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Osteoarthritis (L King, Section Editor)

Intra-articular Therapies for Knee Osteoarthritis: Current Update

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Abstract

Purpose of the review This narrative review highlights recent literature pertaining to available intra-articular (IA) therapeutics such as corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), stem cells therapy, and prolotherapy for knee osteoarthritis (OA) by summarizing recently published treatment guidelines and clinical trials, and discusses opinion and future directions.

Recent findings IA corticosteroid has questionable long-term efficacy in head-to-head comparisons with IA PRP, ketorolac, or normal saline. Combination therapy of IA corticosteroid plus HA may be more effective than a single IA corticosteroid therapy. Significant symptomatic improvement for at least 6 months was detected for combined therapies of IA HA with PRP or diclofenac, compared with single IA HA therapy in small studies. Conflicting results were reported over IA PRP using a variety of comparators such as IA HA, ozone, and normal saline, as well as over IA stem cell therapies, urgently necessitating the standardization of PRP and stem cell products. Prolotherapy may be effective in single or combination regimes in small studies. None of the IA therapies demonstrated serious adverse effects, such as septic arthritis. These findings should be interpreted with caution as the included studies show conflicting results as well as several methodological flaws

such as small sample size, short-term follow-ups, a lack of control group and absence of structural evaluations.
Summary Collectively, these studies have demonstrated the need for further confirmation studies and highlighted the issues of standardization of PRP and stem cell therapies, the placebo effects and cost-effectiveness of IA therapeutics.

Introduction

Knee osteoarthritis (OA) is the commonest articular disease and usually presents in aging populations with chronic joint pain, brief morning stiffness, impaired knee function, difficulty in activities of daily living, and loss of mobility. Examination may be characterized by audible or palpable coarse crepitus, bony enlargements, joint line tenderness, and deformities of the knee joints [1]. It can be defined radiographically and/or symptomatically, and such definitions can affect epidemiological estimates of knee OA [2]. Its estimated global prevalence in persons over 40 years of age is at 22 · 9% in 2020 (correspondingly 654 · 1 million individuals) [3], imposing considerable socioeconomic costs as the direct and indirect costs for OA management being 1 to 2.5% of the gross national product (GNP) in most of developed countries [4].
The current narrative review was aimed at summarizing the efficacy and adverse effects of the currently available IA agents in knee OA such as corticosteroids and hyaluronic acid, platelet-rich plasma, stem cells, and prolotherapy. Moreover, the accuracy rates of available methods of drug injection into knee joint are briefly discussed: blind or landmark-guided method vs ultrasound guidance.
The literature approach was based on the PubMed database over 2 years from 1 January 2021 to 31 December 2023 to reflect current research findings with a search strategy for randomized controlled trials (RCTs) conducted in human beings and written in the English language, focusing on but not limited to the terms “knee osteoarthritis” or “knee arthrosis” in combination with “intra-articular injections” or “injection-based therapy” or “corticosteroid” or “hyaluronic acid” or “platelet-rich plasma” or “stem cells” or “prolotherapy” (see Online Supplementary Material for the full search strategy). Additional articles were identified by using the bibliographies of each paper. We identified 1515 papers from the search results and tried to focus on articles deemed to provide a purposeful increase in our knowledge base.

Recommended management of knee osteoarthritis

No drugs are yet available to modify the structural manifestations of the disease course of knee OA [5]. Current OA management focuses on symptomatic improvement only [6] and is largely palliative in approach despite the OA disease course typically being slowly progressive over years/decades [7]. Treatment options include (1) non-pharmacological management such as weight reduction, life-style changes, dieting, and exercises [8], (2) pharmacological options such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular therapies such as steroids and hyaluronic acids, and (3) surgical interventions which are typically reserved only for end-stage OA, as a last resort [9••]. Recently, paracetamol and opioids have been only conditionally or not recommended by several scientific guidelines [6, 9••, 10]. In addition, the existing treatments have shown only

modest efficacy at best [2], and long-term use of commonly used analgesics are not recommended due to adverse effects in the gastrointestinal, cardiac, or renal systems as patients with knee OA usually have multiple comorbid diseases [9••].

Intra-articular therapies

The IA administration of drugs possesses the advantage of high efficiency while limiting the systemic exposure and off-target effects as drugs are locally administered into the joints [11]. Most available guidelines for knee OA management would not typically advocate the use of IA medications until the second or third line [6, 12] as it is an invasive procedure and not without uncommon but serious complications such as septic arthritis (10–40 persons per 100,000 injections) [13]. Table 1 summarizes recommendations from NICE [9••], AAOS [14••], ACR [10], OARSI [6], ESCEO [12], and PANLAR [15] guidelines related to available IA therapies for knee OA as part of conservative management. IA therapeutics that possess anti-inflammatory properties might be appropriate, for example, during a flare of knee OA and the presence of a large effusion. The patient should be provided with essential information such as the nature of the IA procedure (blind or imaging guided), the potential benefits and risks of IA therapies, as well as post-injection care such as 24- to 48-h post-injection immobilization [16••, 17•].

