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ORIGINAL RESEARCH

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

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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 heterogeneous 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.

Key messages

What is already known about this subject?

- ► Intra-articular therapies are frequently used in clinical practice by a wide range of health professionals from different specialties.Several compounds are currently available for intra-articular administration, from glucocorticoids to the more recent platelet-rich plasma or mesenchymal stem cells. Nonetheless, data on their efficacy in certain diseases are inconsistent and a matter of debate.

What does this study add?

- ► 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.

How might this impact on clinical practice or future developments?

- ► This overview of systematic reviews informed the task force for the 2021 EULAR recommendations for intra-articular therapies and constitutes an evidence base for future updates

INTRODUCTION

Intra-articular therapies (IAT) have been widely used in clinical practice for years to reduce joint pain and improve function.[1] 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.[2 3] However, evidence on the efficacy and safety of available therapies is not always consistent, due in part to methodological limitations in published trials.[4 5]

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.[6–10] 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 index[18] 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

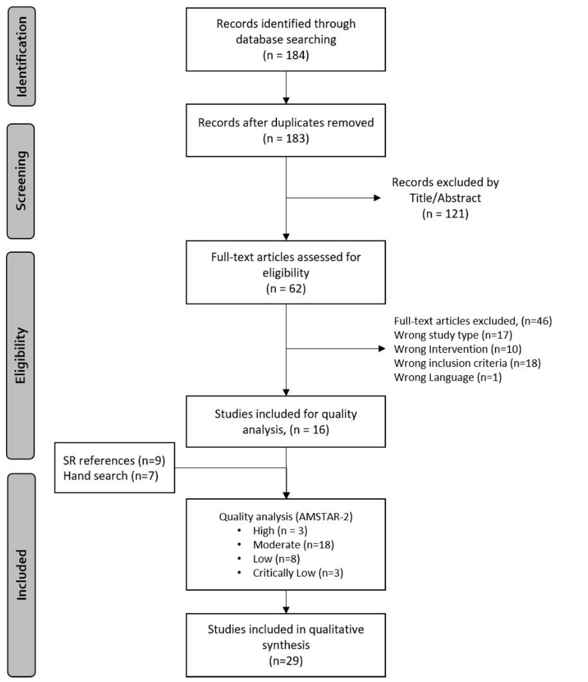

Figure 1 Flow chart of the overview of systematic reviews (SR).

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,[43–45] and RA in 3.[34 46 47] One SR analysed the efficacy of IAT in both KOA and RA.[34] Different HA-containing compounds were assessed in 13 SR,[4–7 22 30 31 33 35 37 40 44 47] PRP in 8,[25–27 29 32 36 39 41 42] GC in 6,[23 28 34 38 43 45] and MSC and yttrium synovectomy in 1 each.[24 46]

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,[21] the effect sizes observed for the intervention on pain and function were small and further reduced to no effect when pooling large-blinded 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).[22] 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.[23] 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.[24] 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

Table 1 Main characteristics of the SR included

Study	Population	Intervention and comparator	Outcomes	Quality
Knee osteoarthritis				
Rutjes *et al*[7]	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*[22]	IC: RCTs, SRs, OS, and CS* 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*[23]	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*[24]	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*[4]	IC: RCTs of patients treated with HA 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*[6]	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*[5]	IC: RCTs of patients 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*[25]	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*[26]	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*[27]	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[28]	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*[29]	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

