function, a
In the literature, several evidence-based guidelines a
ment of knee osteoarthritis (KOA) are available. The
therapeutic options rather than addressing a hierarchy
the real target. Therefore, a question arises: are pati
current management of KOA? Actually, the answe
a change in our therapeutic strategies. In this article, w
that it is time to develop a "treat to target strategy" f

Keywords: osteoarthritis, knee osteoarthritis, treat to

Therapeutic Advances in Musculoskeletal Disease

Original Research

Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

Alberto Migliore, Gianfranco Gigliucci, Liudmila Alekseeva, Sachin Avasthi, Raveendhara R Bannuru, Xavier Chevalier, Thierry Conrozier, Sergio Crimaldi, Nemanja Damjanov, Gustavo Constantino de Campos, Demirhan Diracoglu, Gabriel Herrero-Beaumont, Giovanni Iolascon, Ruxandra Ionescu, Natasa Isailovic, Jörg Jerosch, Jorge Lains, Emmanuel Maheu, Souzi Makri, Natalia Martusevich, Marco Matucci Cerinc, Mihaela Micu, Karel Pavelka, Robert J Petrella, Umberto Tarantino and Raghu Raman

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THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Early Osteoarthritis Questionnaire (EOAQ): a tool to assess knee osteoarthritis at initial stage

Alberto Migliore, Liudmila Alekseeva, Sachin R. Avasthi, Raveendhara R. Bannuru, Xavier Chevalier, Thierry Conrozier, Sergio Crimaldi, Gustavo C. de Campos, Demirhan Diracoglu, Gianfranco Gigliucci, Gabriel Herrero-Beaumont, Giovanni Iolascon, Ruxandra Ionescu, Jörg Jerosch, Jorge Lains, Emmanuel Maheu, Souz Makri, Natalia Martusevich, Marco Matucci-Cerinic, Karen Pavelka, Robert J. Petrella, Raghu Raman and Umberto Tarantino

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Krakow

7-9 October 2021

TEP 2021

"ideal characteristics required for the new intra-articular HA products"

We thank ABIOGEN PHARMA for the unconditional support for this TEP

Board members: ISIAT TEP 2021

Chevalier Xavier

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- Pavelka Karel
- Petrella Robert John
- Tarantino Umberto
- Raman Raghu
- Bannuru Raveendhara R.
- Crimaldi Sergio

The aim of this board is to produce an article suggesting:

The “ideal characteristics required for the new intra-articular HA products” in viscosupplementation

These ideal characteristics should solve the unmet needs of actual viscosupplements

Suggesting ideal features

Clinical characteristics

Differentiating compounds considering

- disease phenotype
- severity
- stage
- rapidity of progression
- disease extension

Symptomatic and structural effects
OA phenotype
OA severity

Age
Anathomical difference in OA
Origin of pain in OA
Comorbidity
Sport
Origin of pain in OA

Suggesting ideal features: Evaluating clinical efficacy

subjective outcome

- pain
- quality of life

Improve quality of life (mood, depression, stress
Patient expectations
Mood
Fatigue

objective outcomes

- joint mobility
- structural damage
- delay of arthrotplasty

Functionality
Mobility (sport, get up)
Muscle-power
walking distance

Suggesting ideal features

Technical characteristics

- Ideal number of injections for cycle
- Ideal number of cycles for the maintenance of effectiveness
- Duration of action
- Time to reach maximum effectiveness
- Chemical characteristics
- Syringe handling
- Optimal dosing
- Volume
- Time of interval between injection
- Articular half-life
- Syringe handling
- Disconfort by patient during injection
- Duration of action

Exploring the opportunity of combination of HA with other ancillary substances

In other words, may combinations help to achieve any of the above mentioned goals?

testo

The final goal should be to establish a large consensus on some statements about the ideal characteristics we need for new intra-articular products in the management of OA

We are searching for innovative products capable to solve unmet needs

We don’t need new products that are a “me too”

Methodology

TEP ISIAT

Step 1: Item generation

Items for "ideal characteristics for the new intra-articular HA products" will be generated in the following step process.

- The first step is to draw up, from an exhaustive review of the literature, a comprehensive list of items about limits and unmet needs in OA of knee;
- This list of items should be drawn up from studies, reviews and guidelines;

Methodology

Step 2: Item reduction

- ✓ The list of items will be discussed with the whole board to reformulate some of them, delete or subdivide others;
- ✓ The aim is to select the most pertinent items to include in the final list;
- ✓ Redundancy of items will be also taken into consideration throughout the item reduction process
- ✓ This meeting also will serve to define the layout of the statements

Final step

-Each statement will be voted (email contacts).

-Statements that will be support by ≥75% of votes will be accepted while those with ≤25% will be rejected.

-Items are subjected to further discussion and subsequent voting where ≥67% support or, in an eventual third round, a majority of ≥50% will be needed;

-Subsequently, the group will be vote on the level of agreement with each of the derived bullet points using a 10-point numerical rating scale (1=do not agree at all, 10=agree completely);

Reporting achievements of actual intra-articular treatment

The actual unmet needs of viscosupplementation

Suggesting ideal features that should define new products

SLR

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Unmet needs in viscosupplementation: towards the definition of an innovative intra-articular product for osteoarthritis

Barcelona, 17-18 December 2022

Systematic Litterature Review

Current achievements of viscosupplementation with IAHA for knee OA

Source:

Pubmed/MEDLINE

Web Of Science

Google Scholar

Study population:

Patients affected by knee OA treated with HA

Types of studies included:

full-text guidelines, meta-analyses, RCT and SLR published since 2000

Research questions:

Limitations of Viscosupplementation

Unmet needs in Viscosupplemetation

Key words

OA

Knee OA

Hyaluronic Acid

Ialuronate

Viscosupplement

Viscosupplementations

Limitations

Pain

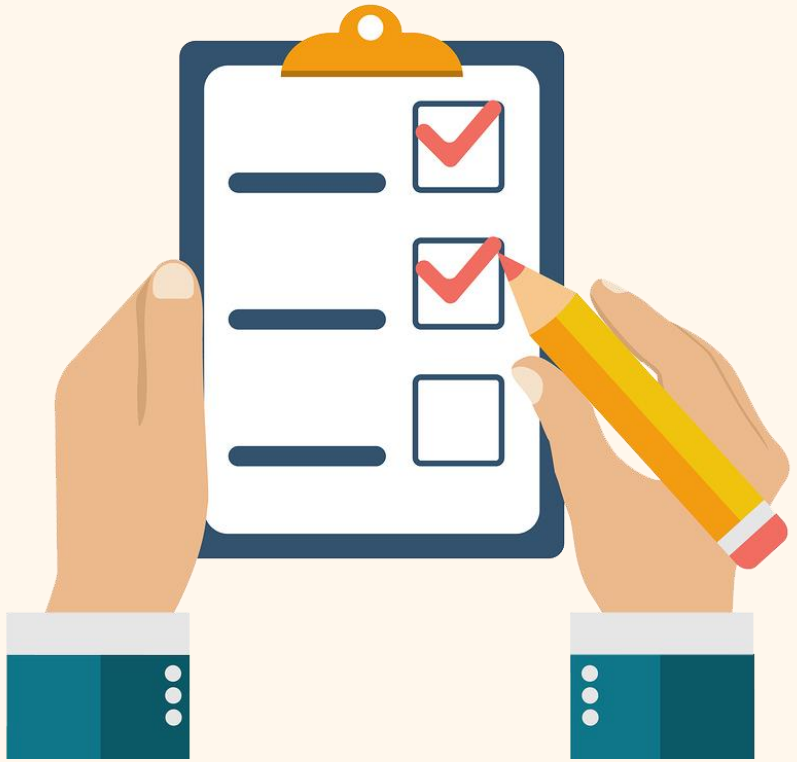
Function

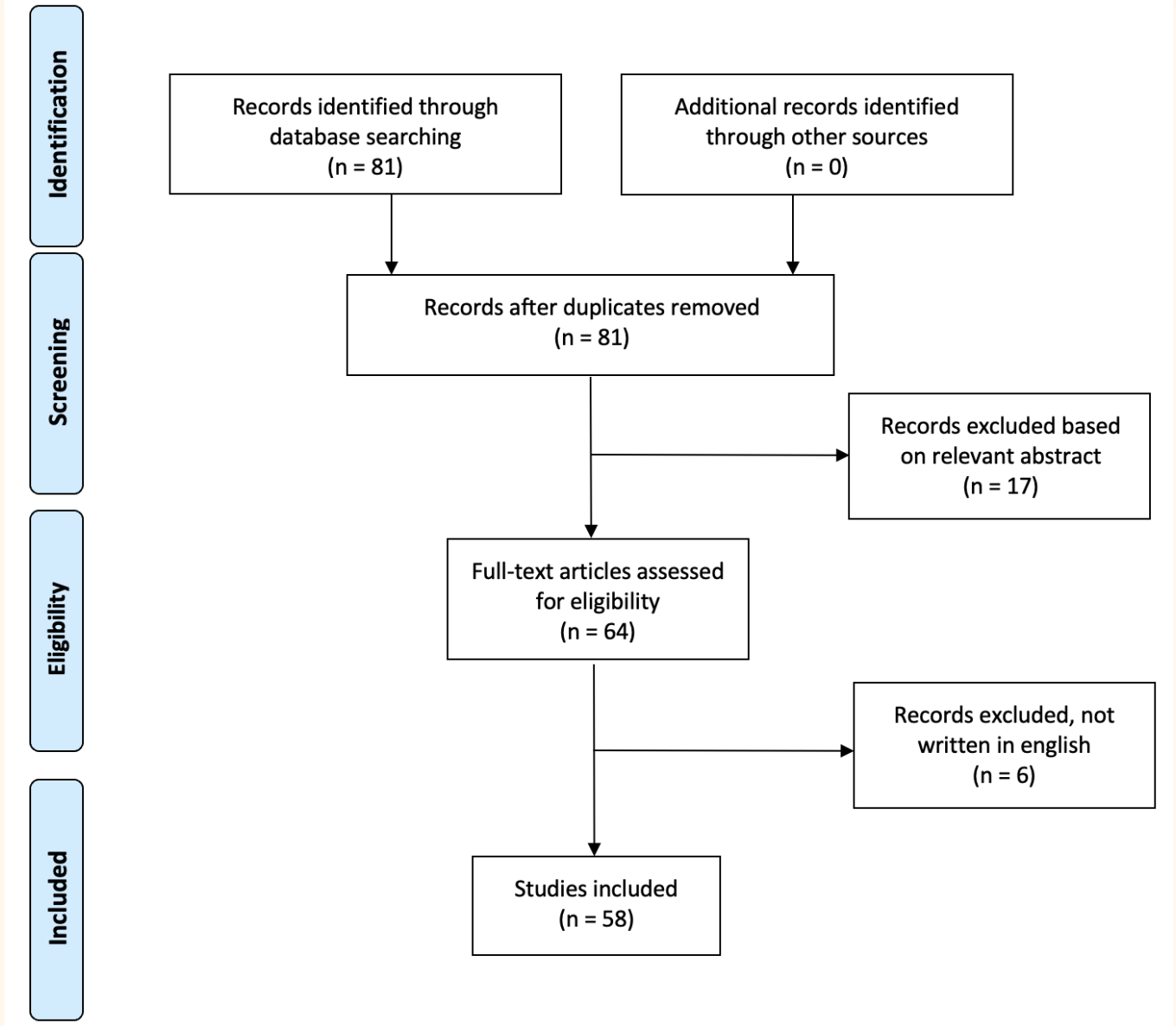
Mobility

Safety

Intrarticular therapy

Intrarticular injection




Identification
Screening
Eligibility
Included
Records identified through database searching (n = 81)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 81)
Records excluded based on relevant abstract (n = 17)
Full-text articles assessed for eligibility (n = 64)
Records excluded, not written in english (n = 6)
Studies included (n = 58)

Results

Studies included:

9 Guidelines

24 RCTs

25 SLR & meta-analyses

	Title	Authors	Publication Year	Key Findings
Guidelines				
1	Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline (3rd Edition). Published August 31, 2021.	American Academy of Orthopaedic Surgeons.	2021	Difference is most evident at 6 weeks and 3 months Worse results in patients with KL grade IV Improvements with HMW cross-linked not maintained when compared to MMW
2	2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee.	Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J.	2020	Limited evidence of benefit when other alternatives have been exhausted or failed to provide satisfactory benefit
3	OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis.	Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojian T, Underwood M, McAlindon TE.	2019	Beneficial effects on pain at and beyond 12 weeks of treatment More favorable long-term safety profile than repeated IACS
4	Arthroscopy Association of Canada Position Statement on Intra-articular Injections for Knee Osteoarthritis.	Arthroscopy Association of Canada, Kopka M, Sheehan B, Degen R, Wong I, Hiemstra L, Ayeni O, Getgood A, Beavis C, Volesky M, Outerbridge R, Matache B.	2019	HMW is likely more effective than LMW Highly cross-linked HA is likely more effective than non–cross linked HA Effects are most pronounced in mild to moderate disease and in the first 26 weeks after injection
5	AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes	Trojian TH, Concoff AL, Joy SM, Hatzenbuehler JR, Saulsberry WJ, Coleman CI.	2016	Decreased WOMAC pain and function scores compared to PBO KL grade II-III High quality evidence age >60 Moderate quality evidence age <60
6	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).	Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M; Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT.	2003	Pain relief may be obtained for several months Benefit may be offset by the slower onset of action and the requirement of 3-5 weekly injections Minimal evidence for a role in disease modification
7	A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis: An International Perspective.	Phillips M, Bhandari M, Grant J, Bedi A, Trojian T, Johnson A, Schemitsch E	2021	Review of 27 guidelines 10 (37%) strong for, 10 (37%) conditional for, 2 (7.4%) uncertain, 2 (7.4%) weak against, 3 (11.1%) strong against Trend toward positive recommendations over time (2003 to 2020)

Study Domains

REDUCTION OF PAIN

FUNCTION

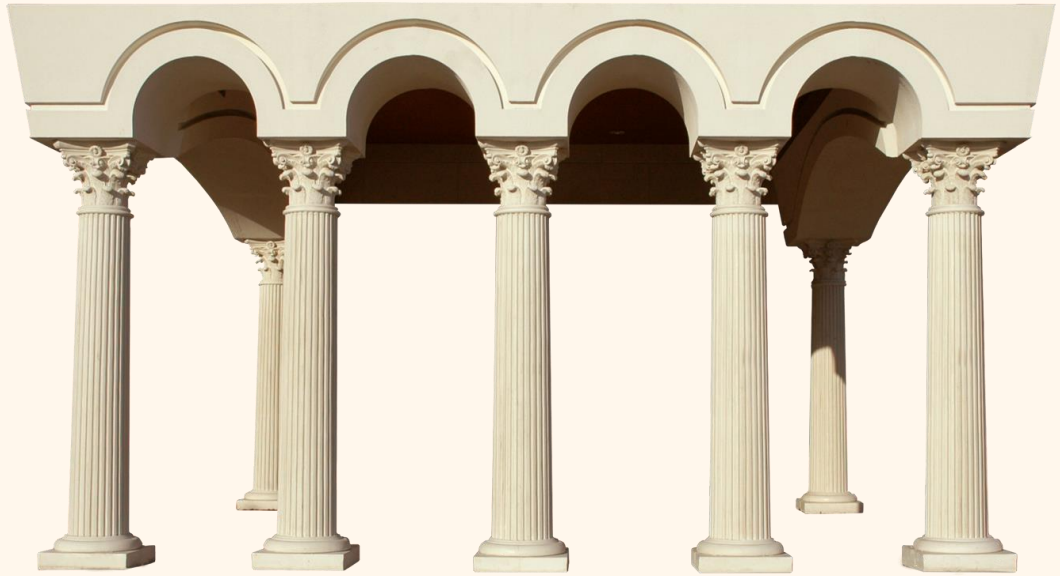
QUALITY OF LIFE

OMERACT/OARSI RESPONSE

TIME TO TOTAL KNEE ARTHROPLASTY

JOINT STRUCTURE AND INTEGRITY

ADVERSE EVENTS



PROPOSED STATEMENTS

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REDUCTION OF PAIN

Arthroscopy Association of C, Kopka M, Sheehan B, et al. Arthroscopy Association of Canada Position Statement on Intra-articular Injections for Knee Osteoarthritis. *Orthop J Sports Med*. 2019; 7(7): 2325967119860110.