On administration of IA therapeutics into the knee joints, either landmark-guided or imaging-guided approach could be used [16••] (Table 2). In the literature, there is strong evidence that ultrasound guidance IA injection provides significantly higher accuracy in administrating the injectates into the knee joints than landmark-guided (blind) injections (96% vs 73%, *n*=89) [18]; (96% vs 84%, *n*=99) [19]. Among 3 different approaches, the superolateral portal (100%) and mid-lateral portal (95%) showed significantly higher accuracy than injections in the medial portal (75%) (*n*=126) [20]. The enhanced injection accuracy achieved with ultrasound needle guidance [21] directly improves patient-reported clinical outcomes, cost-effectiveness [22], and patient satisfaction [23].

Available IA injectates

The commonly used IA injectables in daily practice include corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), stem cell, and prolotherapy.

Corticosteroid

In clinical practice, IA corticosteroid injections are commonly used procedure in knee OA, especially when pain is refractory to physical treatments and oral medications, or to support therapeutic exercise [9••]. The choice of the drug type generally may be triamcinolone, methylprednisolone, or dexamethasone,

Table 1. Recommendations from NICE, AAOS, ESCEO, OARSI, ACR, and PANLAR guidelines related to intra-articular therapies for knee OA

	IA corticosteroids	IA hyaluronic acid	Platelet-rich plasma	Stem cell injection	IA prolotherapy
PANLAR 2016[#]	IIaB	IIaB	IIbC	–	–
ACR 2019[¥]	SR	CRA	SRA	SRA	CRA
OARSI 2019[^]	1B	2	4A	4A	4A
ESCEO 2019[§]	WR	WR	–	–	–
AAOS 2022[¶]	Moderate	Moderate	Limited	–	–
NICE 2022*	R	NR_2	–	–	–

[#]PANLAR recommendations were based on the strength of recommendation (I, IIa, IIb and III) and level of evidence (A, B, or C)

[¥]ACR recommendation grades: A strong recommendation (SR) required high-quality evidence and a large gradient of difference between desirable and undesirable treatment effects. A conditional recommendation (CR) was based on the absence of high-quality evidence and/or evidence of only a small gradient of difference between desirable and undesirable treatment effects. CRA=conditionally recommended against. SRA=strongly recommended against. NR_1= No recommendation due to lack of studies at the time of guideline development (ACR guideline)

[^]OARSI recommendation levels: level 1A- ≥75% "in favor" & >50% "strong recommendation"; level 1B- ≥75% in favor & >50% conditional recommendation; level 2- 60–74% "in favor"; level 3–40%-59% "in favor"; level 4B- 60–74% "against"; Level 4A- ≥75% against & >50% conditional recommendation

[§]ESCEO recommendations: Strong recommendation (SR) given when >75% of votes were cast in favor of "strong do"; Weak recommendation (WR) given when <75% of votes were cast in favor of "strong do"

[¶]AAOS recommendation level: strong recommendation given when the quality of the supporting evidence is high; moderate recommendation given when the benefits exceed the potential harm; limited recommendation means a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm

*NICE recommends (R) treatments based on grading of evidence and formal consensus: R= recommended; NR_2= Non-recommended (NICE guideline)

AAOS American Academy of orthopaedic surgeons; *ACR* American college of Rheumatology; *CR* conditionally recommended, *CRA* conditionally recommended against; *ESCEO* The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; *IA* intra-articular; *NICE* The National Institute for Health and Care Excellence; *OA* osteoarthritis; *OARSI* Osteoarthritis Research Society International; *PANLAR* Pan-American League of Rheumatology Associations; *R* recommended; "–" mean not reported in the guidelines

depending on the clinical experience and preference of the physician. We identified five studies investigating IA corticosteroids in knee OA. In 4 studies, each study used IA normal saline (as a placebo) [24], ketorolac (NSAID) [25], PRP [26], or HA (vs steroid plus HA co-injection) [27] as the comparator group and the remaining study compared the routes of administration (IA vs intramuscular corticosteroid) [28].

