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Osteoarthritis and Cartilage

Letter to the Editor

Comment on "Effectiveness and safety of intra-articular interventions for knee and hip osteoarthritis based on large randomized trials: A systematic review and network meta-analysis (Pereira et al., 2025)"

Dear Editors,

The ESCEO Osteoarthritis Working Group wishes to express several concerns regarding the Network Meta-analysis (NMA) by Pereira et al.[1] on intra-articular (IA) treatments for knee and hip osteoarthritis (OA). While aiming to assess effectiveness and safety, the study has methodological and clinical issues that may undermine its conclusions. The authors do not adhere to established NMA guidelines from the ISPOR (International Society for Pharmacoeconomics and Outcomes Research),[2] Cochrane,[3] PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses),[4] NICE (National Institute for Health and Care Excellence),[5] and GRADE.[6] Below, we highlight key methodological concerns and multiple instances of non-compliance with these established standards.

This NMA inappropriately excludes high-risk-of-bias trials, without conducting a proper sensitivity analysis, despite ISPOR guidelines recommending their assessment through sensitivity analyses or Bayesian weighting rather than outright exclusion. This exclusion may compromise result validity, particularly for platelet-rich plasma (PRP) and intra-articular corticosteroids (IACS), which rely on some of the excluded studies.

Another major issue is the inclusion of investigational treatments (capsaicin, lorecivivint, orgotein, sprifermin, fasitibant) and non-standard dosages, contradicting ISPOR's recommendation to focus on regulatory-approved interventions for real-world applicability. Including these investigational treatments skews comparisons, because early-phase trials often lack rigorous validation.

Additionally, the study incorporates unapproved dosages from dose-finding studies, which are not transparently reported, instead being relegated to Appendix 6, despite ISPOR strongly advising against this practice. These data do not reflect real-world prescribing patterns and may distort efficacy estimates.

The choice of the MCID is not well justified. The study sets −0.37 SMD (9 mm on a 100-mm VAS) as the MCID, without clear justification, disregarding ISPOR guidelines, which emphasize using validated sources for this threshold. NICE guidelines also recognize that even small pain reductions are meaningful, which makes this restrictive threshold potentially misleading. Furthermore, the authors do not seem to satisfactorily address heterogeneity and inconsistency, despite ISPOR and PRISMA-NMA recommendations. High heterogeneity, especially concerning PRP and hyaluronic acid (HA), is not adequately managed with subgroup analysis or Bayesian meta-regression.

Additionally, the study lacks a GRADE assessment, an essential component for evaluating evidence certainty. Without it, the reliability of conclusions is unclear, particularly for indirect comparisons, which limits their usefulness in clinical decision making. Lastly, the study does not assess industry sponsorship bias, despite explicit recommendations in methodological guidelines.

From a clinical perspective, the efficacy evaluation of HA injections raises some concerns. Combining hip and knee trials introduces bias, because hip injections require careful assessment of technique, including ultrasound guidance. Moreover, saline is not a true placebo for IA injections, because it alters various parameters, including joint hydrostatic pressure and cytokine concentrations.[7] A sham injection would have been the more appropriate comparator. Notably, saline has been shown to reduce pain more than oral placebo or paracetamol,[8] which means that concluding that HA is ineffective based on this comparison is misleading. In addition, the study does not account for differences in HA molecular weight, concentration, and dosing, despite HA products being highly variable in terms of molecular composition. Overlooking these factors contradicts previous meta-analyses and real-world data.[9,10]

The study favors triamcinolone but does not account for its short-term efficacy (a few weeks) and potential long-term risks of cartilage degradation. It also does not distinguish between IACS (used for inflammatory flares) and IAHA (for long-term mechanical pain management). Moreover, the study lacks real-world applicability, offering little guidance for OA patients, particularly older adults who are either unresponsive to or contraindicated for oral treatments, especially over the long term.

The reporting of safety outcomes appears to lack consistency and transparency. While 'dropouts due to adverse events (AEs)' are stated as the primary safety outcome, their prevalence is not prominently displayed — appearing in Web-Appendix 15 instead of being presented clearly and prominently in the main text. Furthermore, key safety analyses are reported in Appendix 36. The number of trials analyzed varies widely across outcomes (e.g. 12 trials for dropouts due to AEs, 10 for any AEs, 16 for severe AEs), making interpretation difficult. Moreover, the authors do not report actual dropout or AE counts; nor do they assess their clinical relevance or causality, all of which are fundamental in a robust safety

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evaluation. Instead, they refer to their previous meta-analyses, which did not classify AEs by treatment relationship, leading to potentially misleading conclusions.

Given that their primary argument against IAHA is its supposedly unfavorable benefit/risk balance, this approach appears to be a purely statistical rather than clinically relevant assessment, which raises concerns about scientific integrity. In contrast, other reviews have found no major systemic risks with IAHA, reporting only a local AE rate of ~8% and rare post-injection arthritis.[11]

In conclusion, this study contains several methodological flaws that significantly undermine its validity and raise serious concerns about bias and reliability. The unjustified exclusion of trials, inclusion of experimental treatments and dosages, an overly stringent MCID threshold, the lack of a GRADE assessment, and inconsistent safety data reporting all contribute to a distorted and misleading analysis. Rather than providing meaningful insights, this NMA risks misinforming clinicians, decision makers, and patients by offering a distorted portrayal of intra-articular treatments. In reality, when used appropriately and in well-selected patient subgroups, these IA treatments have been shown to improve pain, function, and quality of life significantly.

Author contributions

Alberto Migliore and Emmanuel Maheu drafted this Letter to the Editor, and Ali Mobasheri and Jean-Yves Reginster critically evaluated and revised it. All authors discussed and reviewed the paper in question, and agreed to the submission and publication of this letter.

Conflicts of interest

The authors wish to declare the following conflicts of interest: Alberto Migliore consults for IBSA, Contura, Heel, and Kiomedine. Ali Mobasheri consults for Sanofi, Viatris, HALEON, Aptissen, Contura, Laboratoires Expanscience, IBSA, and Synartro. Jean-Yves Reginster consults for Viatris, IBSA, and Contura. Emmanuel Maheu has consulted for Fidia, TRB Chemedica, Laboratoires Expanscience, and IBSA.

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