ORIGINAL RESEARCH

Efficacy and safety of intra-articular therapies in rheumatic and musculoskeletal diseases: an overview of systematic reviews

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Additional supplemental material is published online only. To view, please visit the journal online (http://rmdopen.bmj.com/). This overview of systematic reviews provides a summary of the current evidence on the efficacy and safety of most compounds commonly used for intra-articular injections. This overview of systematic reviews informed the 2020 EULAR recommendations. This overview of systematic reviews informed the task force for the 2021 EULAR recommendations.

ABSTRACT

Objective To summarise the evidence on intra-articular therapies (IAT) to inform the 2020 EULAR recommendations.

Methods An overview of systematic reviews (SR) including randomised-controlled trials (RCTs) of IAT in adults with arthropathies was performed up to July 2020. Pain, function, and frequency of adverse events were the main efficacy and safety outcomes, respectively. Quality was assessed with the A MeaSurement Tool to Assess Systematic Reviews (AMSTAR)-2 tool.

Results Of 184 references identified, 16 met the inclusion criteria, and a search of their reference lists identified 16 additional SRs. After quality assessment, 29 were finally included. Of these, 18 focused on knee osteoarthritis (KOA), 6 on hip osteoarthritis (HOA), 3 on shoulder capsulitis (SC), and 3 on rheumatoid arthritis. Overall, hyaluronic acid showed a small effect on pain and function in KOA but not in HOA or shoulder capsulitis. Intra-articular glucocorticoids showed a small effect in pain and function in KOA and function in HOA and SC. Platelet-rich plasma showed benefit in pain and function in KOA but not in HOA. Mesenchymal stem cells behaved similarly. Most SR results were of moderate quality and RCTs included often presented a high risk of bias, mainly due to inadequate blinding and heterogenous results. All interventions were well tolerated with no clear safety differences.

Conclusions This overview underlines that most IAT currently used in KOA, HOA, and SC exert small effects and are well tolerated. However, no firm conclusions can be drawn for inflammatory arthritis due to the limited data found.

INTRODUCTION

Intra-articular therapies (IAT) have been widely used in clinical practice for years to reduce joint pain and improve function. They are used in many joint disorders including osteoarthritis (OA) and rheumatoid arthritis (RA) and delivered by a range of health professionals including clinicians from a range of specialities and also allied healthcare professionals. However, evidence on the efficacy and safety of available therapies is not always consistent, due in part to methodological limitations in published trials.

Currently, many compounds are available as IAT from glucocorticoids (GC)—methylprednisolone acetate (MPA), triamcinolone...
acetonide (TA), and triamcinolone hexacetonide (TH)—radioisotopes—yttrium-90, rhenium-186, etc.—or hyaluronic acid (HA) to more recent therapies such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSC), mostly used for treating OA.5–10 The arrival of the latter three products on the market was accompanied by a vast amount of literature with contradictory results that are still under debate. Furthermore, intra-articular procedures elicit an important placebo effect, something that adds more complexity to its efficacy assessment.5,11–13

As around the world life expectancy, obesity, and sedentary lifestyle increase,14–16 the burden of disease imposed by chronic arthropathies and their comorbidities also increases, thus providing the right scenario for local treatments such as IAT, while the search for disease-modifying osteoarthritic drugs continues.

Based on all this, a task force was assembled by the EULAR to produce recommendations for IAT in arthropathies. The objective of the present work was to inform the task force about the current state of the evidence.

METHODS
Study design
We performed an overview of systematic reviews (SR) following a prespecified protocol. The present study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.17

Eligibility criteria
To be eligible, the SR had to include randomised clinical trials (RCT) assessing IAT in adults (≥18 years old) with any arthropathy, excluding the spine and temporomandibular joints.

Interventions (IAT) could be any of the following: GC, HA, PRP, MSC, radiopharmaceuticals, anaesthetics, opioids or biologicals. Comparators could be any of the above mentioned, any form of intra-articular placebo or drugs administered orally as the standard of care (SoC), such as paracetamol/acetaminophen, non-steroidal anti-inflammatory drugs, pregabalin, tricyclic antidepressants. Studies evaluating botulinum toxin as intervention were excluded since its use was deemed to be irrelevant to the current clinical practice of the specialities represented within the task force. Surgical procedures were also excluded as comparators since they do not represent the SoC in most diseases covered in the current study. SRs assessing multiple comparators, including ozone or botulinum toxin, were included as long as they presented separate comparisons for the interventions mentioned in the inclusion criteria.

All efficacy and safety outcomes were considered, especially change in pain and function with any available measure, such as the Visual Analogue Scale (VAS), Lequesne index18 or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),19 and adverse events (AE), including serious adverse events (SAE), such as local reactions or swelling for the former and infections in the injected joint for the latter.

Search strategy
A search was performed in MEDLINE with the assistance of an expert librarian, from inception to January 2019 and updated in July 2020. The references of the included SRs were reviewed, as well as publications provided by the members of the task force. Details on the complete search strategy are provided in the online supplemental material.

Study selection and data collection
Two investigators (SCR-G and RC-M) independently screened the titles and abstracts to ascertain eligibility. The full texts of the eligible articles were then appraised using the same approach, with discrepancies solved through consensus, including a third investigator (LC) if needed. Data regarding study and population characteristics, inclusion/exclusion criteria, interventions, outcome definition, outcome measures, and follow-up was extracted using a standardised form.

Methodological quality assessment
The same two investigators performed an independent quality assessment of the eligible SRs using the ‘A Measurement Tool to Assess Systematic Reviews (AMSTAR)−2’ tool.20 Briefly, this instrument rates the overall confidence in the results of a given SR by thoroughly analysing seven critical domains. The quality was used as a criterion for inclusion. Only SRs of high or moderate quality were included unless a low quality focused on a disease or intervention not covered by the already included SRs.

Data analysis
The qualitative synthesis was carried out by disease and compound. For binary variables, we extracted the ORs or risk ratios (RR) with their 95% CI. For continuous outcomes, data were retrieved as mean difference (MD) with 95% CI. When different measurements were used for the same outcome, treatment effects were retrieved as standardised mean difference (SMD) with CI. To interpret the magnitude of the effects, we used the criteria proposed by Cohen.21

RESULTS
From a total of 183 references, after removing duplicates, 62 were selected for full-text review and 16 met inclusion criteria. Additionally, 16 SRs were identified through the reference lists of included studies and after an update to July 2020. Hence, 32 SRs underwent quality assessment. Three SRs were rated as of ‘high confidence’, 18 as ‘moderate’, 8 as ‘low’, and 3 as ‘critically low confidence’. Following the prespecified protocol, the latter were excluded. Those rated as of low confidence were finally included due to the low amount of data on the studied compounds. Therefore, 29 SRs were included in the qualitative synthesis. A flowchart is shown in figure 1.
and a list of excluded articles with reasons for exclusion is provided in the online supplemental material.

The main features of the SRs included are summarised in table 1. Knee osteoarthritis (KOA) was analysed in 18 SRs,\(^4^–^7\) 22–35 hip OA in 6,\(^36^–^42\) shoulder adhesive capsulitis in 3,\(^3\) 45–47 and RA in 3.\(^3\) 46 47 One SR analysed the efficacy of IAT in both KOA and RA.\(^3\) 44 Different HA-containing compounds were assessed in 13 SRs,\(^4^–^7\) 22–35 PRP in 8,\(^25^–^27\) 29 32 36 41 42  GC in 6,\(^23\) 28 34 38 43 45 and MSC and yttrium synovectomy in 1 each.\(^24\) 46

![Flow chart of the overview of systematic reviews (SR).](https://example.com/image)

**Figure 1** Flow chart of the overview of systematic reviews (SR).

**Efficacy of intra-articular treatments**

**Knee osteoarthritis**

The main efficacy results are shown in table 2. The most frequent outcomes were pain, function, OMERACT-OARSI responder index, and quality of life (QoL). An SR included the change in joint space width and cartilage volume.\(^31\)

HA compounds were extensively analysed in comparison mostly against IA placebo followed by IA GC. Compared with the former and according to Cohen’s criteria,\(^31\) the effect sizes observed for the intervention on pain and function were small and further reduced to no effect when pooling large-blended RCTs only. An SR analysed the OMERACT-OARSI response and found that patients treated with HA were more likely to achieve such a response than those receiving placebo (RR, 1.11 (1.01 to 1.20)).\(^30\) Likewise, when compared vs IA GC, the effect sizes of the intervention were small on pain and function. Of note, one study favoured IA GC in the 1-week to 2-week assessment and HA from the 7–10 weeks until the 17-week to 29-week evaluations.\(^48\) In other SRs, there were no differences between groups in most RCTs analysed, although pooled OMERACT-OARSI responses reached statistical significance (RR, 1.15 (1.02 to 1.30)).\(^30\) Finally, one SR compared HA compounds and showed an increasing effect with increased molecular weight (MW).\(^25\) Of note, the number of studies included was rather low and no differences were seen in QoL.