Hunter et al. demonstrated significant improvement in WOMAC pain (mean difference = −0.35, p = 0.004) and function (mean difference = −0.26, p = 0.045) in knee OA with radiographic KL grade 2 or 3 when IA injection of 12 mg of liposome formulation (to prolong the local joint residence time) of dexamethasone sodium phosphate (TLC599) was compared to IA normal saline injection at 24-week follow-up (n=76). The percentage of clinically durable responders (defined as > 30% pain reduction as measured by the WOMAC-Pain scale) at 24 weeks was greater in TLC599 group (52% vs 22%; p = 0.0143); however, there was no significant improvement in quality of

Table 2. Published studies investigating intra-articular injectates for the treatment of knee osteoarthritis since 1 Jan 2021

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Corticosteroid									
Hunter et al, 2022	12 mg of liposome formulation of dexamethasone sodium phosphate (TLC599) with 100 µmol phospholipid (PL) (TLC599 12 mg; 1.0 mL)	Knee	2 or 3	26	24 weeks	None	TLC599 at 12 mg demonstrated significantly greater reduction in WOMAC pain and function compared with the placebo; however TLC599 18 mg did not	Treatment-emergent adverse events in 26.9% of the participants treated with TLC599 12 mg and 45.8% of the participants treated with TLC599 18 mg (compared to 16% with placebo)	No formal sample size calculation and no long-term follow-up
	TLC599 at 18 mg DSP with 150 µmol PL (TLC599 18mg; 1.5 mL)			24			Cortisol decreased" in 8 participants and "glucocorticoid deficiency" in 4 participants (all in TLC599-treated subjects). All events were resolved, typically by the next scheduled laboratory assessment		
	placebo (1.5 mL normal saline)			25					
Jurgensmeier et al, 2021	5 ml of 80 mg of triamcinolone with 0.5% ropivacaine 5 ml of 30 mg of ketorolac with 0.5% ropivacaine	Knee & hip	2 or higher	110 (52 hips and 58 knees)	12 weeks	Ultrasound	No significant differences between ketorolac and triamcinolone for HOOS or KOOS and VAS scores	In the triamcinolone group, 2 patients with diabetes reported an elevation in blood glucose during the first week postinjection In the ketorolac group, 2 patients with a headache and nausea or a gastrointestinal bleed	Mixed OA population (hip and knee), no long-term follow-up and sample size calculation was not reported
Nunes-Tamashiro et al, 2022	40 mg (2 mL) of Triamcinolone Hexacetonide	Knee	2 and 3	33	52 weeks	None	No significant differences in VAS pain were found in the inter-group comparison over time The PRP group showed lowest radiographic progression from kl grade 2 to 3 over 52 weeks [TH 17 (51.51%) to 24 (72.72%); SS 17 (51.51%) to 30 (90.90%); PRP 20 (58.82%) to 21 (61.76%)].	No adverse effects were observed	Small sample size, multiple comparison with no statistical adjustment and questionable sensitivities of radiographic scores in structural OA progression
	IA PRP			34					
	2 mL of the saline solution (0.9%)			33					

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Wang et al, 2022	Co-injections of 2 cc of HA plus 1 cc of corticosteroids (10 mg/mL triamcinolone acetonide) weekly for 3 weeks	Knee	2 or 3	28	6 months	Ultrasound	The combined injection exerted significantly (p<0.05) greater effects for pain, physical function, chair-rising time, and KOOS pain than did HA injections alone	No adverse effects in the study	Small sample size, no placebo or corticosteroid group, no structural evaluations
	2 cc of HA (20 mg/2 mL) weekly for 3 weeks			29					
Wang et al, 2022	Single intramuscular injection of triamcinolone acetonide, 40mg (1 mL)	Knee	Not reported	74	24	None	At primary timepoint of 4 weeks, the between group difference in KOOS Score was −3.4(95% CI,−10.1 to 3.3)	The most frequently reported adverse events were hot flush (IM, 10% vs IA, 21%) and headache (IM, 14% vs IA, 18%)	Lack of a placebo-controlled group and being an openlevel
	Single IA injection of triamcinolone acetonide, 40mg (1 mL)			71			rejecting the noninferiority despite IM injection was noninferior to IA injection at 8 (mean difference, 0.7; 95% CI,−6.5 to 7.8) and 24 (mean difference, 1.6; 95% CI,−5.7 to 9.0) weeks.		
Hyaluronic Acid									
Ke et al, 2021	Single 6 ml Hylan G-F 20 injection	Knee	1 to 3	218	24 weeks	None	No superiority of single 6 ml Hylan G-F 20 injection over placebo in symptomatic pain relief over 26 weeks	The most frequent TEAEs were arthralgia (3.2% in each group) and peripheral joint swelling (3.7% in the single 6 ml Hylan G-F 20 injection vs 0.9% the placebo group).	High placebo effects
	Phosphate buffer saline as placebo			220					

