Update on injectables for osteoarthritis

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Osteoarthritis (OA) is a leading cause of musculoskeletal disability worldwide[1]. The Global Burden of Disease study estimated that 595 million people were affected in 2020, and projects a further substantial rise by 2050 as populations age and obesity becomes more prevalent[2]. For patients with end-stage disease, arthroplasty is a highly effective intervention. For the far larger population with early- to moderate-stage OA, treatment options remain limited, confined to predominantly conservative measures including lifestyle modification, analgesia and physiotherapy. This mismatch between a growing burden of symptomatic disease and the absence of consistently effective disease-modifying treatments has created a considerable unmet clinical need. Consequently, there has been a rapid expansion in the development and use of intra-articular injectable therapies.

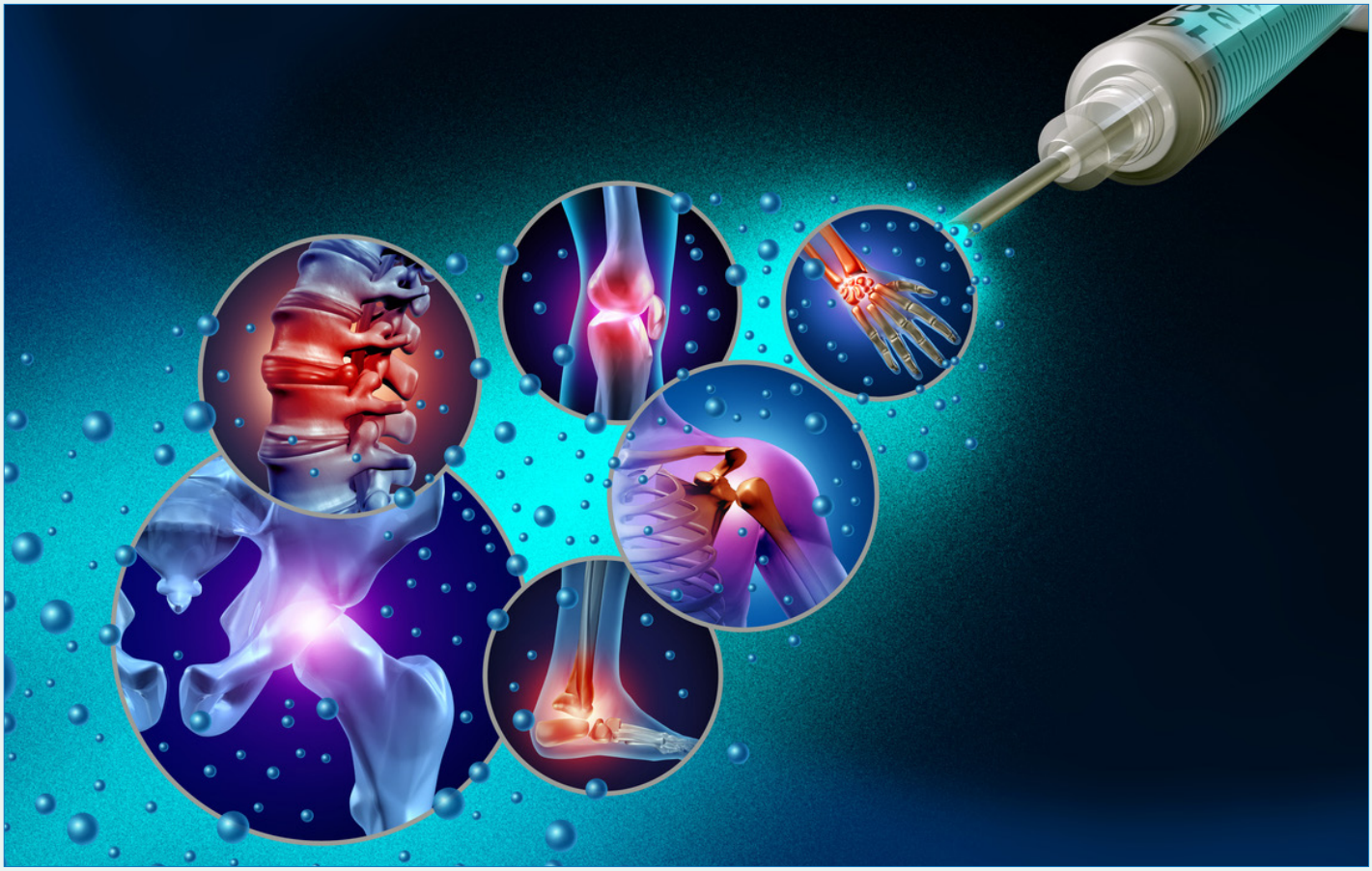
This demand is legitimate, and modulating the intra-articular environment is a promising avenue of research. However, the same unmet need also creates conditions in which therapies may be adopted, marketed and monetised ahead of the evidence, and promoted directly to patients at considerable personal cost and on a slender evidence base. This article offers an update on the principal injectable therapies currently used for OA, examining the quality of the supporting evidence, current guideline recommendations, and their role in clinical practice. It should be stated at the outset that, while several of these agents relieve symptoms, none has been shown to modify the underlying disease or to slow its structural progression. The breadth of agents now available, which may be broadly classified as biologic or non-biologic injectables, is summarised in Table 1.