Table 1 Continued

Study	Population	Intervention and comparator	Outcomes	Quality
Trojian *et al*[30]	IC: RCTs in English including outcomes of interest at ≥8 and <16 weeks. EC: studies comparing IA GC or HA vs surgical procedures	HA vs PBO or IAGC IAGC vs PBO	OMERACT-OARSI response rates, mean change from baseline in WOMAC pain, stiffness or function, frequency of AE. Without hierarchy	Moderate
Gallagher *et al*[31]	IC: RCTs with PBO control, ≥12 m follow-up, data on structural changes EC: not stated	HA or SOC vs PBO†	Primary: changes in JSW or cartilage volume. Secondary: WOMAC total score, WOMAC pain or VAS pain	Moderate
Di *et al*[32]	IC: English-written RCTs EC: unknown methodology or patients with additional conditions‡	PRP vs HA	Primary: WOMAC, IKDC, KOOS, EQ-VAS, Tegner score. Secondary: frequency of AE between groups	Low
Trigkilidas and Anand[35]	IC: RCTs with ≥1 outcome measure on pain or function; freely available as full text from specified sources§ EC: non-RCT and language other than English	HA vs PBO or IAGC	VAS pain, Lequesne, WOMAC without a prespecified hierarchy	Low
Lo *et al*[33]	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% EC: not stated	HA vs PBO	Pain according to a prespecified hierarchy	Low
Hip osteoarthritis				
Ali *et al*[36]	IC: RCTs, with clinical and functional data with any follow-up EC: studies on animals and technical notes	PRP vs HA	VAS pain, WOMAC total, and HHS without a prespecified hierarchy	Moderate
McCabe *et al*[38]	IC: RCTs with patients with HOA (clinical and radiographic) EC: studies without a control group	IAGC vs PBO	Primary: pain according to a prespecified hierarchy Secondary: WOMAC function, Lequesne Index, safety profile	Moderate
Liao *et al*[37]	IC: RCTs of patients with primary HOA EC: stated as the opposite to IC	HA vs PBO	Primary: self-reported pain according to a prespecified hierarchy Secondary: function, OMERACT-OARSI responder index	Moderate
Medina-Porqueres[41]	IC: English or Spanish-written studies of PRP applied in isolation in ≥1 arm to patients with any grade of HOA as per the ACR criteria EC: studies including only children or animals; non-OA injuries, OA in other joints or previous surgery	PRP vs IA control (any)	Primary: VAS pain, HHS, and WOMAC function. Secondary: growth factor's concentration, AE and imaging evaluations	Low
Ye *et al*[42]	IC: RCTs comparing PRP with HA EC: studies without a control group, full-text versions or outcomes data	PRP vs HA	Primary: WOMAC total score, VAS pain, and Harris hip score (HHS) Secondary: n of AE	Low

Continued

Table 1 Continued

Study	Population	Intervention and comparator	Outcomes	Quality
Leite *et al*[40]	IC: RCT with ≥1 of the outcomes of interest EC: RCT comparing HOA vs other sites and HA vs non-IA controls	HA vs IA-injection comparators	Primary: pain Secondary: QoL, OMERACT-OARSI Response, frequency of AEs	Low
Shoulder capsulitis				
Sun *et al*[45]	IC: RCTs comparing IAGC vs no or sham injection or SOC EC: injection volume >0.10 mL (classified as IAGC+distention)	IAGC vs sham or SOC	Primary: VAS pain Secondary: passive external rotation, abduction, flexion, internal rotation,and functional scores and frequency of AEs	Moderate
Buchbinder *et al*[43]	IC: RCTs of shoulder pain comparing IAGC vs PBO, another intervention or different IAGC dosages EC: pain duration <3 weeks, RA, polymyalgia rheumatica, and fracture	IAGC vs PBO, other interventions	Pain, ROM, function, strength, and return to work or school without a prespecified hierarchy	Moderate
Lee *et al*[44]	IC: RCT of capsulitis (confirmed clinically or by US), clearly documenting IC and EC, symptom duration and follow-up >4 weeks EC: uncontrolled studies	HA vs SOC	Pain, ROM, and function/disability scores >1 month after administration, frequency of AEs without a prespecified hierarchy	Moderate
Rheumatoid arthritis				
Heuft-Dorenbosch *et al*[46]	IC: RCTs of RA patients with knee arthritis, enough quality as per the Delphi list. Language restrictions applied¶ EC: not stated	Yttrium synovectomy vs PBO or TH	Knee circumference, ROM, fixed flexion, pain (Likert scale), subjective change, knee effusion, radiological assessment without prespecified hierarchy	Moderate
Silvinato and Bernardo[34]	IC: RCTs of patients with RA and knee arthritis EC: not stated	MPA vs TA, TH, prednisolone	Primary: flare time at 24 weeks, Secondary: patient-reported pain and swelling, ROM, frequency of AEs	Low
Saito and Kotake[47]	IC: English or Japanese-written RCTs of patients with RA and knee arthritis including pain assessment EC: studies with animals or only describing the injection technique	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

*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.

RCTs showed no difference between groups at all time points except for the study by Ye *et al*,[42] 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 2 Main efficacy results of IAT for knee osteoarthritis