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Nishida et al, 2021	Diclofenac etalhyaluronate (DF-HA) DF-HA (30 mg/3 ml in a prefilled syringe)	Knee	2 or 3	218	24 weeks	None	Significant improvement from baseline in the WOMAC pain subscale, measured on a 100-mm VAS, score in treatment group (−23.2 mm), compared to control group (−17.1 mm), with a difference of −6.1 mm (95% confidence interval −9.4, −2.8; $P < 0.001$). The proportions of subjects with improvement from baseline of >20%, >30%, and >50% at week 12 in the DF-HA group versus the placebo group were 78% versus 67%, 71% versus 56%, and 52% versus 38%, respectively	The incidence of serious TEAEs was 1 (0.5%) in the placebo group and 5 (2.3%) in the DF-HA group. The incidence of TEAEs in DF-HA and placebo group: 1 versus zero for GI disorders; 7 vs 3 for CV disorders; 1 vs 1 for renal dysfunction	Frequent IA injection (6 times) and lack of evaluation of NSAID-induced chondrotoxicity
	Placebo (citric acid–sodium citrate buffered solution_3 ml in a prefilled syringe)			220					
Sun et al, 2021	A single IA injection of HA (3 ml, 20 mg/ml) followed by 3 ml PRP (combined injection group)	Kneee	2	39	6 months	None	A significantly greater pain reduction on a VAS score (mean difference: 7.9; $p = 0.020$) in combined injection group, compared with the one-injection group at 6 month follow-up	No serious adverse events occurred following injections. Knee swelling and pain immediately after injection (5 in one injection group vs 6 in combined injection group)	Small sample size, no placebo-controlled group, no structural evaluations
	a single Injection of 3 ml PRP (one-injection group)			39					
Xu et al, 2021	4 mL of PRP plus 2 mL HA (once in 2 weeks for 3 injections)	Knee	2 or 3	48	24 months	None	PRP combined with HA is significantly effective compared with PRP or HA alone at inhibiting ultrasound-detected synovial inflammation and improving pain and function	No systemic complications gwere found.	3 different ultrasound operators in the study, with no report of the inter-rater reliability and lack of MRI detected structural changes
	2 mL of HA (once in 2 weeks for 3 injections)			34					
	4 mL of PRP (once in 2 weeks for 3 injections)			40					
Platelet rich plasma									

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Bennell et al, 2021	3 weekly IA injections of leukocyte-poor PRP 3 weekly IA saline placebo	Knee	2 or 3	144 144	12 months	Ultrasound	Treatment with PRP vs placebo injection resulted in no significant reduction of knee pain on NRS VAS score of −2.1 vs −1.8 points, (difference, −0.4 [95% CI, −0.9 to 0.2] points; $P = .17$) and loss in MRI-detected medial tibial cartilage volume was −1.4% vs −1.2%, (difference, −0.2% [95% CI, −1.9 to 1.5%]; $P = .81$)	No serious related adverse events. Knee joint pain, swelling, and stiffness are reported in more participants in the PRP group than in the placebo group.	Only applied to mild and moderate knee OA in a community setting
Dório et al, 2021	2 IA PRP with a 2-week interval 2 IA plasma (not enriched with platelets) with a 2-week interval 2 IA saline placebo with a 2-week interval	knee	2 or 3	20 21 21	24 weeks	Ultrasound	Change in pain from baseline at week 24 were −2.9 (SD 2.5), −2.4 (SD 2.5) and −3.5 cm (SD 3.3) for PRP, plasma and saline, respectively (p intergroup = 0.499)	Mild transitory increase in pain was reported in higher frequency for PRP group (65% versus 24% and 33% for PRP vs plasma and saline, respectively, $p = 0.02$)	Small sample size, no long-term follow-up, lack of structural evaluations
Park et al, 2021	Single IA injection of 3 ml PRP Single IA injection of HA	Knee	1 to 3	55 55	6 months	None	Significant improvement in IKDC subjective scores at 6 months for PRP (11.5 vs 6.3; $P = 0.029$)	There were no serious adverse events in either group	No placebo-controlled group, use of leukocyte-rich PRP, no structural evaluations
Raeissadat et al, 2021	2 ml of PRP (2 doses with 3 weeks interval) PRGF (2 doses with 3 weeks interval) HA (3 doses weekly) 10 ml of Ozone (3 doses weekly	Knee	2 or 3	52 51 49 48	12 months	None	At the end of the 12th month, only PRP and PRGF groups had better results versus HA and ozone groups in visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Lequesne index ($P < 0.05$)	PRP and PRGF groups had experienced more but not significant post injection pain	A lack of placebo-controlled group, poor blinding to group allocations, no structural evaluations

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Sdeek et al, 2021	3 IA PRP every 2 weeks 3 IA HA every 2 weeks	Knee	2 or 3	95 94	36 months	None	At 36 months, the VAS was much better in platelet rich plasma group (40.9), compared with the HA group (60.3). Reinjection rate was significantly less in the PRP group	post-injection pain reaction was significantly higher in the platelet rich plasma group	Lack of a placebo-controlled group and no structural evaluations
Chu et al, 2022	3 weekly IA PRP 3 weekly IA saline placebo	Knee	2 or 3	308 302	60 months	None	PRP group showed significantly better WOMAC scores throughout the study duration, compared with saline placebo. Decrease in tibiofemoral cartilage volume decreased by a mean value of 1171 mm3 in the P-PRP group and 2311 mm3 in the saline group over 60 months with the significant intergroup difference [1140 mm3 (95% CI–79 to 1320 mm^3), $P<0.001$]	No major complications	Blinding was removed at 2-year follow-up and 93 patients had additional treatments
Lewis et al, 2022	3 weekly IA PRP One PRP injection followed by two saline injections weekly 3 weekly IA saline	Knee	0 to 2	27 47 28	12 months	None	Single or multiple PRP had no symptomatic benefits compared to saline injection up to 12 months	Significant swelling of the joint in PRP groups, compared with saline injection (odds ratio: 3.92 vs 6.71 in single or multiple injections)	Small sample size and no structural evaluations
Wang et al, 2022	Single IA PRP (4 ml) Single IA HA (HyajointPlus)	Knee	1 or 2	54 56	6 months	None	No significant intergroup difference	Four patients in the HA group developed mild joint swelling and with pain after injection	Lack of placebo-controlled group, no long-term follow-up and no structural evaluations