Trojian TH, Concoff AL, Joy SM, et al. AMSSM scientific statement concerningviscosupplementation injections for knee osteoarthritis: Importance for individual patient outcomes. *Br J Sports Med*. 2016; 50(2): 84-92.

DeCaria JE, Montero-Odasso M, Wolfe D, Chesworth BM, Petrella RJ. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: A randomized, controlled study. *Arch Gerontol Geriatr*. 2012; 55(2):310-5.

Hermans J, Bierma-Zeinstra SMA, Bos PK, et al. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. *BMC Musculoskelet Disord*. 2019; 20(1): 196.

Nicholls M, Shaw P, Niazi F, Bhandari M, Bedi A. The impact of excluding patients with end-stage knee disease in intra-articular hyaluronic acid trials: A systematic review and meta-analysis. *Adv Ther*. 2019; 36(1): 147-161.

Bowman EN, Hallock JD, Throckmorton TW, Azar FM. Hyaluronic acid injections for osteoarthritis of the knee: predictors of successful treatment. *Int Orthop*. 2018; 42(4): 733-740.

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): 1-9.

Huang TL, Chang CC, Lee CH, et al. Intra-articular injections of sodium hyaluronate (Hyalgan(R) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord*. 2011; 12(221.

Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol*. 2006; 33(5): 951-6.

Petterson SC, Plancher KD. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: A multicenter, double-blind, randomized, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2019; 27(6): 1992-2002.

Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2012; 20(5): 350-356.

Takamura J, Seo T, Strand V. A single intra-articular injection of Gel-200 for treatment of symptomatic osteoarthritis of the knee is more effective than phosphate buffered saline at 6 months: A subgroup analysis of a multicenter, randomized controlled trial. *Cartilage*. 2019; 10(4): 417-422.

American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline (3rd Edition). 2021 August 31;

Jordan KM, Arden NK, Doherty M, 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). Ann Rheum Dis. 2003; 62(12): 1145-55.

Mojica ES MD, Hurley ET, Blaeser AM, Jazrawi LM, Campbell KA, Strauss EJ. Estimated time to maximum medical improvement of intra-articular injections in the treatment of knee osteoarthritis-a systematic review. Arthroscopy. 2022; 38(3): 980-988.e4.

Day R, Brooks P, Conaghan PG, Petersen M, Multicenter Trial G. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol. 2004; 31(4): 775-82.

Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. Semin Arthritis Rheum. 2018; 48(2): 168-175.

Navarro-Sarabia F, Coronel P, Collantes E, 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(11): 1957-62.

Pain improves 32-64% from baseline (in patients aged 40-80 with mild-to-moderate knee OA defined by baseline VAS ≥40 mm, Lequesne index ≥10, and Kellgren-Lawrence grade II-III) [2, 6, 9-12], and approximately half of patients achieve 50% improvement [13-18].

An innovative IAHA should improve pain by at least 70% as measured on VAS or WOMAC pain subscale in at least 70% of older adults with mild-to-moderate OA.

Patients under age 40 show the same magnitude of benefit as older patients [10, 15, 19, 20]

An innovative IAHA should improve pain by at least 70% as measured on VAS or WOMAC pain subscale in at least 70% of adults age >18 with mild-to-moderate OA.

Early pain evaluations show some improvement 4-6 weeks after injection [15-17, 22].

An innovative IAHA should improve pain within 1-2 weeks.

Maximum improvement is generally achieved at 8-12 weeks and remain sustained for at least 26 weeks, but lesser effect is seen by 52 weeks in some patients [1, 4, 10, 13, 14, 18-23].

An innovative IAHA should reach maximum effect on pain within 1-2 weeks, maintain the effect for at least 38 weeks, and wear off no earlier than 52 weeks.

Carryover effects from 3-4 additional injection cycles allows for continued beneficial effect on pain [24, 25].

Injection of an innovative IAHA should be repeated annually, with sustained benefit on pain up to 52 weeks per treatment cycle.

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FUNCTION

Huang TL, Chang CC, Lee CH, et al. Intra-articular injections of sodium hyaluronate (Hyalgan(R)) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. BMC Musculoskelet Disord. 2011; 12(221.

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(4): 276-81.

Gormeli G, Gormeli CA, Ataoglu B, et al. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017; 25(3): 958-965.

Maia PAV, Cossich VRA, Salles-Neto JI, Aguiar DP, de Sousa EB. Viscosupplementation improves pain, function and muscle strength, but not proprioception, in patients with knee osteoarthritis: A prospective randomized trial. Clinics (Sao Paulo). 2019; 74(e1207.

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): 1-9.

Day R, Brooks P, Conaghan PG, Petersen M, Multicenter Trial G. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol. 2004; 31(4): 775-82.

Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006; 26(4): 314-9.

Karlsson J, Sjogren 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(11): 1240-8.

Function/stiffness improves 40-56% from baseline on WOMAC subscales and 19% on IKDC score in adults of all ages with mild-to-moderate knee OA (KL II-III) [14, 20, 21].

An innovative IAHA should improve function by at least 70% as measured on WOMAC subscales or at least 40% as measured on IKDC score in adults with mild-to-moderate OA.

Early function/stiffness evaluations show some improvement 4-6 weeks after injection [21, 26].

An innovative IAHA should improve function within 1-2 weeks.

Improvement in function/stiffness can be maintained for up to 9-12 months [13, 14, 20, 23, 27, 28].

An innovative IAHA should maintain effect on function for at least 52 weeks.

Carryover effects from 3-4 additional injection cycles allows for continued beneficial effect on function [25].

Injection of an innovative IAHA should be repeated annually, with sustained benefit on function up to 52 weeks per treatment cycle.

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QUALITY OF LIFE

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): 1-9.

Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006; 33(5): 951-6.

Gormeli G, Gormeli CA, Ataoglu B, et al. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017; 25(3): 958-965.

Navarro-Sarabia F, Coronel P, Collantes E, 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(11): 1957-62.

Hangody L, Szody R, Lukasik P, et al. Intraarticular injection of a cross-linked sodium hyaluronate combined with triamcinolone hexacetonide (Cingal) to provide symptomatic relief of osteoarthritis of the knee: A randomized, double-blind, placebo-controlled multicenter clinical trial. Cartilage. 2018; 9(3): 276-283.

QoL tools (OARSI global assessment, SF-36, and EuroQoL) show that most adults of all ages with mild-to-moderate knee OA (KL II-III) can achieve at least 20% improvement [13, 15, 21, 25].

An innovative IAHA should improve QoL by at least 30-50% on OARSI global assessment, SF-36, or EuroQoL scales in adults with mild-to-moderate OA.