Most SRs of HA reported moderate to high heterogeneity between studies, as well as publication bias and other biases, mostly concerning inadequate blinding, allocation concealment, and reporting.

Against placebo, GC compounds showed small to moderate effect sizes for pain and function in the short-term (until 3 months), and no differences in QoL, stiffness or joint space width.\(^29\) Among GC compounds, MPA shows a faster onset of effect on pain and function than TA or TH at 6 weeks.\(^34\) No differences were detected after this time-point as well as in OMERACT-OARSI response and no pooled analysis was performed for this comparison. As with HA, authors underline inadequate blinding and allocation concealment as possible sources of bias in the included RCTs.

PRP was evaluated mostly against HA and, secondarily, versus placebo. Compared with HA, PRP showed a small to null effect on pain, function, and stiffness. Two SRs pooled composite scores (WOMAC total score and IKDC) and found better responses with PRP than HA at 6 and 12 months showing large effects.\(^27\) 49 Kanchanatawan et al\(^25\) found an improved EQ-VAS at 12 months with PRP.\(^25\) For PRP versus placebo, no differences were seen in the targeted outcomes, except for the composite scores, in which the pooled effect was large; this effect disappeared when only high-quality trials were pooled. Between-trial heterogeneity was high, in terms of PRP composition, endpoints, and comparators. Also, the SRs rated included RCTs as with moderate to high risk of bias, especially due to inadequate allocation concealment, blinding of participants, and outcome assessment.

A network meta-analysis analysed the effect of MSC against different comparators, including placebo, HA, or IA GC.\(^44\) The effect of MSC was moderate to large on pain and moderate for the KOOS at 12 months, whereas no effect was observed on the WOMAC total score at 6 months. High-dose adipose-derived MSC showed a longer effect. Overall, studies included in this SR were rated as of low risk of bias; nonetheless, there was evidence of publication bias for pain measured by VAS. Unfortunately, most branches of the meta-analysis were underpowered to draw conclusions on which strategy is better in clinical practice.

**Hip osteoarthritis**

The main results on hip OA are summarised in table 3. The most frequent outcomes measured were pain and function, the latter measured using the Harris Hip Score (HHS) and the OMERACT-OARSI response criteria.

PRP was the most frequent compound studied in hip OA, and all comparisons were against HA. Almost all
| Study | Population | Intervention and comparator | Outcomes | Quality |
|-------|------------|----------------------------|----------|---------|
| Rutjes et al<sup>22</sup> | IC: RCTs EC: not stated. | HA vs sham or no intervention | Primary: pain intensity Secondary: function, SAEs, withdrawal due to AEs | High |
| Newberry et al<sup>23</sup> | IC: RCTs, SRs, OS, and CS<sup>*</sup> EC: non-English language studies and conference abstracts. | HA vs PBO or other HA | Primary: delay or avoidance of TKR Secondary: function, QoL, number of AE | High |
| Jüni et al<sup>23</sup> | IC: RCT of patients treated with GC either IA or subacromial. EC: RCT including only patients with inflammatory arthritis | IA GC vs sham, PBO or SOC | Primary: pain and function at 4–6 weeks Secondary: pain and function at subsequent time points, QoL, JSN, SAEs, withdrawals due to AEs | High |
| Ding et al<sup>24</sup> | IC: RCTs reporting ≥1 of the outcomes of interest. EC: use of PRP or MSC+ surgery or lack of a non-cell-based control | MSC vs PBO, HA or IAGC | WOMAC, KOOS, VAS, SAEs without a prespecified hierarchy | Moderate |
| Bannuru et al<sup>4</sup> | IC: RCTs with data on safety outcomes EC: non-RCT studies | HA vs HA or PBO | Number of AEs, SAEs, withdrawals due to AEs without a prespecified hierarchy | Moderate |
| Bannuru et al<sup>6</sup> | IC: RCTs with data for ≥1 outcome measure of pain. EC: studies not including pain outcomes of interest | HA vs IAGC | Primary: pain according to a prespecified hierarchy at different time-points | Moderate |
| Bannuru et al<sup>6</sup> | IC: RCTs with primary KOA with data on ≥2 interventions of interest and on ≥1 measure of pain, function or stiffness. EC: not stated | HA vs PBO HA vs IAGC IAGC vs PBO | Primary: pain at 3 months according to a prespecified hierarchy Secondary: function and stiffness at 3 months | Moderate |
| Kanchanatawan et al<sup>25</sup> | IC: RCTs of adults with primary KOA with ≥1 of the outcomes of interest and enough data to extract and pool EC: not stated | PRP vs HA or PBO or sham | WOMAC total and subscores, Lequesne score, EuroQol-VAS, IKDC subjective scores, number of AEs without a prespecified hierarchy | Moderate |
| Xu et al<sup>26</sup> | IC: RCTs with ≥30 randomised patients, ≥1 month follow-up, quantitative outcome assessment, <20% of dropouts EC: not stated | PRP vs HA, PBO | Pain and function (VAS, WOMAC, IKDC, Lequesne) without a prespecified hierarchy | Moderate |
| Dai et al<sup>27</sup> | IC: RCTs comparing PRP vs controls for prespecified outcomes EC: not stated | PRP vs HA or PBO | Primary: WOMAC pain and function scores. Secondary: WOMAC total score, IKDC, Lequesne, frequency of AE | Moderate |
| Arroll and Goodyear-Smith<sup>28</sup> | IC: PBO-controlled RCTs assessing the efficacy of IAGC EC: not stated | IAGC vs PBO | Primary: improvement of symptoms Secondary: pain, response to the OA research scale | Moderate |
| Shen et al<sup>29</sup> | IC: RCT comparing any PRP vs another IAT with ≥12 w follow-up EC: studies without IA control group, other PRP or PRP+surgery | PRP vs HA or PBO | Primary: WOMAC pain, function and total at 3, 6, and 12 months Secondary: number of patients with AEs | Moderate |

Continued
| Study          | Population                                                                 | Intervention and comparator          | Outcomes                                                                 | Quality  |
|---------------|-----------------------------------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------|----------|
| Trojan et al  | IC: RCTs in English including outcomes of interest at ≥8 and <16 weeks.     | HA vs PBO or IAGC IAGC vs PBO        | OMERACT-OARSI response rates, mean change from baseline in WOMAC pain,  | Moderate |
|               | EC: studies comparing IA GC or HA vs surgical procedures                     |                                        | stiffness or function, frequency of AE. Without hierarchy                |          |
| Gallagher et al | IC: RCTs with PBO control, ≥12 m follow-up, data on structural changes       | HA or SOC vs PBO†                     | Primary: changes in JSW or cartilage volume. Secondary: WOMAC total score, | Moderate |
|               | EC: not stated                                                               |                                        | WOMAC pain or VAS pain                                                   |          |
| Di et al      | IC: English-written RCTs                                                   | PRP vs HA                              | Primary: WOMAC, IKDC, KOOS, EQ-VAS, Tegner score. Secondary: frequency of AE | Low      |
|               | EC: unknown methodology or patients with additional conditions‡             |                                        | between groups                                                            |          |
| Trigkilidas and Anand | IC: RCTs with ≥1 outcome measure on pain or function; freely available as full text from specified sources§ | HA vs PBO or IAGC                   | VAS pain, Lequesne, WOMAC without a prespecified hierarchy               | Low      |
| Lo et al      | IC: Blinded—RCTs comparing HA (≥3 injections) vs PBO with data on pain and 8-week minimum follow-up and drop-out rate of <50% | HA vs PBO                              | Pain according to a prespecified hierarchy                               | Low      |
|               | EC: not stated                                                               |                                        |                                                                          |          |
| **Hip osteoarthritis** |                                                                                     |                                        |                                                                          |          |
| Ali et al     | IC: RCTs, with clinical and functional data with any follow-up              | PRP vs HA                              | VAS pain, WOMAC total, and HHS without a prespecified hierarchy          | Moderate |
|               | EC: studies on animals and technical notes                                  |                                        |                                                                          |          |
| McCabe et al | IC: RCTs with patients with HOA (clinical and radiographic)                 | IAGC vs PBO                            | Primary: pain according to a prespecified hierarchy                      | Moderate |
|               | EC: studies without a control group                                          |                                        | Secondary: WOMAC function, Lequesne Index, safety profile               |          |
| Liao et al    | IC: RCTs of patients with primary HOA                                         | HA vs PBO                              | Primary: self-reported pain according to a prespecified hierarchy        | Moderate |
|               | EC: stated as the opposite to IC                                             |                                        | Secondary: function, OMERACT-OARSI responder index                      |          |
| Medina-Porqueres | IC: English or Spanish-written studies of PRP applied in isolation (any)  |
|               | in ≥1 arm to patients with any grade of HOA as per the ACR criteria        | PRP vs IA control                      | Primary: VAS pain, HHS, and WOMAC function. Secondary: growth factor’s  | Low      |
|               | EC: studies including only children or animals; non-OA injuries, OA in other joints or previous surgery |                                        | concentration, AE and imaging evaluations                                |          |
| Ye et al      | IC: RCTs comparing PRP with HA                                              | PRP vs HA                              | Primary: WOMAC total score, VAS pain, and Harris hip score (HHS)        | Low      |
|               | EC: studies without a control group, full-text versions or outcomes data    |                                        | Secondary: n of AE                                                      |          |