Study	Follow-up	Outcomes	Effect estimate	Comments
Hyaluronic acid vs placebo				
Rutjes *et al*[7]	3 mo	Pain	Overall (ES, 0.37 (0.28 to 0.46)), favouring HA Large-blinded RCTs (ES, 0.11 (0.04 to 0.18)), 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*[22]	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-5D)	
Gallagher *et al*[31]	12–24 mo	Pain	2 RCTs—no between-group difference (VAS)	
		Δ JSW	2 RCTs—no between-group difference	
		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	
Bannuru *et al*[5]	3 mo	Pain	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
		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	
Trojian *et al*[30]	2–6 mo	Pain	SMD, 0.19 (0.06 to 0.32), favouring HA (WOMAC)	NMA. SMD refers to Hedges' g Results obtained for the time of best response No publication bias
		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[35]	1–6 mo	Pain	5 RCTs—no between-group difference (VAS)	No pooled analysis
			7 RCTs—favoured HA (VAS) (small effect)	
		Function	5 RCTs—no between-group difference (WOMAC, Lequesne)	
			7 RCTs—favoured HA (WOMAC) (small effect, Lequesne)	
Lo *et al*[33]	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* [6]	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
	3–6 wk		ES, −0.01 (−0.23 to 0.21), no between-group difference	
	7–10 wk		ES, 0.22 (0.05 to 0.49), favouring HA	
	11–16 wk		ES, 0.35 (0.03 to 0.66), favouring HA	
	17–29 wk		ES, 0.39 (0.18 to 0.59), favouring HA	
Bannuru *et al* [5]	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	
Trojian *et al*[30]	4–40 mo	Pain	ES, −0.06 (−0.28 to 0.16), no between-group difference	NMA SMD refers to Hedges' g Results retrieved at the time of best response No publication bias
		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[35]	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				

Continued

Table 2 Continued

Study	Follow-up	Outcomes	Effect estimate	Comments
Newberry *et al* [22]	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 No pooled analysis *Results of the same study[54] at 2 time-points
			1 RCT—LMW vs HMW. SMD, 0.053 (−0.66 to 0.77), no difference	
			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*[23]	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[28]	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* [5]	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[34]	1–6 mo	Pain	1-RCT—MPA vs TH. No between-group difference (VAS)	*Results of the same study at 2 time-points ¥Results of the same study at 2 time-points No pooled analysis
	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-RCT¥—MPA vs TH, favouring MPA (VAS)	
	2 mo		1-RCT¥—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	
Platelet-rich plasma vs placebo				

Continued

Table 2 Continued

Study	Follow-up	Outcomes	Effect estimate	Comments
Xu *et al*[49]	6 mo	Composite scores#	Overall, SMD −2.13 (−3.29 to −0.98), favouring PRP	#Effects of pooled results from WOMAC and IKDC scores
Dai *et al*[27]	6–12 mo	Pain	1 RCT—favoured PRP (WOMAC)	
		Function	1 RCT—favoured PRP (WOMAC)	
Kanchanatawan *et al*[25]	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				
Xu *et al*[26]	6 mo	Composite scores¶	Overall, SMD = −0.85 (−1.43 to −0.28) favouring PRP	¶ Refers to observed effects when pooling results from WOMAC and IKDC scores
			High-quality RCTs, SMD = −0.09 (−0.30 to 0.11). No difference	
		Pain	SMD=0.35 (−0.36 to 1.06) (VAS). No difference	
		Function	MD=−0.20 (−1.00 to 0.60) (Lequesne). 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*[29]	3–12 mo	Pain	MD=−3.77 (−5.07 to −2.47), favouring PRP (WOMAC)	Results obtained from pooling outcomes at 3, 6, and 12 months
		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*[27]	6 mo	Pain	MD=−1.54 (−4.27 to 1.20). No between-group difference	§Results from pooling WOMAC total, IKDC,**EQ** and Lequesne Index
	12 mo		MD=−2.83 (−4.26 to −1.39), favouring PRP	
	6 mo	Function	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§	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*[25]	6–12 mo	Composite scores§	MD= −15.4 (−28.6 to −2.30), favouring PRP (WOMAC total)	§Results for WOMAC total and IKDC reached the prespecified MCID
			MD=8.83 (5.88 to 11.78), favouring PRP (IKDC)	
		Pain	No between-group difference (WOMAC)	
		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*[32]	1–12 mo	Pain	5 RCTs—favoured PRP (VAS, WOMAC)	No pooled analysis
			1 RCT—no between-group difference (VAS)	
		Function	3 RCTs—favoured PRP (WOMAC, Lequesne, KOOS)	
			3 RCTs—no between-group difference (WOMAC, Lequesne, etc)	
		Stiffness	2 RCTs—favoured PRP (WOMAC)	
			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

Table 2 Continued

Study	Follow-up	Outcomes	Effect estimate	Comments
Ding *et al*[24]	6 mo	Composite scores	SMD=−0.36 (−0.90 to 0.18). No difference (WOMAC total) vs controls	NMA. Controls include HA, PBO, and GC. High-dosage adipose-derived MSC showed a longer effect
	12 mo		SMD=0.68 (0.07 to 1.30), favouring MSC (KOOS) vs controls	
	12 mo	Pain	SMD= −1.05 (−1.46 to −0.64), favouring MSC vs controls	