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Yurtbay et al, 2022	Single dose of PRP (5 ml)	Knee	1 to 3	62	24 months	None	The VAS scores of the PRP groups significantly improved, compared with those in the NS groups at 3, 6 and 12 months ($p < 0.001$). Three doses of PRP (4.16 ± 2.13) were significantly effective than a single dose of PRP (5.79 ± 1.99) at 12 months ($p < 0.001$). No statistically significant difference between the groups in the VAS scores at 24 months	an increase in knee pain after 10 days of the injection (16%) followed by dizziness (11.8%), tachycardia (10.9%), sweating (9.2%), knee swelling (7.2%), headache (5.1%), syncope (2.9%), and gastritis (0.8%)	No structural evaluations
	Single dose of saline			59					
	Three doses of PRP			63					
	Three doses of saline			53					
Stem Cells									
Anz et al, 2021	Single IA injection of BMAC	Knee	2 to 4	45	24 months	None	No statistically significant differences in IKDC (P =0.90; 95% CI, 26.2 to 7.0) or WOMAC (P = 0.79; 95% CI, 26.2 to 4.8) scores over time between the groups	Not reported	high loss to follow-up (24% and 32% at 24 months for the BMAC and PRP groups) and no placebo-controlled group
	Single IA injection of PRP			39					
Boffa et al, 2022	Single IA injection of BMAC in one knee	Knee bilaterally	1 to 4	56	24 months		Compared to HA, BMAC showed a higher improvement for VAS pain at 12 (2.2 vs 1.7, p = 0.04) and 24 months (2.2 vs 1.4, p <0.01).	No significant difference in severe adverse events (7.1% vs 5.4% in BMAC and HA groups)	No placebo-controlled group and structural evaluations
	Single IA injection of HA in the other knee			56					
Prolotherapy									
Waluyo et al, 2021	5 IA HA injections on weeks 1, 2, 3, 4 and 5	Knee	not reported	21	12 weeks	None	Significant inter-group difference was noted (-3 vs -2 for prolotherapy vs HA groups on NRS pain score; p=0.04)	All participants experienced expected mild-to moderate post-injection pain within 2–3 days	Small sample size, no placebo-controlled group and high drop-out rates
	3 IA dextrose injections on weeks 1, 5 and 9			26					

Table 2. (continued)

Authors/publication year	Intervention and comparators	OA site	Radiographic severity (KL)	Sample size (patients)	Follow-up duration	Injection guidance	Efficacy data	Safety data	Study limitations
Hsieh et al, 2022	3 weekly IA HA and hypertonic dextrose (7-mL 25% dextrose injection (3.5mL of 50% dextrose mixed with 3.5mL of 2% lidocaine) followed by a 2-mL 10 mg/dL HA injection	Knee	2 or 3	52	6 months	Ultrasound	HA plus dextrose coinjections resulted in significant improvements in stair climbing time and physical function at 6 months, compared with HA plus normal saline coinjection	Not reported	Lack of placebo-controlled group, no long-term follow-up, no structural evaluations
	3 weekly IA HA and normal saline (7-mL injection of 3.5 mL of normal saline with 3.5 mL of 2 %lidocaine followed by a 2-mL 10 mg/dL HA)			52					

BMAC bone marrow aspiration concentrate, *DF-HA* diclofenac etalhyaluronate, *DMOAD* disease-modifying osteoarrhritis drug, *HA* hyaluronic acid, *HOOS* hip disability and osteoarthritis outcome score, *IA* intra-articular, *IKDA* International Knee Documentation Committee, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *MRI* magnetic resonance imaging, *NRS* numerical rating score, *PRP* platelet-rich plasma, *VAS* Visual Analogue Scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

life on EQ-5D questionnaires. No major or unexpected safety issues were detected [24]. A larger and well-designed pivotal study (ClinicalTrials.gov identifier: NCT04123561) is currently ongoing to confirm this efficacy profile. In a 3-month study comparing the IA administration of 80 mg of triamcinolone with 30 mg of ketorolac under ultrasound guidance in patients with hip (n=52) or knee OA (n=58), no significant between-group differences in HOOS or KOOS and VAS scores with minimal adverse effects were reported [25]. In a 52-week study comparing the single IA injection among three groups (40 mg of triamcinolone hexacetonide (n=33) vs PRP (n=34) vs the saline solution (n=33)), no significant differences were found in the inter-group comparison over time except for superiority of the triamcinolone hexacetonide group over the other two groups at 4 weeks). The PRP group showed the lowest radiographic progression from KL grade 2 to 3 over 52 weeks among the three groups [triamcinolone from 52 to 73%; saline 52 to 91%; PRP from 59 to 62%] [26]. However, the study has several limitations such as small sample size, multiple comparison with no statistical adjustment and questionable sensitivities of radiographic scores in assessing the structural progression of knee OA.