Continued
RCTs showed no difference between groups at all time points except for the study by Ye et al. favouring PRP. Regarding function, no differences were seen using the WOMAC function subscore or the HHS. An SR of four RCTs with high heterogeneity and unclear or high risk of bias showed inconclusive results.41 50 51

**Table 1**

| Study                                    | Population                                                                 | Intervention and comparator | Outcomes                                                                 | Quality |
|------------------------------------------|-----------------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------------|---------|
| Leite et al40                            | IC: RCT with ≥1 of the outcomes of interest                                 | HA vs IA-injection comparators | Primary: pain, Secondary: QoL, OMERACT-OARSI Response, frequency of AEs  | Low     |
|                                          | EC: RCT comparing HOA vs other sites and HA vs non-IA controls              |                              |                                                                          |         |
| Sun et al45                              | IC: RCTs comparing IAGC vs no or sham injection or SOC                      | IAGC vs sham or SOC          | Primary: VAS pain, Secondary: passive external rotation, abduction, flexion, internal rotation, and functional scores and frequency of AEs | Moderate|
|                                          | EC: injection volume >0.10 mL (classified as IAGC-distention)               |                              |                                                                          |         |
| Buchbinder et al43                       | IC: RCTs of shoulder pain comparing IAGC vs PBO, another intervention or different IAGC dosages | IAGC vs PBO, other interventions | Pain, ROM, function, strength, and return to work or school without a prespecified hierarchy | Moderate|
|                                          | EC: pain duration <3 weeks, RA, polymyalgia rheumatica, and fracture        |                              |                                                                          |         |
| Lee et al44                              | IC: RCT of capsulitis (confirmed clinically or by US), clearly documenting IC and EC, symptom duration and follow-up >4 weeks | HA vs SOC                    | Pain, ROM, and function/disability scores >1 month after administration, frequency of AEs without a prespecified hierarchy | Moderate|
|                                          | EC: uncontrolled studies                                                   |                              |                                                                          |         |
| Rheumatoid arthritis                     |                                                                           |                              |                                                                          |         |
| Heuf't-Dorenbosch et al46                | IC: RCTs of RA patients with knee arthritis, enough quality as per the Delphi list. Language restrictions applied¶ | Yttrium synovectomy vs PBO or TH | Knee circumference, ROM, fixed flexion, pain (Likert scale), subjective change, knee effusion, radiological assessment without prespecified hierarchy | Moderate|
|                                          | EC: not stated                                                             |                              |                                                                          |         |
| Silvinato and Bernardo34                 | IC: RCTs of patients with RA and knee arthritis                             | MPA vs TA, TH, prednisolone  | Primary: flare time at 24 weeks, Secondary: patient-reported pain and swelling, ROM, frequency of AEs | Low     |
|                                          | EC: not stated                                                             |                              |                                                                          |         |
| Saito and Kotake47                       | IC: English or Japanese-written RCTs of patients with RA and knee arthritis including pain assessment | HA vs PBO                    | Primary: global pain measured with Likert scale at 1 week, Secondary: inflammation measured with Likert scale, Condition of the knee with Likert scale, safety profile | Low     |
|                                          | EC: studies with animals or only describing the injection technique         |                              |                                                                          |         |

*Only data from RCTs were retrieved for the analyses on the present study.
†Only data for the HA vs PBO comparison were retrieved.
‡Additional conditions included meniscal tears, inflammatory arthritis, among others.
§Free full-texts available from the Warwick University Library or Google Scholar.
¶Articles written in Dutch, English, French, German, or Spanish.

AE, adverse events; CS, case series; EC, exclusion criteria; EQ-VAS, Euro Quality of Life – Visual Analogue Scale; freq of AE, frequency of adverse events; GC, glucocorticoids; HA, hyaluronic acid; HHS, Harris Hip Score; HOA, hip osteoarthritis; IA, intra-articular; IAT, intra-articular therapies; IC, inclusion criteria; IKDC, International Knee Documentation Committee; JSN, joint space narrowing; JSW, joint space width; KOA, Knee Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score; MPA, methylprednisolone acetate; MSC, mesenchymal stem cells; OS, observational studies; PBO, placebo; PRP, platelet-rich plasma; QoL, quality of life; RCT, randomised-controlled trials; ROM, range of motion; SAE, serious adverse events; SoC, standard of care; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide; TKR, total knee replacement; US, ultrasonography; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
## Table 2  Main efficacy results of IAT for knee osteoarthritis