Non-biologic injectables act through pharmacological or mechanical means (for example corticosteroids and hyaluronic acid (HA)), whereas biologic injectables are derived from living cells or tissues (for example platelet-rich plasma (PRP) and cell-based therapies). The overwhelming majority of high-quality evidence relates to the knee, and this review is weighted accordingly. While some findings may be cautiously extrapolated to other joints, the evidence base outside the knee is considerably thinner. Extrapolation beyond the knee should therefore be undertaken with caution.

Biologic	Non-biologic
Autologous blood products (PRP, platelet-poor plasma, autologous conditioned serum, autologous protein solution)	**Corticosteroids** (methylprednisolone acetate, triamcinolone acetonide)
Cell-based, point-of-care (bone marrow aspirate concentrate, microfragmented adipose tissue, stromal vascular fraction)	**Hyaluronic acid** (low, moderate and high molecular weight; cross-linked)
Cell-based, culture-expanded (mesenchymal stromal cells, autologous chondrocytes)	**NSAIDs** (ketorolac, tenoxicam)
Perinatal tissue-derived (amniotic suspension allograft, umbilical cord and Wharton's jelly preparations)	**Prolotherapy agents** (dextrose, ozone)
Cell-free biologics (exosomes, extracellular vesicles)	**Injectable hydrogels** (polyacrylamide)
	Disease-modifying agents (Wnt-pathway modulators, recombinant fibroblast growth factor 18; investigational)

NSAIDs, non-steroidal anti-inflammatory drugs; PRP, platelet-rich plasma.

Table 1: Illustrative examples of intra-articular injectable therapies for knee osteoarthritis, grouped into biologic and non-biologic agents.



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Corticosteroids

Intra-articular corticosteroids comprise a family of agents differing in solubility, onset and duration of action, the most widely used of which are methylprednisolone acetate and triamcinolone acetonide. Their principal mechanism of action is a potent local anti-inflammatory effect on the joint synovium to provide short-lived symptomatic benefit without disease modification. A recent systematic review and meta-analysis of Level I studies confirmed a clinically relevant benefit over placebo that exceeded the minimal clinically important difference (MCID) of included pain and function outcome scores (WOMAC and VAS) only at short-term follow-up, (up to six weeks), with the effect diminishing thereafter and with repeated injection[4].

The use of intra-articular corticosteroids is widespread within practice in the UK. However, guideline bodies differ in emphasis but broadly concur on their indications: National Institute for Health and Care Excellence (NICE) offers conditional support when other measures are inadequate[5], while the American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI) recommend the use of intra-articular steroid injections for short-term relief and particularly during inflammatory flares[6,7]. There is growing concern regarding chondrotoxicity with these agents, with both dose- and duration-dependent deleterious effects on cartilage demonstrated in preclinical studies and, in one randomised trial, greater cartilage volume loss than saline[8]. It has also been associated, largely in observational and imaging studies, with accelerated OA progression, subchondral insufficiency fracture and osteonecrosis[9]. Injection close to arthroplasty also raises periprosthetic infection risk, with intra-articular corticosteroid within three months of knee arthroplasty has been associated with increased infection rates[10].

Viscosupplementation (hyaluronic acid)

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan and a key contributor to the viscoelastic properties of synovial fluid. In knee OA, the molecular weight and concentration of native HA fall, providing the rationale for viscosupplementation to restore these properties of the synovial fluid. HA represents a broad spectrum of agents that vary significantly with regards to their molecular weight, cross-linking and the addition of stabilising agents primarily designed to increase intra-articular half-life. Despite this, its presence within the joint remains short following injection[11]. >>

The evidence base for viscosupplementation is large but divided. A recent systematic review and meta-analysis by Pereira *et al*.[12] found that the benefit for knee OA pain consistently fell below the MCID, with trial-sequential analysis suggesting further trials are unlikely to alter this conclusion, and also observed a risk of increased serious adverse events. In contrast, several recent large reviews, including an umbrella review by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), report statistically significant benefit for pain and function, with effect sizes comparable to NSAIDs and greatest in less advanced disease and with high-molecular-weight preparations[13]. Several of these positive syntheses, including ESCEO-supported work, carry industry funding, whereas the more conservative independent analysis underpinning NICE guidance placed benefit below the MCID. This discrepancy partly reflects heterogeneity between products and supports the argument that HA should not be regarded as a single class. Reflecting the more conservative reading, NICE advises against offering HA for osteoarthritis[5].