Improvement in QoL can be seen at 3 months and maintained for up to 9-12 months [15, 21, 29].

An innovative IAHA should maintain effect on QoL for at least 52 weeks.

Carryover effects from 3-4 additional injection cycles allows for continued beneficial effect on QoL [25].

Injection of an innovative IAHA should be repeated annually, with sustained benefit on QoL up to 52 weeks per treatment cycle.

OMERACT/OARSI RESPONSE

Karlsson J, Sjogren 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(11): 1240-8.

Trojian TH, Concoff AL, Joy SM, et al. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: Importance for individual patient outcomes. Br J Sports Med. 2016; 50(2): 84-92.

Hermans J, Bierma-Zeinstra SMA, Bos PK, et al. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. BMC Musculoskelet Disord. 2019; 20(1): 196.

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): 1-9

Navarro-Sarabia F, Coronel P, Collantes E, 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(11): 1957-62.

OMERACT- OARSI set of responder criteria

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High improvement in pain or in function ≥50%
and absolute change ≥20

↙ Yes ⇩ Response

↘ No ⇩

Improvement in at least 2 of the 3 following:

- pain ≥20% and absolute change ≥10
- function ≥20% and absolute change ≥10
- patient's global assessment ≥20% and absolute change ≥10

↙ Yes ⇩ Response

↘ No ⇩ No Response

Most adults with mild-to-moderate knee OA (KL II-III) can be classified as OMERACT/OARSI responders at weeks 12-26 [6, 10, 13].

An innovative IAHA should yield OMERACT/OARSI response in all patients with mild-to- moderate knee OA within 1-2 weeks.

Rates of OMERACT/OARSI response improve over time [6, 10, 13] and carryover effects from additional injection cycles allows for continued beneficial effect up to 40 months and potentially further increase response rates [25].

An innovative IAHA should yield increasing OMERACT/OARSI response rates over time, with sustained response up to 52 weeks per treatment cycle.

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TIME TO TKA

Berkani S, Courties A, Eymard F, et al. Time to total knee arthroplasty after intra-articular hyaluronic acid or platelet-rich plasma injections: A systematic literature review and meta-analysis. J Clin Med. 2022; 11(14).
Ong KL, Anderson AF, Niazi F, et al. Hyaluronic acid injections in Medicare knee osteoarthritis patients are associated with longer time to knee arthroplasty. J Arthroplasty. 2016; 31(8): 1667-73.
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(12): e0145776.
Concoff A, Niazi F, Farrokhyar F, et al. Delay to TKA and costs associated with knee osteoarthritis care using intra-articular hyaluronic acid: Analysis of an administrative database. Clin Med Insights Arthritis Musculoskelet Disord. 2021; 14(1179544121994092.
Shewale AR, Barnes CL, Fischbach LA, et al. Comparison of low-, moderate-, and high-molecular-weight hyaluronic acid injections in delaying time to knee surgery. J Arthroplasty. 2017; 32(10): 2952-2957 e21.
Dasa V, Lim S, Heeckt P. Real-world evidence for safety and effectiveness of repeated courses of hyaluronic acid injections on the time to knee replacement surgery. Am J Orthop (Belle Mead NJ). 2018; 47(7).

Patients treated with IAHA show prolonged time from diagnosis to TKA, with a 9- to 12-month delay until surgery [30-34]. Administrative claims databases show that at least 90% of patients receiving at least 5 courses of IAHA showed prolonged time to TKA to at least 3 years after diagnosis, and that increased benefit is seen with each successive course of treatment [32, 33, 35].

An innovative IAHA should delay time to arthroplasty by at least 52 weeks in patients with KL IV OA and indefinitely in patients with KL II-III OA.

JOINT STRUCTURE AND INTEGRITY

Conrozier T, Balblanc JC, Richette P, et al. Early effect of hyaluronic acid intra-articular injections on serum and urine biomarkers in patients with knee osteoarthritis: An open-label observational prospective study. J Orthop Res. 2012; 30(5): 679-85.

Henrotin Y, Bannuru R, Malaise M, et al. Hyaluronan derivative HYMOVIS(R) increases cartilage volume and type ii collagen turnover in osteoarhritic knee: data from MOKHA study. BMC Musculoskelet Disord. 2019; 20(1): 293.

Ishijima M, Nakamura T, Shimizu K, et al. Different changes in the biomarker C-terminal telopeptides of type II collagen (CTX-II) following intra-articular injection of high molecular weight hyaluronic acid and oral non-steroidal anti-inflammatory drugs in patients with knee osteoarthritis: A multi-center randomized controlled study. Osteoarthritis Cartilage. 2022; 30(6): 852-861.

Deberg MA, Labasse AH, Collette J, et al. One-year increase of Coll 2-1, a new marker of type II collagen degradation, in urine is highly predictive of radiological OA progression. Osteoarthritis Cartilage. 2005; 13(12): 1059-65.

Altman R, Bedi A, Manjoo A, et al. Anti-inflammatory effects of intra-articular hyaluronic acid: A systematic review. Cartilage. 2019; 10(1): 43-52.

Urine and serum biomarkers of collagen degradation indicative of increased cell turnover potentially indicate improved joint structure and integrity [36-38] and predict long-term radiologic progression [37, 39].

An innovative IAHA alone or in combination with steroid should increase collagen turnover.

HMW IAHA has been shown to promote anti-inflammatory responses and suppress pro-inflammatory cytokines [40], potentially improving joint integrity.

An innovative IAHA alone or in combination with steroid should reduce joint inflammation.

SOCIETÀ ITALIANA G.U.I.D.A.
PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

ADVERSE EVENTS

Miller LE, Fredericson M, Altman RD. Hyaluronic acid injections or oral nonsteroidal anti-inflammatory drugs for knee osteoarthritis: Systematic review and meta-analysis of randomized trials. Orthop J Sports Med. 2020; 8(1): 2325967119897909.
Concoff A, Sancheti P, Niazi F, Shaw P, Rosen J. The efficacy of multiple versus single hyaluronic acid injections: A systematic review and meta-analysis. BMC Musculoskelet Disord. 2017; 18(1): 542.
McElheny K, Toresdahl B, Ling D, Mages K, Asif I. Comparative effectiveness of alternative dosing regimens of hyaluronic acid injections for knee osteoarthritis: A systematic review. Sports Health. 2019; 11(5): 461-466.
Miller LE, Bhattacharyya S, Parrish WR, et al. Safety of intra-articular hyaluronic acid for knee osteoarthritis: Systematic review and meta-analysis of randomized trials involving more than 8,000 patients. Cartilage. 2021; 13(1_suppl): 351S-363S.

A total of 6% of patients report local skin reaction and 12% report injection-site pain with IAHA compared to 8% and 5%, respectively, with oral NSAIDs [41].

An innovative IAHA should be associated with fewer than 5% of patients experiencing injection-site adverse events.