| Study | Follow-up | Outcomes | Effect estimate | Comments |
|-------|-----------|----------|----------------|----------|
| **Hyaluronic acid vs placebo** | | | | |
| Rutjes et al<sup>7</sup> | 3 mo | Pain | Overall (ES, 0.37 (0.28 to 0.46)), favouring HA | Effect size defined as between-group differences in means divided by the pooled SD at end of follow-up. Minimal clinically important difference = (−0.37 ES) |
| | | Function | Overall (ES, 0.33 (0.04 to 0.22)), favouring HA | | |
| | | | Large-blinded RCTs (ES, 0.09 (0.00 to 0.17)), favouring HA | | |
| Newberry et al<sup>22</sup> | 1–12 mo | Function | SMD=0.23 (0.01 to 0.45), favouring HA (WOMAC) | Consistent effect in sensitivity analysis for too short (<4 weeks) or too long (>52 weeks) RCTs |
| | | QoL | 3 RCTs—no between-group difference (SF-36, EuroQol-SD) | | |
| Gallagher et al<sup>31</sup> | 12–24 mo | Pain | 2 RCTs—no between-group difference (VAS) | | |
| | | Δ Cartilage volume | 1 RCT—favoured HA with 2.60% (1.20–4.10) less cartilage volume lost in the medial compartment and 2.80% (0.90–4.70) less in the lateral compartment | | |
| | Function | SMD=0.23 (0.13 to 0.34), favouring HA | | |
| | | Stiffness | SMD=0.34 (Cr I, 0.26 to 0.42), favouring HA | MA result of a Bayesian hierarchical random-effects model for mixed multiple treatment comparisons |
| Bannuru et al<sup>6</sup> | 3 mo | Pain | SMD, 0.34 (Cr I, 0.26 to 0.42), favouring HA | NMA. SMD refers to Hedges’ g Results obtained for the time of best response No publication bias |
| | Function | SMD, 0.3 (Cr I, 0.20 to 0.40), favouring HA | | |
| | Stiffness | SMD, 0.23 (Cr I, 0.13 to 0.34), favouring HA | | |
| Trojan et al<sup>43</sup> | 2–6 mo | Pain | SMD, 0.19 (0.06 to 0.32), favouring HA (WOMAC) | | |
| | Function | SMD, 0.19 (0.05 to 0.32), favouring HA (WOMAC) | | |
| | Stiffness | SMD, 0.12 (0.03 to 0.27), favouring HA (WOMAC) | | |
| | O-O Resp | RR, 1.11 (1.01 to 1.20), favouring HA | | |
| Trigkilidas and Anand<sup>35</sup> | 1–6 mo | Pain | 5 RCTs—no between-group difference (VAS) | No pooled analysis |
| | Function | 7 RCTs—favoured HA (VAS) (small effect) | | |
| | | 5 RCTs—no between-group difference (WOMAC, Lequesne) | | |
| | | 7 RCTs—favoured HA (WOMAC) (small effect, Lequesne) | | |
| Lo et al<sup>33</sup> | 2–12 mo | Pain | Overall, SMD=0.32 (0.17 to 0.47) | Evidence of publication bias |
| | | Excluding high MW, SMD=0.19 (0.10 to 0.27) | | |
| **Hyaluronic acid vs glucocorticoids** | | | | |
| Bannuru et al<sup>6</sup> | 1–2 wk | Pain | ES, 0.39 (0.12 to 0.65), favouring IAGC | ES: refers to Hedges’ g corrected for small samples Effects remained consistent after multivariable and sensitivity analysis |
| | | Function | ES, −0.01 (−0.23 to 0.21), no between-group difference | | |
| | | Stiffness | ES, 0.22 (0.05 to 0.49), favouring HA | | |
| | 3–6 wk | | ES, 0.35 (0.03 to 0.66), favouring HA | | |
| | 7–10 wk | | ES, 0.39 (0.18 to 0.59), favouring HA | | |
| | 11–16 wk | | ES, 0.39 (0.26 to 0.52), favouring HA | | |
| | 17–29 wk | | ES, 0.39 (0.26 to 0.52), favouring HA | | |
| Bannuru et al<sup>6</sup> | 3 mo | Pain | SMD, 0.02 (Cr I, −0.12 to 0.17), no between-group difference | NMA |
| | Function | SMD, 0.24 (Cr I, 0.06 to 0.43), favouring HA | | |
| | Stiffness | SMD, 0.20 (Cr I, 0.0 to 0.41), no between-group difference | | |
| Trojan et al<sup>43</sup> | 4–40 mo | Pain | ES, −0.06 (−0.28 to 0.16), no between-group difference | NMA |
| | Function | ES, −0.29 (−0.53 to −0.05), favouring HA | | |
| | Stiffness | ES, −0.17 (−0.50 to 0.16), no between-group difference | | |
| | O-O Resp | RR, 1.15 (1.02 to 1.30), favouring HA | | |
| Trigkilidas and Anand<sup>35</sup> | 1–6 mo | Pain | 1 RCT—favoured HA at 6 months (VAS) | No pooled analysis |
| | Function | 1 RCT—no between-group difference | | |

**Hyaluronic acid compounds comparison**
| Study                          | Follow-up | Outcomes | Effect estimate | Comments                                                                 |
|-------------------------------|-----------|----------|----------------|--------------------------------------------------------------------------|
| Newberry et al<sup>22</sup>   | 1–12 mo   | Function | 1 RCT—LMW vs MMW. SMD, −0.326 (−0.52 to −0.13), favouring MMW  | All comparisons using the WOMAC function subscale                        |
|                               |           |          | 1 RCT—LMW vs HMW. SMD, 0.053 (0.66 to 0.77), no difference     | No pooled analysis                                                       |
|                               |           |          | 1 RCT—LMW vs HMW. SMD, −0.882 (−1.09 to −0.68), favouring HMW |                                                                    |
|                               |           |          | 1 RCT—MMW vs HMW. SMD, −0.01 (−0.21 to 0.19), no difference    |                                                                         |
|                               | 3 mo      | QoL      | 1 RCT—LMW vs HMW, favouring LMW (EuroQol-5D)                  |                                                                           |
|                               | 12 mo     |          | 1 RCT—LMW vs HMW, favouring HMW (EuroQol-5D)                  |                                                                           |
|                               |           |          | 1 RCT—LMW vs HMW. No between-group difference (SF-36)        |                                                                           |
| Glucocorticoids vs placebo    |           |          |                                                             |                                                                          |
| Jüni et al<sup>23</sup>       | 2 wk      | Pain     | SMD = −0.48 (−0.70 to −0.27), favouring IAGC                | For pain and function, effects were reduced in large trials (>50 patients/ arm) |
|                               | 2 mo      |          | SMD = −0.41 (−0.61 to −0.21), favouring IAGC                |                                                                           |
|                               | 3 mo      |          | SMD = −0.22 (−0.44 to 0.00), no between-group difference    |                                                                           |
|                               | 6 mo      |          | SMD = −0.07 (−0.25 to 0.11), no between-group difference    |                                                                           |
|                               | 2 wk      | Function | SMD = −0.43 (−0.72 to −0.14), favouring IAGC                |                                                                           |
|                               | 2 mo      |          | SMD = −0.36 (−0.63 to −0.09), favouring IAGC                |                                                                           |
|                               | 3 mo      |          | SMD = −0.13 (−0.37 to 0.10), no between-group difference    |                                                                           |
|                               | 6 mo      |          | SMD = 0.06 (−0.16 to 0.28), no between-group difference      |                                                                           |
|                               | 6 mo      | QoL      | SMD = −0.01 (−0.30 to 0.28), no between-group difference    |                                                                           |
|                               |           |          | JSW SMD = −0.02 (−0.49 to 0.46), no between-group difference |                                                                           |
| Arroll and Goodyear-Smith<sup>28</sup> | 2 wk     | Pain     | WMD = −16.47 (−22.92 to −10.03), favouring IAGC            | Pooling studies with the highest dose                                     |
|                               | 2 wk     | Improvement of symptoms | RR 1.66 (1.37 to 2.01), favouring IAGC                    |                                                                           |
|                               | 3–4 mo   |          | RR 2.09 (1.20 to 3.65), favouring IAGC                       |                                                                           |
| Bannuru et al<sup>5</sup>     | 3 mo      | Pain     | SMD, 0.32 (Cr I, 0.16 to 0.47), favouring IAGC              | NMA                                                                      |
|                               |          | Function | SMD, 0.06 (Cr I, −0.13 to 0.26), no between-group difference |                                                                           |
|                               |          | Stiffness| SMD, 0.03 (Cr I, −0.19 to 0.25), no between-group difference |                                                                           |
| Glucocorticoid compounds comparison |           |          |                                                             |                                                                          |
| Silvinato and Bernardo<sup>34</sup> | 1–6 mo  | Pain     | 1-RCT—MPA vs TH. No between-group difference (VAS)          | *Results of the same study at 2 time-points                              |
|                               | 6 wk     |          | 1-RCT—MPA vs TA vs prednisolone, favouring MPA (VAS)         |                                                                           |
|                               | 3 mo     |          | 1-RCT—MPA vs TA vs prednisolone, no between-group difference|                                                                           |
|                               | 1 month  |          | 1-RCTY—MPA vs TH, favouring MPA (VAS)                       |                                                                           |
|                               | 2 mo     |          | 1-RCTY—MPA vs TH. No between-group difference (VAS)          |                                                                           |
|                               | 1–6 mo   | Function | 1-RCT—MPA vs TH. No between-group difference (WOMAC)        |                                                                           |
|                               | 1–3 mo   |          | 1-RCT—MPA vs TA vs prednisolone. No difference (Lequesne)    |                                                                           |
|                               | 2 mo     |          | 1-RCT—MPA vs TH. No between-group difference (Lequesne)      |                                                                           |
|                               | 2 mo     | O-O Response | 1-RCT—MPA vs TH. No between-group difference             |                                                                           |
| Study                          | Follow-up | Outcomes       | Effect estimate |
|-------------------------------|-----------|----------------|-----------------|
| Xu et al<sup>18</sup>         | 6 mo      | Composite scores<sup>#</sup> | Overall, SMD = −2.13 (−3.29 to −0.98), favouring PRP | #Effects of pooled results from WOMAC and IKDC scores |
| Dai et al<sup>27</sup>        | 6–12 mo   | Pain           | 1 RCT—favoured PRP (WOMAC) |
|                               |           | Function       | 1 RCT—favoured PRP (WOMAC) |
| Kanchanatawan et al<sup>26</sup> | 6–12 mo   | Pain           | No between-group difference (WOMAC) |
|                               |           | Function       | No between-group difference (WOMAC) |
|                               |           | Stiffness      | No between-group difference (WOMAC) |