In a 6-month study in knee OA, weekly IA co-injections of corticosteroids plus hyaluronic acid (HA) for 3 weeks (n=28) provided statistically significant improvement in WOMAC-pain (P = .005) and physical function (P = .005), chair-rising time (P = .032), and KOOS-pain (P = .001) from 1 week to 6 months, compared with HA injections alone (n=29) [27]; however, the outcome longer than 6 months is unknown. In a multicenter, open-label, randomized clinical noninferiority trial comparing the IA vs IM administration routes for steroids in symptomatic knee OA, noninferiority could not be declared with between-group mean difference in the KOOS pain score was −3.4 (95% CI, −10.1 to 3.3; effect size = −0.17) favoring the IA route at the primary time point (4 weeks) [28]. Lack of a placebo-controlled group and being an open-level study are study limitations.

Summary

The IA corticosteroid therapy provided short-term symptomatic benefits in knee OA but long-term benefits seem to be less likely even in combination therapies with other IA therapeutics. Extended release IA steroids which can prolong joint residence time are currently under intense research.

Hyaluronic acid

Viscosupplementation with hyaluronic acid (HA) in knee OA has been extensively researched since 1971 [29] and 2438 papers has been published between 2002 and 2021 [30]; however, its role in knee OA management still generates debate in terms of clinical benefits [9••, 30] as the published data were limited by the high heterogeneity of effect sizes perhaps due to different HA formulations, different periods of follow-up, and differences in injection schedules and IA techniques [17•]. In the recent literature, four papers were identified, comparing HA with placebo (n=2) [31, 32] and PRP (n=2) [33, 34].

A 26-week study in Chinese patients with knee OA (n=440) did not establish superiority of single 6 ml Hylan G-F 20 injection over IA placebo using

the WOMAC pain score while walking. Percentages of positive responders over 26 weeks, defined as a ≥ 2-point improvement from baseline, was not significantly different (67% in the treatment arm vs. 68% in the placebo arm) [31]. As a note, the placebo effects were marked in the Chinese clinical compared with the European trial (44% vs 29%), which used a similar trial design and methodology (n=253) [35]. When diclofenac etalhyaluronate (DF-HA), which is diclofenac covalently linked to HA, was administered once every 4 weeks for 20 weeks (a total of 6 injections) in Japanese patients with knee OA, a statistically significant improvement in the WOMAC pain subscale, measured on a 100-mm VAS, in the active treatment group was detected at 12 weeks compared to the placebo group, with a difference of −6.1 mm (95% confidence interval −9.4, −2.8; $P < 0.001$); however, there was no significant difference at week 24 (n=440). Anaphylactic reactions were observed in 2 subjects receiving DF-HA [32]. The limitations are the need to frequent IA injection, which may lead to an increased risk of joint infections [17•] and the lack of evaluation of chondrotoxicity caused by NSAIDs which have been suggested to be deleterious to joint cartilage [36].

A single IA injection of HA (3 ml, 20 mg/ml) followed by 3 ml PRP (the combined-injection group) showed statistically significant pain reduction on a VAS score (mean difference: 7.9; p = 0.020), compared with a single injection of 3 ml PRP (the one-injection group) at 6-month follow-up (n=78). No serious adverse events occurred following injections. As a note, at 3-month follow-up, the subgroup of patients with baseline VAS pain > 56.4 mm in the one-injection group revealed a significantly greater reduction in VAS pain score than the combined injection group [33]. In another 24-month study, PRP combined with HA (48 knees) is significantly effective compared with PRP alone (40 knees) or HA alone (34 knees) at improving pain and function and acts through inhibiting synovial inflammation detected on ultrasound and reducing inflammatory cytokine content[34]. In a recent systematic review and meta-analysis including 7 studies (n=941), PRP combined with HA provided better clinical improvement (standardized mean difference≥0.30), such as pain and function beyond 6-month follow-up than PRP alone with no significant difference in the incidence of side effects [37], presumably due to their synergistic therapeutic effects on the proliferation of chondrocytes and cartilage repair demonstrated in a rabbit model [38].