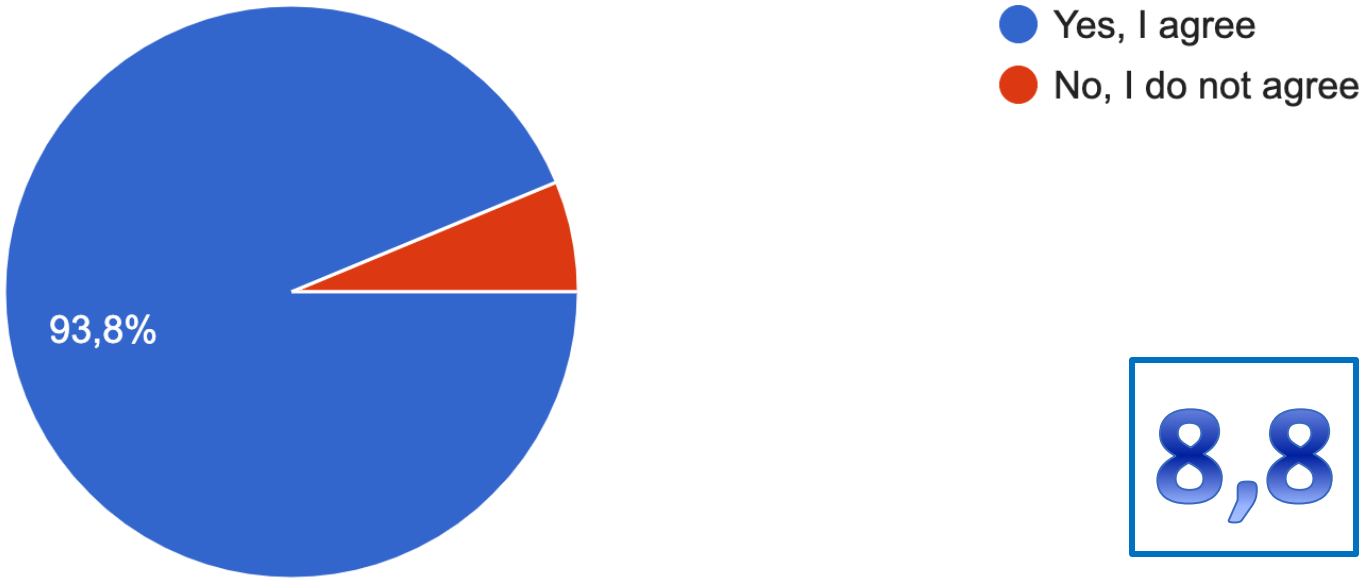
Treatment regimens requiring 1-3 injections have been associated with fewer adverse events overall than did regiments requiring ≥5 injections weekly [41, 42], although other studies show no optimal number of injections [43, 44].

An innovative IAHA should be administerd once per year to minimize treatment-related adverse events.

Round 1

REDUCTION OF NOCICEPTIVE PAIN 1 An innovative IAHA should improve nociceptive pain by 50-70% as measured on NRS or WOMAC pain subscal...least 70% of patients with mild-to-moderate OA.

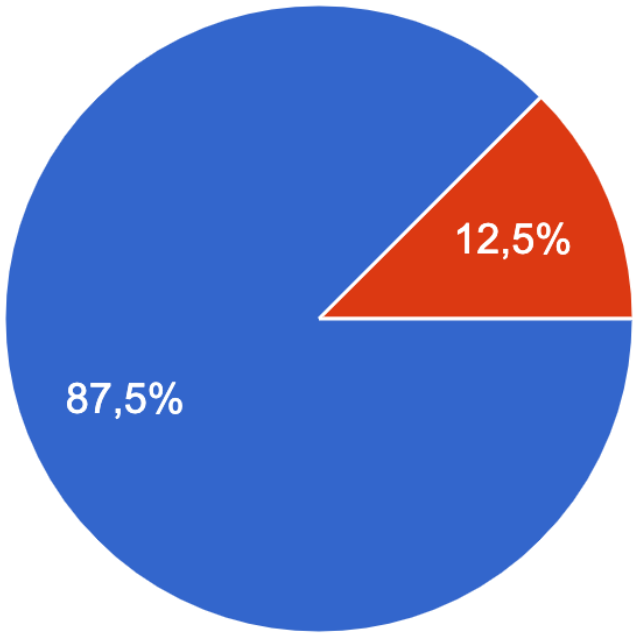
16 risposte



8,8

REDUCTION OF NOCICEPTIVE PAIN 2 An innovative IAHA should produce initial benefit on nociceptive pain within 1-2 weeks in at least 70% of patients with mild-to-moderate OA.

16 risposte



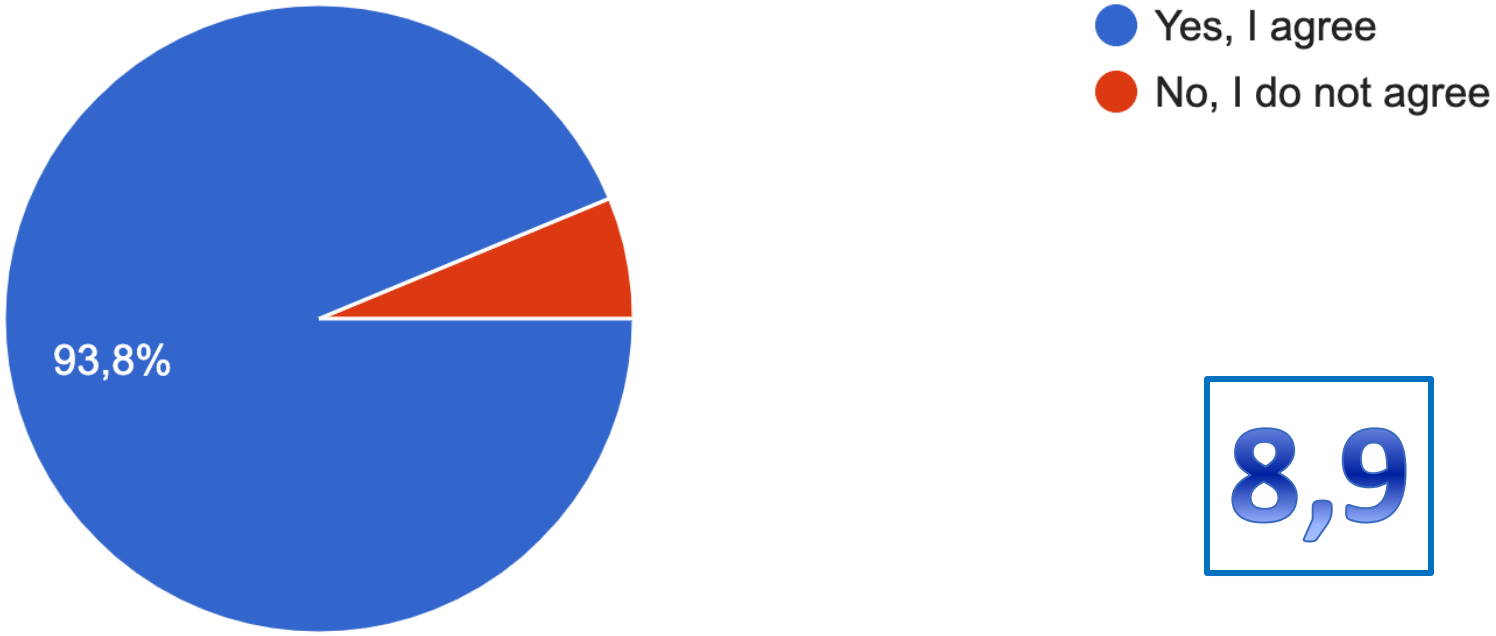
Yes, I agree

No, I do not agree

8,3

REDUCTION OF NOCICEPTIVE PAIN 3 An innovative IAHA should maintain beneficial effect on nociceptive pain for 9 to 12 months.

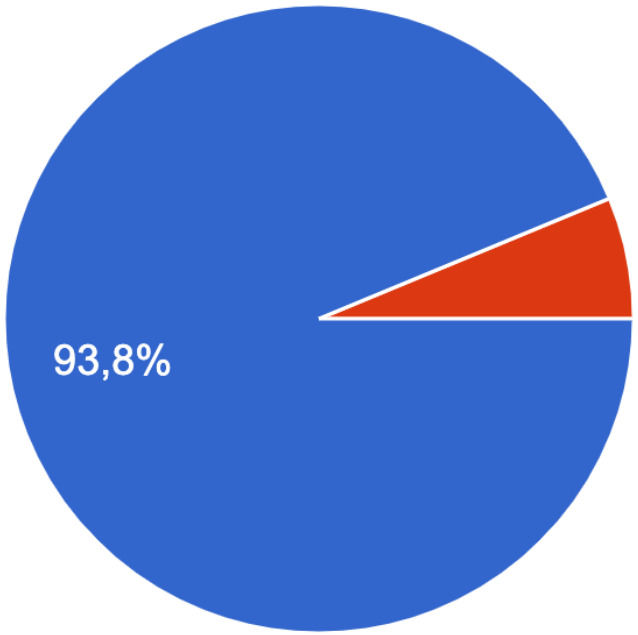
16 risposte



8,9

REDUCTION OF NOCICEPTIVE PAIN 4 Injection of an innovative IAHA should be repeated after 9 to 12 months if the patient again becomes symptomatic.