### Platelet-rich plasma vs hyaluronic acid

| Study                          | Follow-up | Outcomes       | Effect estimate |
|-------------------------------|-----------|----------------|-----------------|
| Xu et al<sup>18</sup>         | 6 mo      | Composite scores<sup>¶</sup> | Overall, SMD = −0.85 (−1.43 to −0.28), favouring PRP |
|                               |           | Pain           | High-quality RCTs, SMD = −0.09 (−0.30 to 0.11). No difference |
|                               |           | Function       | MD=0.35 (0.36 to 1.06) (VAS). No difference |
|                               | 3 mo      | WOMAC total    | MD=−7.10 (−17.02 to 2.82). No between-group difference |
|                               | 12 mo     |                | MD=−8.93 (−27.56 to 9.71). No between-group difference |
| Shen et al<sup>29</sup>       | 3–12 mo   | Pain           | MD=−3.77 (−5.07 to −2.47), favouring PRP (WOMAC) |
|                               |           | Function       | MD=−13.91 (−18.53 to −9.28), favouring PRP (WOMAC) |
|                               |           | WOMAC total    | MD=−17.39 (−22.32 to −12.46), favouring PRP |
| Dai et al<sup>27</sup>        | 6 mo      | Pain           | MD=−1.54 (−4.27 to 1.20). No between-group difference |
|                               | 12 mo     | Function       | MD=−2.83 (−4.26 to −1.39), favouring PRP |
|                               | 6 mo      |                | MD=−4.39 (−10.51 to 1.74). No between-group difference |
|                               | 12 mo     |                | MD=−12.53 (−14.58 to −10.47), favouring PRP |
|                               | 6 mo      | Composite scores<sup>§</sup> | SMD=0.68 (−0.04 to 1.41). No between-group difference |
|                               | 12 mo     |                | SMD=1.05 (0.21 to 1.89), favouring PRP |
| Kanchanatawan et al<sup>26</sup> | 6–12 mo   | Composite scores<sup>§</sup> | MD= −15.4 (−28.6 to −2.30), favouring PRP (WOMAC total) |
|                               |           | Pain           | MD=8.83 (5.88 to 11.78), favouring PRP (IKDC) |
|                               |           | Function       | No between-group difference (WOMAC) |
|                               |           | Stiffness      | No between-group difference (WOMAC) |
|                               |           | QoL            | MD=7.37 (4.33 to 10.05), favouring PRP (EQ-VAS) |
| Di et al<sup>32</sup>         | 1–12 mo   | Pain           | 5 RCTs—favoured PRP (VAS, WOMAC) |
|                               |           | Function       | 1 RCT—no between-group difference (VAS) |
|                               |           | Stiffness      | 2 RCTs—no between-group difference (WOMAC) |
|                               |           | O-O Response   | 1 RCT—favoured PRP |
|                               |           | QoL            | 3 RCTs—no between-group difference (EQ-VAS, SF-36) |

### Mesenchymal stem cells vs controls

Continued
No differences were observed for pain, function, nor OMERACT-OARSI response between HA and placebo or MPA. McCabe et al.\textsuperscript{38} on the contrary, reported an OR=7.8 (2.7–22.8) for reaching an OMERACT-OARSI response in patients treated with IA GC versus placebo. The latter SR included four RCTs, three of which showed better results in function (activities of daily life and WOMAC function subscore). All studies were deemed as having a low to moderate risk of bias and no evidence of publication bias.

**Shoulder capsulitis**

Table 4 summarises the main efficacy results for shoulder capsulitis. Pain was only measured using VAS and function evaluated by the range of motion (ROM). Additionally, specific composite scores such as the Shoulder Pain and Disability Index (SPADI), the American Shoulder and Elbow Surgeons score and (ASES), and the Constant score were applied. HA and IAGC were the interventions evaluated and most comparisons were against placebo. One SR\textsuperscript{34} assessed the former and found no differences for pain or function. On the contrary, IAGC were evaluated in two SRs and a small effect was observed favouring the intervention on pain, ROM, and the SPADI whereas no differences were seen for the ASES and the Constant score.

Overall, there was high heterogeneity between studies regarding injection techniques dose and type of compound as well as comparators. Major sources of bias were inadequate blinding of participants and personnel, inadequate allocation concealment, and possible small study bias.

**Rheumatoid arthritis**

The main results of IAT in RA are also shown in table 4. Outcomes varied widely and included pain, ROM, global inflammation, number of flares, and grip strength. HA, IAGC, and yttrium synovectomy were the interventions assessed. Saito and Kotake\textsuperscript{47} observed better performance of HA over placebo for pain, global inflammation, and self-reported effectiveness. Brazilian Medical Association\textsuperscript{34} found no differences in the number of flares, ROM, morning stiffness, grip strength, Ritchie articular index, or thermography index, between MPA, TA, or TH. In one RCT, TH performed better in pain (VAS) at 1 week of follow-up but there were no between-group differences at 2 to 6 weeks. Finally, Heuft-Dorenbosch \textit{et al.}\textsuperscript{36} found no differences in pain between yttrium synovectomy and placebo or IAGC, whereas the former performed better in ROM and knee circumference (1 RCT) versus placebo. Conversely, ROM was best improved in the IAGC-treated group (vs yttrium synovectomy). Two out of three SRs assessing treatments for RA were deemed as of low quality and included a very low number of RCTs with evidence of small study bias and unclear or inadequate allocation concealment, as well as participant and provider blinding.

**Safety of intra-articular treatments**

Twenty-two SRs provided data on safety (table 5). In most cases, the outcome reported was the frequency of AEs (any), while some articles also analysed SAEs and withdrawals due to AEs.

HA compounds were compared against placebo in a network meta-analysis specifically designed to assess safety in KOA.\textsuperscript{4} No between-group differences were observed for any AE but local reactions and withdrawal due to AEs favoured placebo versus HA. Other SRs analysing HA compounds reported similar results for any AEs, SAEs, and withdrawals due to AE.

Of note, Rutjes \textit{et al.}\textsuperscript{7} found a higher risk of local reactions, SAEs, and withdrawals with HA versus sham or no interventions. In this SR, the pooled RR of SAEs from 14 RCTs was 1.41 (1.02 to 1.97), consistent when pooling only large-blinded RCTs (RR=1.55 (1.07 to 2.24)). Said SAEs consisted of 27 events in visco supplementation patients versus 21 in control patients. Most frequent disorders were related to the gastrointestinal system (2 vs 8), cardiovascular system (5 vs 2), cancer (6 vs 0), and musculoskeletal system (4 vs 2). The authors underlined that the poor quality of reporting safety data of the RCTs analysed made the understanding of the probable causes for these observations difficult.
Table 3 Main efficacy outcomes for hip osteoarthritis