Results are ordered by compounds and quality. The colour of the cell denotes quality: the darker the higher the quality. All effect sizes (ESs) are presented as a point estimate (95% CI) unless otherwise noted.
Cr I, credible intervals; EQ-VAS, Euro Quality of Life – Visual Analogue Scale; EuroQol-5D, Euro Quality of Life – 5 Dimension questionnaire; GC, glucocorticoids; HA, hyaluronic acid; HMW, high molecular weight; IAGC, intra-articular glucocorticoids; IAT, intra-articular therapies; IKDC, International Knee Documentation Committee; ΔJSW, change in joint space width; KOOS, Knee injury and Osteoarthritis Outcome Score; LMW, low molecular weight; MCID, minimal clinically important difference; MD, mean difference; MMW, medium molecular weight; mo, months; MPA, methylprednisolone acetate; MSC, mesenchymal stem cells; NMA, network meta-analysis; O-O Resp, OMERACT-OARSI Responder Index; PBO, placebo; PRP, platelet-rich plasma; QoL, quality of life; RCT, randomised controlled trials; RR, relative risk; SF-36, Short Form 36 health survey; SMD, standardised mean difference; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide; VAS, Visual Analogue Scale; wk, weeks; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

No differences were observed for pain, function nor OMERACT-OARSI response between HA and placebo or MPA. McCabe *et al*,[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[44] 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[47] observed better performance of HA over placebo for pain, global inflammation, and self-reported effectiveness. Brazilian Medical Association[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 *et al*[46] 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.[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 *et al*[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*[40]	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*[37]	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.[55] 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*[38]	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)	
				1 RCT—no between-group difference	
			ROM	1 RCT—favoured IAGC	
				1 RCT—no between-group difference	
Platelet-rich plasma					
Medina-Porqueres *et al*[41]	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)	
			Stiffness	1 RCT—favoured HA (WOMAC)	
				1 RCT—no between-group difference (WOMAC)	

Continued

Table 3 Continued

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Ye *et al*[42]	PRP vs HA	2 months	Pain	WMD=−0.38 (−0.61 to −0.14), favouring PRP (vs HA)	All comparisons vs HA
		6 months		WMD=−0.14 (−0.40 to 0.12), no between-group difference	
		12 months		WMD=−0.0 (−0.34 to 0.12), no between-group difference	
		2 months	Function	WMD=2.07 (−2.66 to 6.79) (HHS), no difference	
		6 months		WMD=2.78 (−6.64 to 12.20) (HHS), no difference	
		12 months		WMD=0.71 (−6.33 to 7.75) (HHS), no difference	
		6 months		WMD=−2.84 (−6.25 to 0.57) (WOMAC), no difference	
		12 months		WMD=−3.13 (−6.62 to 0.36) (WOMAC), no difference	
Ali *et al*[36]	PRP vs HA	2–12 months	Pain	1 RCT—favoured PRP (VAS)	All comparisons vs HA
				2 RCTs—no between-group difference (VAS)	
			Function	1 RCT—no between-group difference (HHS)	
				1 RCT—favoured PRP (WOMAC)	
				1 RCT—no between-group difference (WOMAC)	

All effect sizes are presented as the point estimate (95% CI) unless otherwise stated.
ADL, activities of daily life; HA, hyaluronic acid; HHS, Harris Hip Score; IAGC, intra-articular glucocorticoids; MD, mean difference; MPA, methylprednisolone acetate; O-O Resp, OMERACT-OARSI Responder Index; PBO, placebo; PRP, platelet-rich plasma; RCT, randomised-controlled trials; SMD, standardised mean difference; VAS, Visual Analogue Scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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%).[30]

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*.[37] Other SRs of HA for shoulder capsulitis and RA also did not report differences between groups.[44 47]

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*[23] 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*[41] 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

Table 4 Main efficacy outcomes for shoulder capsulitis and rheumatoid arthritis

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Shoulder capsulitis					
Lee *et al*[44]	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*[43]	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*[45]	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[47]	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

Table 4 Continued

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Silvinato and Bernardo [34]	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	N° of flares	1 RCT—MPA vs TA. No between-group difference	
			ROM	1 RCT—MPA vs TA. No between-group difference	
		1–6 weeks	Morning stiffness	1 RCT—MPA vs TH vs prednisolone. No difference	
			Grip strength	1 RCT—MPA vs TH vs prednisolone. No 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*[46]	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		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.

remaining, were reduced when pooling only large studies with low risk of bias or longer follow-up.[5 7 22 30 31 35] HA showed a better OMERACT-OARSI response in KOA versus placebo and IA GC.[5 6 30 35] 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.[22] 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.[47]

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.[34]

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.[25 27 29 32 39] This trend was not present in HOA, with only a few RCTs showing modest effects on pain.[36 39 41 42] One consistent observation between studies was that the PRP effect lasted longer than its comparators (mostly HA).