16 risposte



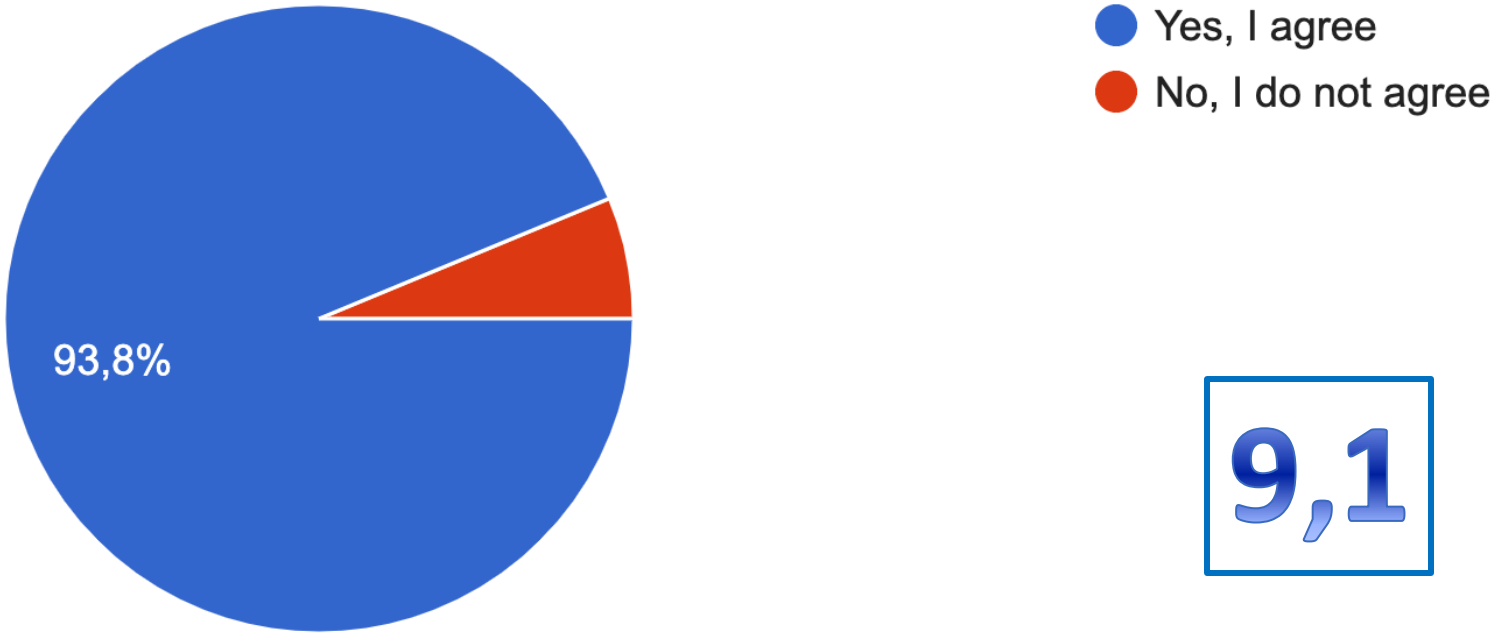
Yes, I agree

No, I do not agree

8,9

FUNCTION 5 An innovative IAHA should improve function between 50-70% as measured on WOMAC subscales and Lequesne index in patients with mild-to-moderate OA.

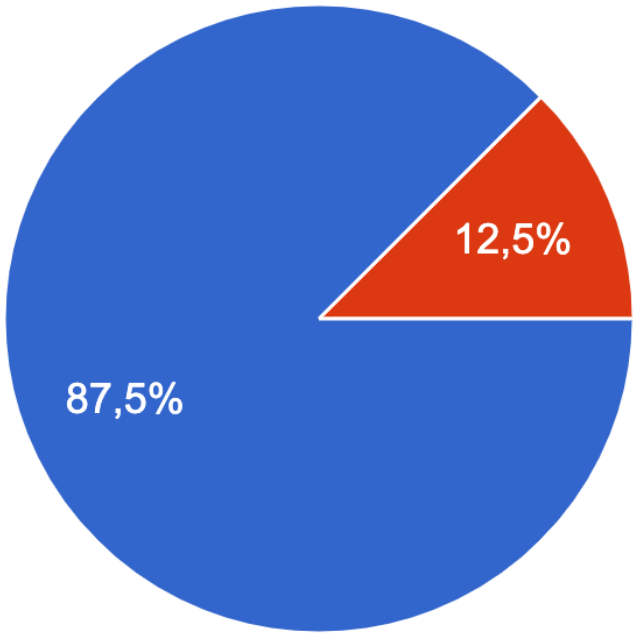
16 risposte



9,1

FUNCTION 6 An innovative IAHA should produce initial benefit on joint function within 1-2 weeks in at least 70% of patients.

16 risposte



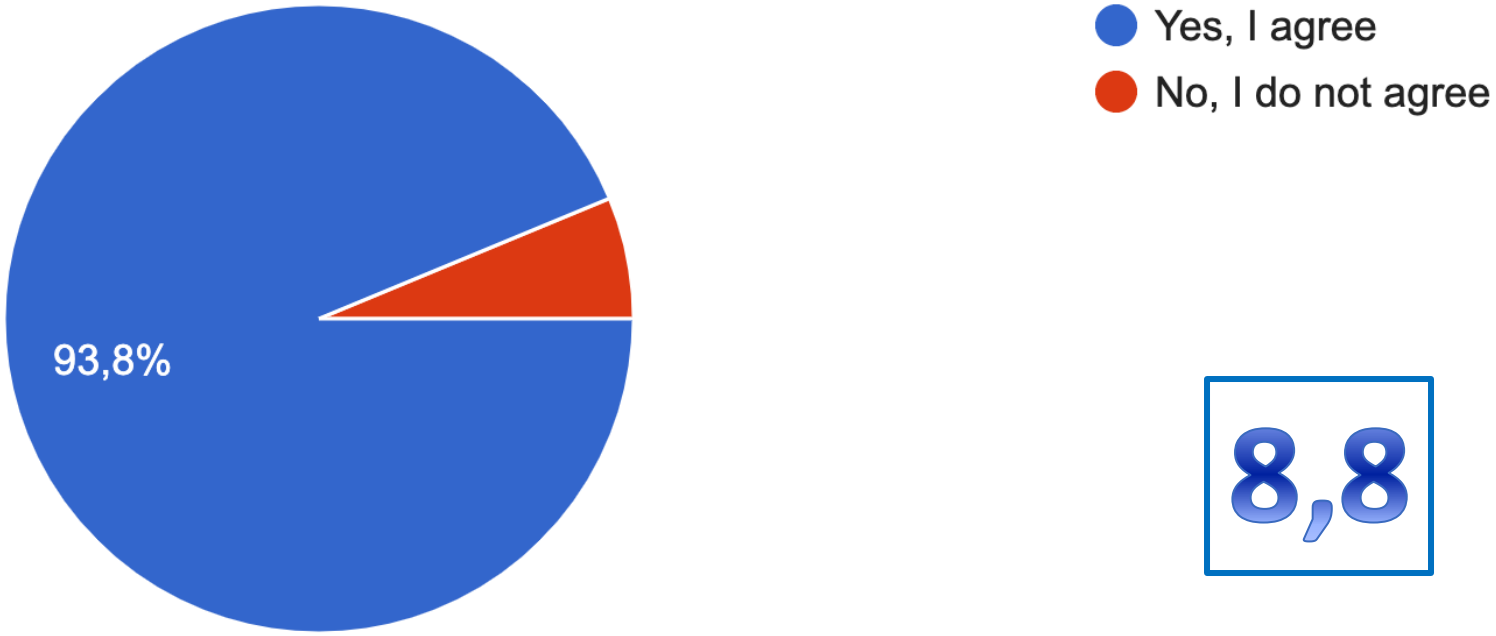
Yes, I agree

No, I do not agree

8,2

FUNCTION 7 An innovative IAHA should maintain beneficial effect on joint function for 9 to 12 months.