| Study               | Comparison | Follow-up | Outcomes | Effect estimate                      | Comments                                                                 |
|---------------------|------------|-----------|----------|--------------------------------------|--------------------------------------------------------------------------|
| **Hyaluronic acid** |            |           |          |                                      |                                                                          |
| Leite et al<sup>40</sup> | HA vs PBO, PRP, MPA | 1–12 months | Pain     | No between-group difference vs PRP (VAS) |                                                                          |
|                     |            | 3 months  |          | No between-group difference vs PBO (VAS) |                                                                          |
|                     |            | 1–12 months | O-O Resp | No between-group difference vs MPA    |                                                                          |
|                     |            | 3 months  |          | No between-group difference vs PBO    |                                                                          |
| Liao et al<sup>37</sup> | HA vs PBO or IAGC | 2 weeks   | Pain     | SMD = −0.18 (−0.47 to 0.10), no between-group difference | Data on pain was obtained as per a previously described hierarchy.<sup>55</sup> Analyses use IAGC and PBO as comparators. |
|                     |            | 4 weeks   |          | SMD = −0.14 (−0.46 to 0.18), no between-group difference |                                                                          |
|                     |            | 2–6 months |          | SMD = −0.14 (−0.46 to 0.18), no between-group difference |                                                                          |
|                     |            | 2 weeks   | Function | SMD = −0.14 (−0.52 to 0.24), no between-group difference |                                                                          |
|                     |            | 4 weeks   |          | SMD = −0.16 (−0.34 to 0.03), no between-group difference |                                                                          |
|                     |            | 2–6 months |          | SMD = −0.28 (−0.60 to 0.05), no between-group difference |                                                                          |
| **Glucocorticoids** |            |           |          |                                      |                                                                          |
| McCabe et al<sup>38</sup> | IAGC vs PBO | 1–3 months | Pain     | SMD = −1.90 (−4.07 to 0.26), no between-group difference | Comparisons vs PBO                                                       |
|                     |            | 2 months  | O-O Resp | OR = 7.8 (2.7–22.8), favouring IAGC  |                                                                          |
|                     |            |          | Function | 3 RCTs—favoured IAGC (ADL, WOMAC function) |                                                                          |
|                     |            |          | ROM      | 1 RCT—no between-group difference    |                                                                          |
|                     |            |          |          | 1 RCT—no between-group difference    |                                                                          |
|                     |            |          |          | 1 RCT—favoured IAGC                 |                                                                          |
|                     |            |          |          | 1 RCT—no between-group difference    |                                                                          |
| **Platelet-rich plasma** |            |           |          |                                      |                                                                          |
| Medina-Porqueres et al<sup>41</sup> | PRP vs HA | 1 month   | Pain     | MD = −0.58 (−1.82 to 0.65) (VAS), no difference | All comparisons vs HA                                                    |
|                     |            | 6 months  |          | MD = 0.20 (−1.36 to 1.77) (VAS), no difference |                                                                          |
|                     |            | 12 months |          | MD = −0.42 (−1.80 to 0.96) (VAS), no difference |                                                                          |
|                     |            | 2–12 months | Function | 3 RCTs—no between-group difference (HHS) |                                                                          |
|                     |            |          |          | 1 RCT—favoured HA (WOMAC)            |                                                                          |
|                     |            |          |          | 1 RCT—no between-group difference (WOMAC) |                                                                          |
|                     |            |          |          | 1 RCT—favoured HA (WOMAC)            |                                                                          |
|                     |            |          |          | 1 RCT—no between-group difference (WOMAC) |                                                                          |

Continued
Results on withdrawal due to AEs were obtained after pooling 23 RCTs, but the effect disappeared when restricting the analysis to large-blinded RCTs. One SR reported significant differences between HA and IA GC, favouring the latter for joint pain after injection (17% vs 3.2%).

Safety results for HA in HOA were also reassuring, with no between-group differences observed for any of the outcomes of interest, except for an episode of septic arthritis, reported in an RCT (vs placebo) included in the SR by Liao et al. Other SRs of HA for shoulder capsulitis and RA also did not report differences between groups.

IA GC behaved similarly to placebo without any differences in safety outcomes in all SRs included in this overview for KOA, HOA, shoulder capsulitis, or RA. Of note, Juni et al also did not find differences between IAGC versus sham or no intervention, on any AEs, SAEs, or withdrawals due to AEs. Also, this trend remained consistent when comparing different IA GC compounds and doses. In the same line, SRs on PRP for KOA and HOA showed similar safety profiles than its comparators (mostly HA), except for an RCT in the SR by Medina-Porqueres et al that found significantly more pain after injection in the PRP group. Finally, results for MSC on KOA were in line with the previously described.

**DISCUSSION**

To our knowledge, this is the first overview of published SR summarising the efficacy and safety of the most frequently used IA treatments. Based on the available literature, we assessed the performance of five treatment groups in four arthropathies. Most studies evaluated the effects of IAT on KOA and HOA. The average quality of the SRs was moderate, and high heterogeneity was a constant, prompting authors to be conservative when concluding. Most compounds evaluated presented a small effect for relieving pain and improving function, but with inconsistent results and a high risk of bias in most cases. Regarding safety, the frequency of AEs was low, and only a few SAEs were reported, without clear differences between the different injectables assessed.

HA compounds showed a modest effect on pain and function in KOA and RA and no effect on HOA or shoulder capsulitis. Of note, the effects seen for the former, despite
| Study               | Comparison       | Follow-up | Outcomes | Effect estimate                      | Comments                                                                                                                                 |
|---------------------|------------------|-----------|----------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| **Shoulder capsulitis** |                  |           |          |                                      |                                                                                                                                           |
| Lee et al<sup>44</sup> | HA vs PBO        | 3–6 months| Pain     | 1 RCT—no between-group difference (VAS) |                                                                                                                                           |
|                     |                  |           |          |                                      |                                                                                                                                           |
|                     |                  |           | Function | 1 RCT—no between-group difference (Constant score) |                                                                                                                                           |
|                     |                  |           |          | 1 RCT—no between-group difference (ROM) |                                                                                                                                           |
| Buchbinder et al<sup>43</sup> | IAGC vs PBO      | 4 weeks   | Pain     | 1 RCT—no between-group difference (VAS) (vs PBO) |                                                                                                                                 |
|                     |                  |           |          |                                       |                                                                                                                                           |
|                     |                  | 6 weeks   |          | 1 RCT—no between-group difference (VAS) (TA 40 mg vs 10 mg) |                                                                                                                                 |
|                     |                  | 4 weeks   | Function | 1 RCT—no between-group difference (ROM) |                                                                                                                                           |
|                     |                  | 6 weeks   |          | 1 RCT—favour higher dose (ROM) (TA 40 mg vs 10 mg) |                                                                                                                                 |
|                     |                  | 4 weeks   | Success frequency | 1 RCT—no between-group difference |                                                                                                                                 |
| Sun et al<sup>45</sup> | IAGC vs PBO      | 4–6 weeks | Pain     | MD=1.28 cm (0.75 to 1.82) (VAS), favouring IAGC | Comparisons with sham or no injection Passive external rotation and abduction were significantly improved in IAGC-treated patients (vs PBO) at all 3 time-points |
|                     |                  | 12–16 weeks|          | MD=1.00 cm (0.47 to 1.52) (VAS), favouring IAGC |                                                                                                                                 |
|                     |                  | 24–26 weeks|          | MD=0.65 cm (0.19 to 1.10), favouring IAGC |                                                                                                                                 |
|                     |                  | 4–6 weeks  | Composite scores | MD=16.62 (11.16 to 22.09), favouring IAGC (SPADI) |                                                                                                                                 |
|                     |                  | 12–16 weeks|          | MD=13.46 (8.15 to 18.77), favouring IAGC (SPADI) |                                                                                                                                 |
|                     |                  | 24–26 weeks|          | MD=9.91 (2.32 to 17.50), favouring IAGC (SPADI) |                                                                                                                                 |
|                     |                  | 4–6 weeks  |          | MD=5.30 (4.38 to 14.98), no difference (ASES) |                                                                                                                                 |
|                     |                  | 12–16 weeks|          | MD=12.20 (2.55 to 21.85), favouring IAGC (ASES) |                                                                                                                                 |
|                     |                  | 24–26 weeks|          | MD=7.30 (2.02 to 16.62), no difference (ASES) |                                                                                                                                 |
|                     |                  | 12–16 weeks|          | MD=5.70 (0.59 to 11.99), no difference (Constant score) |                                                                                                                                 |
|                     |                  | 4–6 weeks  | Function | MD=20.26° (9.70 to 30.83) favouring IAGC (ROM—Int Rotation) |                                                                                                                                 |
|                     |                  | 12–16 weeks|          | MD=0.81° (0.18 to 1.44) favouring IAGC (ROM—Int Rotation) |                                                                                                                                 |
|                     |                  | 24–26 weeks|          | MD=3.88° (0.51 to 7.25) favouring IAGC (ROM—Int Rotation) |                                                                                                                                 |
| **Rheumatoid arthritis** |                  |           |          |                                      |                                                                                                                                           |
| Saito and Kotake<sup>47</sup> | HA vs PBO        | 1 week    | Pain     | RR=1.64 (1.14 to 2.35), favouring HA | Outcomes were measured with a Likert scale ranging from ‘no improvement’ to ‘marked improvement’                                          |
|                     |                  |           | Global Inflammation | RR=1.61 (1.34 to 1.92), favouring HA |                                                                                                                                 |
|                     |                  |           | Overall effectiveness | RR=1.50 (1.14 to 1.97), favouring HA |                                                                                                                                 |

Continued
remaining, were reduced when pooling only large studies with low risk of bias or longer follow-up. HA showed a better OMERACT-OARSI response in KOA versus placebo and IA GC. Only one SR assessed the effects of different HA compounds in KOA and observed differences in favour of those with higher MW on the WOMAC, but authors acknowledge there were too few studies to conclude about the superiority of one group over another. Regarding its effect on RA, it should be noted that the only SR addressing this topic included five RCTs performed in Asian populations and efficacy was measured using scales that are seldom used, and evidence of publication bias, so the results should be interpreted with caution.