Summary

While symptomatic benefits of IA HA therapies may be statistically significant, most clinical outcomes do not reach clinical significance. They are frequently being used in combination with other IA agents, expecting the chances of longer-term benefits compared with single-therapy regime. More research in the cost-effectiveness of such combination therapies is required.

Platelet-rich plasma

Platelet-rich plasma (PRP) definitions vary but one group suggested it be defined by its absolute platelet concentration > 1 $\times 10^6$/μL or a fivefold increase in platelet concentration from baseline [39]. PRP may have the capacity to reverse pro-inflammatory processes and promote tissue repair

via the release of many biologically active factors, such as growth factors and cytokines for restoration of the articular homeostasis [40]. Nine recent papers have been identified for IA PRP in knee OA.

In some studies, PRP has been found to be significantly effective in reducing the symptoms [41–44] and MRI-detected cartilage loss [45], compared with HA [41–43] or ozone [42] or normal saline placebo [44, 45] up to 36 [43] or 60 [45] months. However, in the other studies, it was reported that PRP is not superior to the placebo [46–48] or HA [49] in improving pain and function [46–49] and preventing the structural progression of the disease [46] up to 12 months [46, 48]. Regarding the frequency of single-dose PRP injection, PRP injections could be repeated at 6-month intervals as the effect of a single-dose PRP decreased significantly after 6 months[44]. In a recent meta-analysis of IA PRP versus comparative cohorts retrieved until 1 December 2021 which included 24 PRP clinical trials with HA(n=11), corticosteroid (n=6), normal saline (n=5), exercise therapy (n=3), and clinical relevance of outcome improvements (VAS and WOMAC scores) cannot be determined despite statistical significant findings and examination of structural changes showed no difference between the comparative groups. In addition, a paucity of high-quality studies, substantial heterogeneity of included studies, mostly small sample sizes, relatively short-term follow-up (mostly 6-month follow-ups) were noted [50••]. Recently, the American Academy of Orthopaedic Surgeons downgraded their strength of recommendation of PRP to "limited" due to inconsistent evidence [14••].

Summary

Current evidence is of low quality and is based on clinical trials with high risk of bias, great heterogeneity among clinical trials, and serious methodological flaws. Future high-quality studies using larger sample sizes, longer study durations and good methodologies are required.

Stem cell therapy

Due to multilineage differentiation potential, stem cell injections have been proposed as an innovative regenerative therapy for knee OA. However, a recent systematic review reported a paucity of RCT in this area, high risk of bias in the available studies, and a lack of long-term results [51]. We identify two papers related to stem cell therapies compared with PRP [52] or HA [53] in knee OA.

In a 24-month RCT comparing bone marrow aspiration concentrate (BMAC) and PRP in knee OA (n=84), WOMAC scores at 24 months improved by 14.5 points (41%) from baseline in the BMAC group and 12.4 points (38%) in the PRP group with no significant inter-group differences, disputing the beneficial effects of BMAC, given the added morbidity and expense of a bone marrow aspirate in the general OA population (an average cost of US $714 for PRP and US $3000 for BMAC). The study was limited by a high loss to follow-up (24% and 32% at 24 months for the BMAC and PRP groups) and no placebo group[52]. In another study conducted in 56 patients with bilateral knee OA, single IA BMAC injection was administered into one knee and single IA HA injection into the contralateral knee, each patient thereby

acting as their own control and eliminating the need for sham bone marrow aspirations to maintain blindness. Compared to HA, BMAC showed a greater improvement in VAS pain at 12 months (2.2 vs 1.7, $p = 0.04$) and 24 months (2.2 vs 1.4, $p < 0.01$) with no serious adverse events [53].

Summary

Conflicting results are noted between the comparative groups (BMAC vs PRP or HA) in two recent clinical trials, highlighting inconclusive evidence and the need for future high-quality studies.

Prolotherapy

In prolotherapy, small amounts of an irritant solution such as hyperosmolar dextrose (d-glucose) with concentrations ranging from 12.5 to 25% are injected into painful joints to restore joint stability by promoting the tensile strength of joint stabilizing structures, such as ligaments, tendons, and joint capsules [54]. We identified two recent studies.

In a small study conducted in knee OA (n=47), IA dextrose prolotherapy demonstrated a significant reduction in NRS pain scores over 12 weeks, compared with HA injection (−3 vs −2 for prolotherapy vs HA groups on NRS; p=0.04) [55]. In another 6-month study (n=104), HA plus dextrose co-injections under ultrasound guidance provided more significant improvements in stair climbing time and physical function at 6 months, compared with HA plus normal saline co-injection[56].

Summary

Despite statistically significant results in the recent studies, there is uncertain clinical relevance/significance due to small sample size, short-term follow-ups, a lack of control group, and absence of structural evaluations.