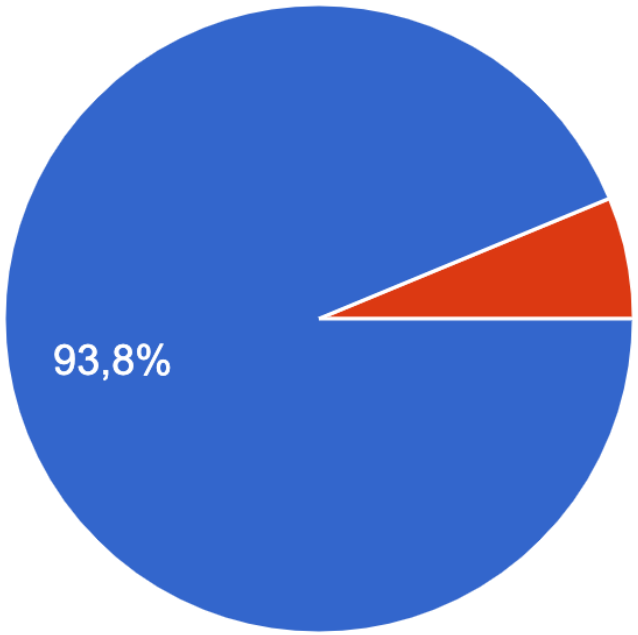
16 risposte

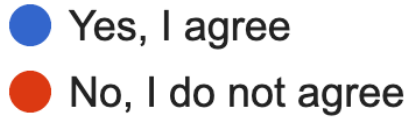


8,8

FUNCTION 8 Injection of an innovative IAHA should be repeated after 9 to 12 months if the patient again becomes symptomatic and requires functional improvement.

16 risposte

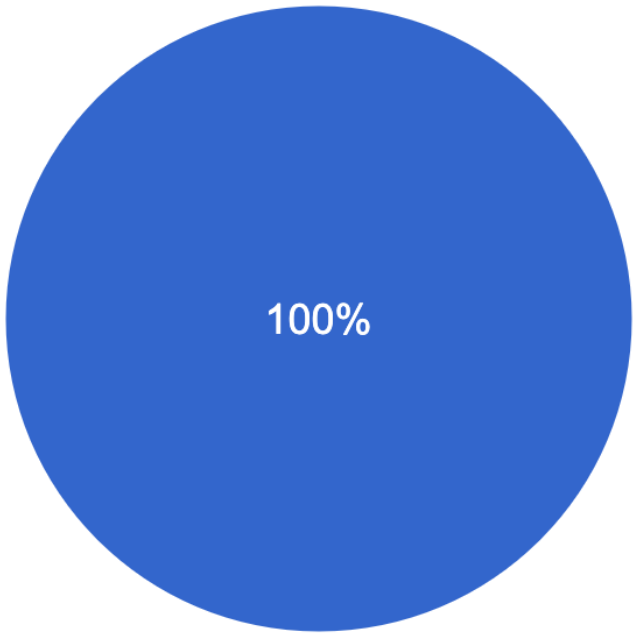


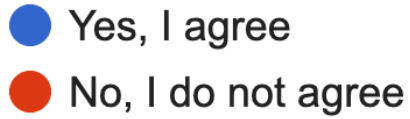


9,0

QUALITY OF LIFE 9 An innovative IAHA should improve the perception of quality of life by 30-50% in patients with mild-to-moderate OA.

16 risposte

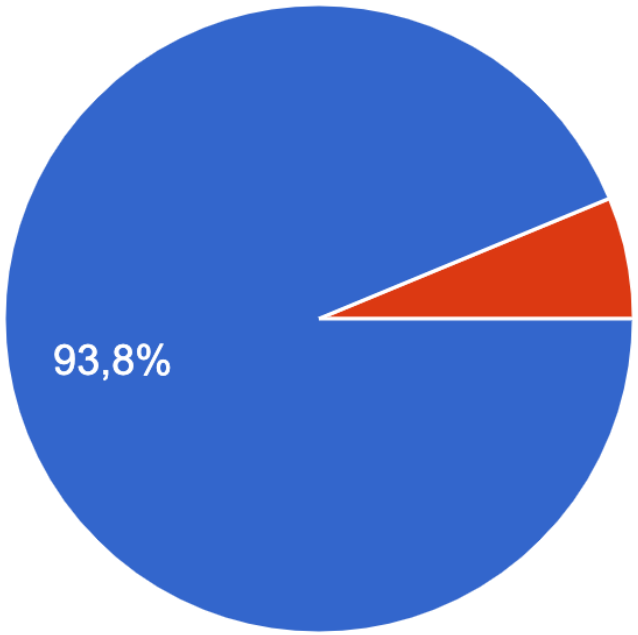




8,6

QUALITY OF LIFE 10 An innovative IAHA should maintain beneficial effect on the perception of quality of life for 9 to 12 months.

16 risposte



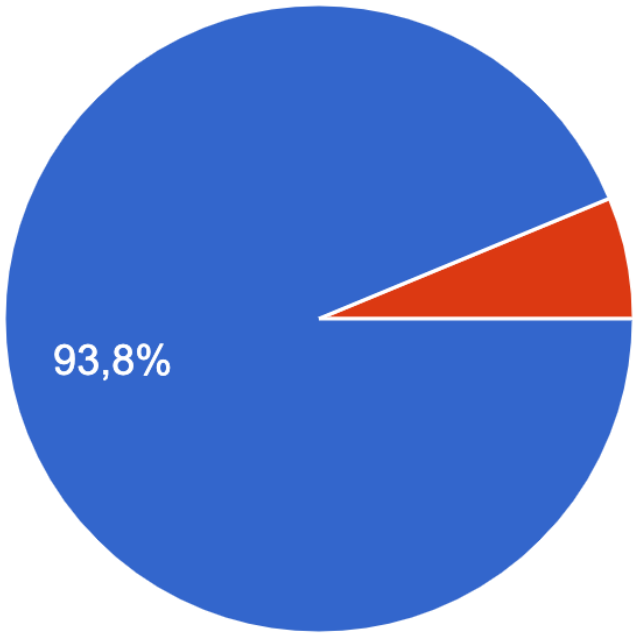
Yes, I agree

No, I do not agree

8,7

QUALITY OF LIFE 11 Injection of an innovative IAHA should be repeated after 9 to 12 months if required to maintain an appropriate quality of life .