Table 5 Main safety outcomes of all included compounds

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Knee osteoarthritis					
Bannuru *et al*[4]	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*[5]	HA vs PBO HA vs IAGC IAGC 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: 0.0 (64.6) vs 5.5 (57.2)	
				IAGC vs PBO: No data	
			SAEs	HA vs PBO: 0 (0.9) vs 0 (0)	
				HA vs IAGC: 0.0 (2.0) vs 0.0 (4.3)	
				IAGC vs PBO: No data	
			Withdrawal due to AEs	HA vs PBO: 0.9 (3.9) vs 1.0 (2.6)	
				HA vs IAGC: 1.9 (3.7) vs 2.7 (6.0)	
				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: 2.2 (21.8) vs 3.0 (9.1)	
				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: 0 (0) vs 0 (0)	
				IAGC vs PBO: 0 (0) vs 0 (0)	
Newberry *et al*[22]	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 join 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	

Continued

Table 5 Continued

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Trojian *et al*[30]	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		Any AE	11 RCTs—no between-group difference	
			SAEs	11 RCTs—no between-group differences	
			Withdrawal due to AEs	4 RCTs—no between-group differences	
Rutjes *et al*[7]	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. ¥RR 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)	
			Withdrawal due to AEs¥	RR=1.33 (1.01 to 1.74)	
Jüni *et al*[23]	IAGC vs sham or no intervention	2 weeks to 6 months	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)	
Brazilian Medical Association[34]	MPA vs TA or TH or BP	4–24 weeks	Any AE	1 RCT—o AE reported	
				1 RCT—no data on AE	
				1 RCT—no between-group differences	
Shen *et al*[29]	PRP vs HA or IAGC or PBO	3–12 months	Any AE	RR=1.40 (0.80 to 2.45).	Comparisons were mainly with HA
			SAE	No SAEs were identified	
Kanchanatawan *et al*[25]	PRP vs HA or PBO	6–12 months	Any AE	RR=0.85 (0.57 to 1.28) (vs HA)	
				RR=6.30 (0.34 to 117.48) (vs PBO)	
			SAEs	No data reported	
Dai *et al*[27]	PRP vs HA or PBO	6–12 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	
Di *et al*[32]	PRP vs HA	1–12 months	Any AE	1 RCT—significantly more pain in PRP group	
				1 RCT—reported no AEs	
				1 RCT—o safety data reported	
				4 RCT—no between-group differences	
			SAE	5 RCT—reported no SAEs	
Ding *et al*[24]	MSC vs PBO or HA or IAGC	6–12 months	Any AE	No data reported	
			SAE	OR=1.95 (0.89 to 4.26)	

Continued

Table 5 Continued

Study	Comparison	Follow-up	Outcomes	Effect estimate	Comments
Hip osteoarthritis					
Leite *et al*[40]	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. (vs PBO)	
Liao *et al*[37]	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*[38]	IAGC vs PBO	1–3 months	Any AE	2 RCTs—none reported 2 RCTs—no between-group differences	
Medina-Porqueres *et al*[41]	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*[42]	PRP vs HA	2–12 months	Any AE	RR=0.95 (0.40 to 2.24)	
Shoulder capsulitis					
Lee *et al*[44]	HA vs PBO	3–6 months	Any AE	2 RCTs—no AE reported 2 RCTs—no data on AE	
Buchbinder *et al*[43]	TA 40 mg vs TA 10 mg	4–6 weeks	Any AE	No between-group differences	
Sun *et al*[45]	IAGC vs PBO	4–26 weeks	Any AE	3 RCTs—no between-group differences 5 RCTs—no data on AE	
Rheumatoid arthritis					
Saito and Kotake[47]	HA vs PBO	1 week	Any AE	RR=0.98 (0.94 to 1.02)	
Silvinato and Bernardo[34]	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 controlledl trials; RR, relative risk; SAE, serious adverse events; TA, triamcinolone acetonide; TH, triamcinolone hexacetonide.

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.[24] 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.[46]

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.[5 6 30 31 33 35–37 39 43 44] 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.[4 7]

Striking differences were seen regarding the number of published articles for the different compounds studied with HA the intervention which has been most widely 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[5 23 35]; 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.[52 53] 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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