The body of evidence of IA GC in the target diseases was smaller compared with that of HA, very likely due to greater industry support for HA. Similarly, its effect versus placebo on pain and function in KOA ranged from a small, but significant, short-term effect to no effect. In contrast, IA GC showed a better, although modest, performance on HOA and shoulder capsulitis. Likewise, no evidence of an effect on QoL or joint space narrowing was observed. One SR compared different IAGC compounds in KOA and found no differences in the outcomes of interest, except for a longer effect of MPA compared with TH.  

Although IA GC have been among the most widely used tools for managing inflammatory arthritis for years, our search strategy did not retrieve any SR including RCTs comparing them against PBO. Only one study evaluated three different GC compounds in RA and found no differences between them in all outcomes evaluated except for pain VAS at 1 week of follow-up in which the analysis favoured TH.

SRs including RCTs on PRP are still limited and our strategy only retrieved articles assessing its performance on KOA and HOA. There were only a few RCTs included and substantial overlapping between SRs. Overall, better performance for pain and function was seen in KOA with large effects reported when pooling composite scores compared with placebo or HA. This trend was not present in HOA, with only a few RCTs showing modest effects on pain. One consistent observation between studies was that the PRP effect lasted longer than its comparators (mostly HA).

### Table 4 Continued

| Study                  | Comparison                                      | Follow-up   | Outcomes | Effect estimate                                                   | Comments                                                                 |
|------------------------|------------------------------------------------|-------------|----------|------------------------------------------------------------------|--------------------------------------------------------------------------|
| Silvinato and Bernardo | MPA vs TH, TA or prednisolone                  | 4–24 weeks  | Pain     | 1 RCT—MPA vs TA. No between-group difference (VAS)               | #Results of the same study at 2 time-points                              |
|                         |                                                | 1 week      |          | 1 RCT—MPA vs TH vs prednisolone. Favour TH (VAS)#                 |                                                                          |
|                         |                                                | 2–6 weeks   |          | 1 RCT—MPA vs TH vs prednisolone. No difference (VAS)#            |                                                                          |
|                         |                                                | 4–24 weeks  | No° of flares | 1 RCT—MPA vs TA. No between-group difference                  |                                                                          |
|                         |                                                | 1–6 weeks   | Morning stiffness | 1 RCT—MPA vs TH vs prednisolone. No difference |                                                                          |
|                         |                                                |             | ROM      | 1 RCT—MPA vs TA. No between-group difference                  |                                                                          |
|                         |                                                |             | Ritchie articular index | 1 RCT—MPA vs TH vs prednisolone. No difference |                                                                          |
|                         |                                                |             | Thermography index | 1 RCT—MPA vs TH vs prednisolone. No difference |                                                                          |
| Heuft-Dorenbosch et al | Yttrium synovectomy vs PBO or TH              | 6–12 months | Pain     | 2 RCTs—no between-group difference                              | No differences in any other outcome (subjective change, knee effusion, etc) |
|                         |                                                | 6 months    | ROM      | 1 RCT—favouring yttrium synovectomy (vs PBO)                     |                                                                          |
|                         |                                                | 12 months   | ROM      | 1 RCT—favouring TA (vs yttrium synovectomy)                     |                                                                          |
|                         |                                                | 12 months   | Knee circumference | 1 RCT—favouring yttrium (vs PBO) |                                                                          |

All effect sizes are presented as the point estimate (95% CI) unless otherwise stated. ASES, American Shoulder and Elbow Surgeons score; HA, hyaluronic acid; IAGC, intra-articular glucocorticoids; MD, mean difference; MPA, methylprednisolone acetate; PBO, placebo; RCT, randomised controlled trials; ROM, range of motion; Int Rotation, internal rotation; RR, relative risk; SPADI, Shoulder Pain and Disability Index; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide; VAS, Visual Analogue Scale.
| Study           | Comparison              | Follow-up | Outcomes        | Effect estimate                                                                 | Comments                                                                 |
|-----------------|-------------------------|-----------|-----------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Knee osteoarthritis** |                         |           |                 |                                                                                 |                                                                          |
| Bannuru et al<sup>4</sup> | HA vs PBO              | 4–52 weeks| Any AEs         | No between group differences (vs PBO)                                           | NMA specifically aimed at analysing safety. Comparisons are between PBO and all RCTs of individual HA products. No pooled analysis of HA as a group was carried on. |
|                 | Local reactions         |           |                 | Analyses favoured PBO for 2/17 products assessed                                |                                                                          |
|                 | Withdrawal due to AEs   |           |                 | Analyses favoured PBO for 1/11 products assessed                                |                                                                          |
| Bannuru et al<sup>5</sup> | HA vs PBO              | 2–6 months| Any AE          | HA vs PBO: 16 (54.6) vs 21.7 (56.0)                                             | No pooled analysis was carried on. Results are median (IQR) of event rates, % |
|                 | HA vs IAGC              |           |                 | HA vs IAGC: 0.0 (64.6) vs 5.5 (57.2)                                             |                                                                          |
|                 | IAGC vs PBO             |           |                 | IAGC vs PBO: No data                                                           |                                                                          |
|                 | SAEs                    |           |                 | HA vs PBO: 0 (0.9) vs 0 (0)                                                      |                                                                          |
|                 | HA vs IAGC              |           |                 | HA vs IAGC: 0.0 (2.0) vs 0.0 (4.3)                                               |                                                                          |
|                 | IAGC vs PBO             |           |                 | IAGC vs PBO: No data                                                           |                                                                          |
|                 | Withdrawal due to AEs   |           |                 | HA vs PBO: 0.9 (3.9) vs 1.0 (2.6)                                               |                                                                          |
|                 | HA vs IAGC              |           |                 | HA vs IAGC: 1.9 (3.7) vs 2.7 (6.0)                                               |                                                                          |
|                 | IAGC vs PBO             |           |                 | IAGC vs PBO: 0.0 (3.5) vs 0.0 (1.7)                                              |                                                                          |
|                 | Local reactions         |           |                 | HA vs PBO: 8.4 (14.4) vs 4.7 (16.1)                                              |                                                                          |
|                 | HA vs IAGC              |           |                 | HA vs IAGC: 2.2 (21.8) vs 3.0 (9.1)                                              |                                                                          |
|                 | IAGC vs PBO             |           |                 | IAGC vs PBO: 3.3 (17.9) vs 6.9 (8.0)                                             |                                                                          |
|                 | Septic joint            |           |                 | HA vs PBO: 0 (0) vs 0 (0)                                                        |                                                                          |
|                 | HA vs IAGC              |           |                 | HA vs IAGC: 0 (0) vs 0 (0)                                                        |                                                                          |
|                 | IAGC vs PBO             |           |                 | IAGC vs PBO: 0 (0) vs 0 (0)                                                        |                                                                          |
| Newberry et al<sup>22</sup> | HA vs PBO              | 1–12 months| Local reactions | OR 0.70 (0.48 to 1.03). No between-group difference                             |                                                                          |
|                 | Joint pain              |           |                 | OR 0.83 (0.60 to 1.15). No between-group difference                              |                                                                          |
|                 | Serious joint reactions |           |                 | OR 0.77 (0.25 to 2.31). No between-group difference                              |                                                                          |
|                 | Other AE                |           |                 | OR 1.26 (0.94 to 1.68). No between-group difference                              |                                                                          |
|                 | Other SAE               |           |                 | OR 0.62 (0.23 to 1.57). No between-group difference                              |                                                                          |
| Study                  | Comparison | Follow-up | Outcomes | Effect estimate | Comments |
|-----------------------|------------|-----------|----------|-----------------|----------|
| Trojan et al<sup>30</sup> | HA vs PBO  | 2–6 months | Joint pain | 1 RCT—HA vs IAGC —17% vs 3.2%, p<0.05 | Some RCTs did not report data on withdrawal due to AE |
|                       | IAGC vs PBO |           |          | 10 RCT—no between-group difference |          |
|                       | HA vs IAGC  |           |          | 11 RCTs—no between-group difference |          |
|                       |            |           | ANY AE   | 11 RCTs—no between-group differences |          |
|                       |            |           | SAEs     | 11 RCTs—no between-group differences |          |
|                       |            |           | Withdrawal due to AEs | 4 RCTs—no between-group differences |          |
| Rutjes et al<sup>7</sup> | HA vs sham or no intervention | 3 months | Local reactions | RR=1.34 (1.13 to 1.60) | †RR for SAE resulted from pooling 14 RCTs. VRR for withdrawals resulted from pooling 23 RCTs. The effect was not maintained when pooling large unblinded RCTs. |
|                       |            |           | ANY AE   | RR=1.04 (0.99 to 1.09). No between-group differences |          |
|                       |            |           | SAEs†     | Overall, RR=1.41 (1.02 to 1.97) Large blinded RCTs, RR=1.55 (1.07 to 2.24) RR=1.33 (1.01 to 1.74) |          |
| Brazilian Medical Association<sup>34</sup> | MPA vs TA or TH or BP | 4–24 weeks | ANY AE   | RR=0.89 (0.64 to 1.23) |          |
|                       |            |           | SAEs     | RR=0.63 (0.15 to 2.67) |          |
|                       |            |           | Withdrawal due to AEs| RR=0.33 (0.05 to 2.07) |          |
| Jüni et al<sup>23</sup> | IAGC vs sham or no intervention | 2 weeks to 6 months | ANY AE | RR=1.40 (0.80 to 2.45). No SAEs were identified | Comparisons were mainly with HA |
|                       |            |           | SAEs     | RR=0.85 (0.57 to 1.28) (vs HA) RR=6.30 (0.34 to 117.48) (vs PBO) |          |
| Shen et al<sup>29</sup> | PRP vs HA or IAGC or PBO | 3–12 months | ANY AE | RR=0.63 (0.20 to 1.98) (vs HA) RR=2.63 (0.04 to 158.93) (vs PBO) |          |
|                       |            |           | SAEs     | No data reported |          |
| Kanchanatawan et al<sup>25</sup> | PRP vs HA or PBO | 6–12 months | ANY AE | RR=1.85 (0.63 to 5.57) |          |
|                       |            |           | SAEs     | No data reported |          |
| Dai et al<sup>27</sup> | PRP vs HA or PBO | 6–12 months | ANY AE | RR=2.63 (0.04 to 158.93) |          |
|                       |            |           | SAEs     | No data reported |          |
| Di et al<sup>32</sup>  | PRP vs HA  | 1–12 months | ANY AE   | 1 RCT—significantly more pain in PRP group 1 RCT—reported no AEs 1 RCT—safety data reported 4 RCT—no between-group differences SAE |          |
|                       |            |           | SAEs     | 5 RCT—reported no SAEs |          |
| Ding et al<sup>24</sup> | MSC vs PBO or HA or IAGC | 6–12 months | ANY AE | No data reported |          |
|                       |            |           | SAEs     | OR=1.95 (0.89 to 4.26) |          |