16 risposte



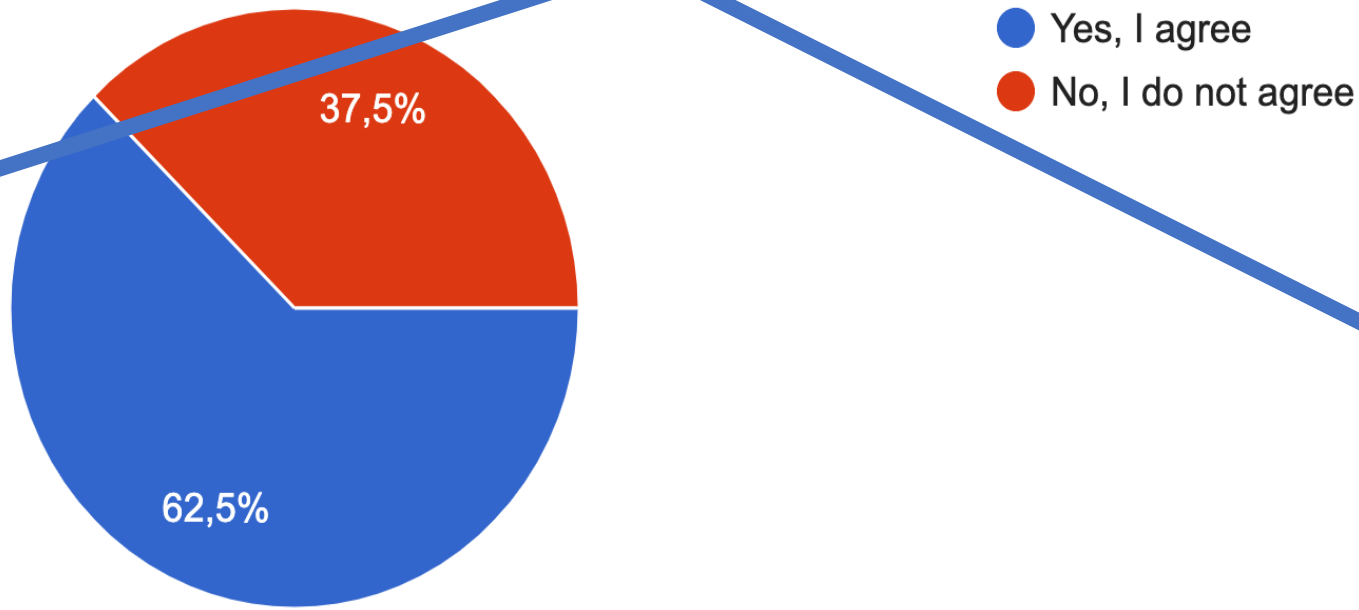
Yes, I agree

No, I do not agree

9,0

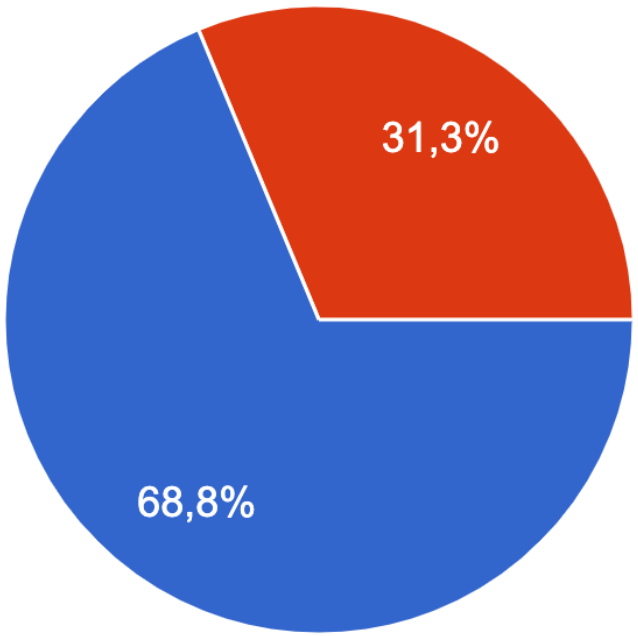
TIME TO SURGERY 12 An innovative IAHA should delay indication for arthroplasty for at least 3 years in patients with OA.

16 risposte



JOINT STRUCTURE AND INTEGRITY 13 An innovative IAHA should demonstrate beneficial effect on the natural history of the disease, including on joint structure.

16 risposte

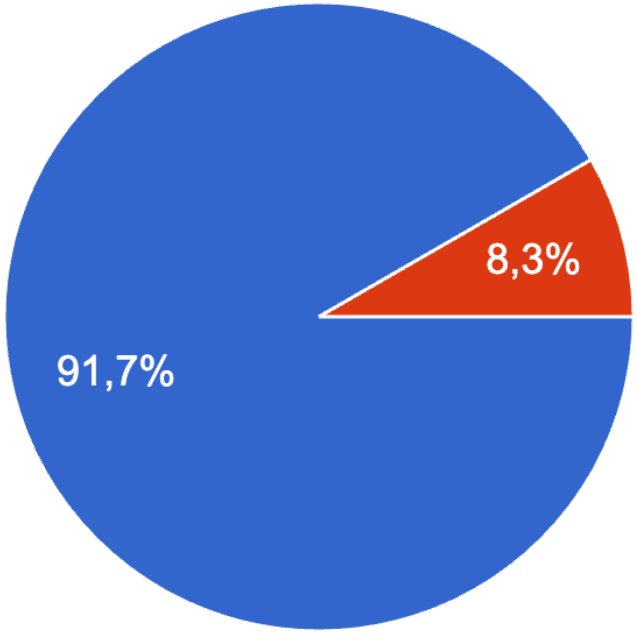


Yes, I agree
No, I do not agree

Secondo round

JOINT STRUCTURE AND INTEGRITY 13 An innovative IAHA should demonstrate beneficial effect on slowing down the development of the disease.

12 risposte

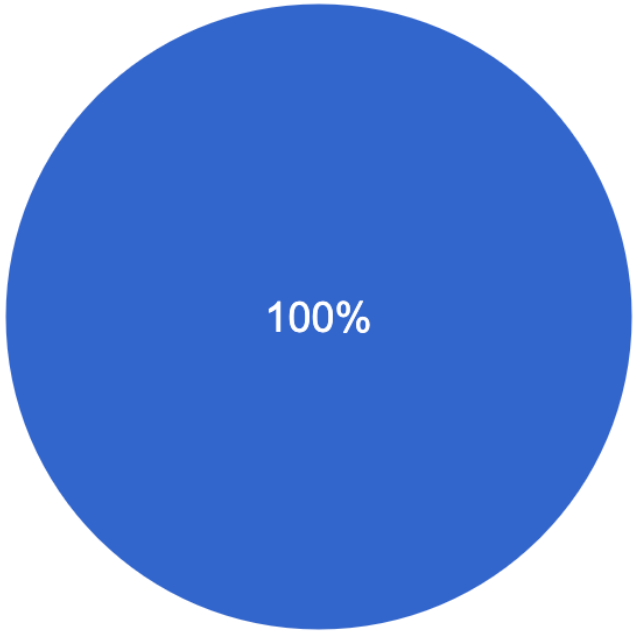


Yes, I agree
No, I do not agree

9,3

ADVERSE EVENTS 14 An innovative IAHA should be associated with local reactions in fewer than 5% of patients and with no systemic adverse events, even after multiple injections.

16 risposte



Yes, I agree

No, I do not agree

9,8

CONCLUSIONI

- Nuovi prodotti per la terapia IA per essere realmente innovativi devono superare gli attuali standard di efficacia sui sintomi e la progressione della malattia e
- Devono possedre un profilo di sicurezza pari agli attuali o superiore
- Combinazioni di HA e altre sostanza devono essere esplorate per raggiungere questi obiettivi

SOCIETÀ ITALIANA G.U.I.D.A. PER LA GESTIONE UNIFICATA E INTERDISCIPLINARE DEL DOLORE MUSCOLO-SCHELETRICO E DELL'ALGODISTROFIA

Grazie per l'attenzione

Athens 5-7 October 2023