Opinion and future directions

Placebo effects

IA saline is a commonly used placebo in control groups in RCTs of IA therapies, and it can produce remarkable pain relief that may reach the values of minimal clinically important difference (MCID) [57]. In a recent meta-analysis, the placebo effects of IA saline at 6 month follow-up generated a significant improvement on 0–100 VAS pain score [−13.4 (−21.7/−5.1)], in WOMAC function sub-score [−10.1 (−12.2,-8.0)] and the pooled responder rate was 56% by using the OMERACT-OARSI criteria [58]. Therefore, in the clinical trials where pain and function are used as the primary endpoints, the placebo effects of IA saline should be accounted for in planning the trial design [59]. As the IA saline injection may be more than a "mere" placebo due to dilution effects in the joint environment [60], the underlying mechanisms of placebo effects and their predictors as well as the comparative effects of sham vs saline injections should be examined in robust study designs[5].

Trial quality and reasons why many injectates are not recommended in guidelines

In evidence-based medicine, the quality of clinical trials is one of the core factors for translating the research results into clinical practice. Increased risk of bias at the individual study level, inconsistent results among included clinical trials for a particular intervention, potential for small study effects and imprecision of the effect estimates often leads to the downgrading of the evidence in formulating the treatment recommendations[6]. In HA and PRP clinical trials, the use of different formulations, trade names, preparation methods, and frequency of injections leads to conflicting results among the studies, thereby reducing the strength of recommendations for these treatment options. Another core factor is cost-effectiveness or in terms of out-of-pocket costs. As an example, a single PRP injection has an average out-of-pocket cost of $714 and BMAC costs on average $3000. Given the degree and duration of efficacy between the two treatment options are not different, patients could elect to receive 4 PRP injections over the course of treatment for the same cost as a single BMC injection [52]. Similarly, IA HA cost per injection ranges from $300 to $600 USD, while a single steroid injection ranges from $10 to $50 USD [25].

Drug delivery systems for sustained release

As IA therapies directly targets the recognized pathogenetic tissues within the joint, lower doses than oral formulations are required due to higher bioavailability. Despite this advantage, there are several issues for IA administration which include pain and swelling during/after injection, uncommon but serious complication of septic arthritis and a short joint residence time due to rapid clearance of the IA therapeutics by the body. Therefore, a variety of drug delivery systems (DDS) have been developed with the aim of increasing the joint residence time of IA therapeutics. An ideal DDS should have such properties as controlled and/or sustained release of IA therapeutics for long-term effectiveness without a need of frequent injections [61] and adequate disease-modifying capacity, biocompatibility, and biodegradability [62]. New smart drug delivery strategies, which utilized hydrogels methods, nanoparticles and microparticles may enhance the opportunity for detecting the ideal long-lasting IA therapeutics [63].

Concomitant use of local anesthetics and chondrotoxicity

As IA injection may have pain and some discomfort to the patients, local anesthetics such as lidocaine are often added to the injectates in many studies described above. In recent systematic reviews, dose-dependent and time-dependent chondrotoxic effects of local anesthetics, presumably through mitochondrial dysfunction have been reported in vitro experimental and in vivo animal studies [64, 65]. However, it is uncertain whether these data from chondrocyte cultures or animal models might be transferrable to

human tissues [64]. In the most recent in vivo study, single intra-articular knee injection of 10 ml of 2% lidocaine did not influence the chondrocyte viability and showed fast post-injection reduction of synovial lidocaine concentration (more than 40 times) [66]. Future studies which determine the chondrotoxicity of local anesthetics should be conducted.

Conclusion

Despite quick improvement in pain and function, IA corticosteroid has questionable efficacy on head-to-head comparisons with other comparators such as IA PRP, ketorolac, or normal saline in the long term. Combination therapy of IA corticosteroid plus HA may be more effective than a single IA corticosteroid therapy but needs further confirmation study in larger sample size. Although IA HA failed to show symptomatic improvement compared with normal saline, significant improvement in pain and function at least over 6 months was detected in providing combined therapies of HA with PRP or diclofenac, compared with single HA therapy in small studies, which similarly require further research. Conflicting results were reported over IA PRP using a variety of comparators such as HA, ozone and normal saline with some studies having follow-up durations of 36 or 60 months. Similarly, divergent results are reported for stem cells therapies. Therefore, standardization of PRP and stem cell products are in urgent need. Prolotherapy may be effective in single or combination regimes in small studies. None of the IA therapies included in the review demonstrated serious adverse effects nor septic arthritis. Joint injection accuracy and clinical outcomes are higher with imaging-guidance. Future studies should address the issues of product standardization, placebo effects, possible adverse effects of IA NSAID or local anesthetics on the cartilage, drug delivery systems, and cost-effectiveness of different IA therapeutics.

Author contributions

WMO and DJH contributed to the study concept and design. WMO conducted the data search and drafted the first version of the manuscript. DJH and WMO critically revised the manuscript for important intellectual content.

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Declarations

Conflict of interest
WMO has no conflict of interest. DJH provides consulting advice on scientific advisory boards for Pfizer, Lilly, TLCBio, Novartis, Tissuegene, Biobone.

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