Continued
MSCs appear to be a potentially promising treatment for OA, but SRs including RCTs are scarce. Our strategy only retrieved one SR in KOA that met our inclusion criteria. Moderate to large effects were seen for KOOS and pain, respectively, that lasted until 12 months of follow-up. However, the data in which to draw firm conclusions were scarce. Finally, our thorough search retrieved one SR that evaluated radioisotopic synovectomy for RA in which a modest effect was seen over placebo, whereas it was outperformed by IA GC for some outcomes, such as ROM.

Although we are aware that safety is best studied in large long-term observational studies, we retrieved information regarding AEs from the SRs of RCTs. Of note, many of them did not report on this aspect. The SR specifically aimed at analysing this for individual HA compounds versus different comparators found a frequency of any AE remarkably low and no increased risk or only for local reactions.

### Table 5

| Study          | Comparison                  | Follow-up       | Outcomes          | Effect estimate                  | Comments                                                                 |
|---------------|-----------------------------|-----------------|-------------------|----------------------------------|--------------------------------------------------------------------------|
| Leite et al   | HA vs PBO or MPA            | 1–12 months     | Any AE            | RR=1.07 (0.78 to 1.48) (vs PBO)   | RR=2.24 (0.24 to 20.85) (vs MPA) 3 RCTs—no between-group differences.    |
| Liao et al    | HA vs PBO                   | 2 weeks to 6 months | Any AE            | 4 RCTs—no between-group differences | SAE 1 RCT—one septic arthritis episode on the HA group Withdrawal due to AEs 1 RCT—no between-group differences |
| McCabe et al  | IAGC vs PBO                 | 1–3 months      | Any AE            | 2 RCTs—none reported             | 2 RCTs—no between-group differences                                      |
| Medina-Porqueres et al | PRP vs HA                       | 1–12 months     | Any AE            | 1 RCT—more pain in PRP group (p<0.05) 1 RCT—reported one sup haematoma on PRP group |
| Ye et al      | PRP vs HA                   | 2–12 months     | Any AE            | RR=0.95 (0.40 to 2.24)           |                                                                 |
| Lee et al     | HA vs PBO                   | 3–6 months      | Any AE            | 2 RCTs—no AE reported            | 2 RCTs—no data on AE                                                    |
| Buchbinder et al | TA 40 mg vs TA 10 mg         | 4–6 weeks       | Any AE            | No between-group differences     |                                                                         |
| Sun et al     | IAGC vs PBO                 | 4–26 weeks      | Any AE            | 3 RCTs—no between-group differences 5 RCTs—no data on AE                 |
| Saito and Kotake | HA vs PBO                      | 1 week          | Any AE            | RR=0.98 (0.94 to 1.02)           |                                                                         |
| Silvinato and Bernardo | MPA vs TH or TA             | 1–6 months      | Any AE            | 1 RCT—no AE reported             | 1 RCT—no data on AE                                                     |

All effect sizes are presented as the point estimate (95% CI) unless otherwise stated.

AE, adverse events; HA, hyaluronic acid; IAGC, intra-articular glucocorticoids; MPA, methylprednisolone acetate; MSC, mesenchymal stem cells; NMA, Network Meta-analysis; PBO, placebo; PRP, platelet-rich plasma; RCT, randomised controlled trials; RR, relative risk; SAE, serious adverse events; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide.
studied to date. However, this was not translated into a better quality of evidence, preventing authors from drawing firm conclusions regarding many of the studied outcomes. Most of the trials included in the different SRs, especially the ones of PRP and MSC, were highly heterogeneous in terms of the composition of the PRP or the kind of MSC and the procedures used to deliver them. The overall risk of bias within all SRs in this work was high, mostly because of inadequate blinding, allocation concealment, selective reporting, or publication bias.

It should be also noted that, even although all compounds studied presented modest effect sizes, many authors underlined the fact that a proportion of the effect may be due to the placebo effect that accompanies injections, something that should be acknowledged when interpreting their results.

This overview of SR has some strengths, such as the comprehensive summary of the currently available IAT including a large number of RCTs. However, it has some limitations. First, including only SRs of RCTs might have precluded the analysis of more recent studies still not included in said reviews, as well as a deeper evaluation of some treatments, such as MSC in OA or GC in inflammatory arthropathies. Second, for the most frequent diseases affecting the shoulder, SRs usually analyse both IA and peri-articular procedures together, which fell out of the scope of the present work, thus leading us to exclude them. Third, most information analysed in this work concerned some frequently assessed outcomes, such as pain and function, but only a few studies examined structural outcomes like joint space narrowing or cartilage volume loss, which are currently receiving more attention. Finally, a more thorough search in additional databases would have been desirable; but given the large amount of hits retrieved and the fact that we were looking for SRs, the potential selection bias would be kept at a minimum.

In summary, the evidence shows that IAT in the most frequent arthropathies is well tolerated, with a very low frequency of AEs, but only marginally efficacious in the short-to-medium-term when compared with placebo. Nonetheless, it should be noted that the limited data found regarding the efficacy and safety of IAT in inflammatory arthropathies prevented us from drawing firm conclusions.
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