Platelet-rich plasma and autologous blood products

Autologous blood products refer to any preparation derived from a patient's own whole blood. These are attractive due to the established presence of cells and factors with immunomodulatory and pro-regenerative properties, and the ease of access and low morbidity associated with harvesting whole blood[14]. Autologous blood products include a spectrum of preparations which can be broadly categorised into platelet-rich plasma (PRP), platelet-poor plasma (PPP), and autologous anti-inflammatory preparations (AAIs)[15]. Similar preparations with different trade names and descriptions continue to be introduced, making terminology of these therapies difficult to follow. These preparations differ principally in what is concentrated: PRP contains platelets, and hence their growth factors, at above-baseline levels; PPP is the platelet-depleted plasma fraction; and autologous anti-inflammatory preparations, such as autologous conditioned serum, are produced by incubating whole blood (for example with glass beads) to enrich anti-inflammatory cytokines, particularly the interleukin-1 receptor antagonist.

Platelet-rich plasma (PRP) is the most widely used orthobiologic for knee OA. The rationale is to deliver a supraphysiological concentration of platelets and their pro-regenerative and immunomodulatory cytokines into the joint. As with the other agents, the intended effect is symptomatic: there is no convincing evidence that PRP alters structural disease progression. There has been a substantial body of literature evaluating PRP in the setting of knee OA, comprising more than 50 randomised trials[16,17]. Recent meta-analyses suggest PRP provides greater improvements in pain and function than HA, corticosteroid and placebo, with one large analysis reporting a clinically significant improvement that was influenced by platelet concentration[18], and a network meta-analysis ranking PRP above bone marrow aspirate concentrate, HA and corticosteroid at six months and beyond[19]. Emerging data, also suggest that higher platelet concentration and total delivered platelet dose are associated with better outcomes, although this dose-response signal derives from meta-regression rather than head-to-head comparison[18]. Such network rankings order treatments within a specific set of studies and are strongly influenced by small trials at high risk of bias; a favourable ranking does not, in itself, establish clinically meaningful benefit[18].

This picture is not uniform, however. The largest and most rigorous placebo-controlled trial (RESTORE), found PRP no better than saline for symptoms or cartilage volume at 12 months[20], and analyses restricted to large, low risk-of-bias trials report only small effects for all agents[21]. Much of the favourable data derives from smaller, higher-risk studies. The placebo response to intra-articular injection is substantial and prolonged, peaking at around four to eight months, so a substantial proportion of any apparent benefit is non-specific and study results must be interpreted with caution[22].

The principal caveat remains heterogeneity. 'PRP' denotes any preparation with a platelet concentration above baseline, and commercial systems differ markedly in platelet dose, leucocyte content, activation and protocol, so products labelled 'PRP' may be biologically distinct, complicating interpretation of the literature[23]. This under-appreciated variability is the main reason several professional bodies recommend against routine use, and why NICE permits PRP only with special arrangements for clinical governance, consent, and audit or research[5,24]. Other autologous blood products (autologous conditioned serum, autologous protein solution, platelet-poor plasma) share the same heterogeneity and rest on a more conflicting evidence base.

Combination therapy is also of growing interest, pairing PRP's biological effects with the mechanical and anti-inflammatory properties of HA. Some comparative data, including network analyses in knee and hip OA, suggest that combined PRP and HA may offer greater functional benefit than either alone, although the evidence remains limited and heterogeneous[3]. This remains hypothesis-generating rather than a basis for routine combined use.

Cell-based and other biologic injectables

The most widely used cell-based orthobiologic therapies used for OA are mesenchymal stromal cells (MSCs) or related therapies, bone marrow aspirate concentrate (BMAC), microfragmented adipose tissue, stromal vascular fraction, autologous chondrocytes, and amniotic or placental products[14]. They are frequently, and misleadingly marketed as 'stem cell' treatments, although mesenchymal stromal cells form only a small proportion of the preparation and probably act through paracrine signalling rather than engraftment. Across these therapies the picture is consistent: highly heterogeneous preparations, frequent reliance on uncontrolled or biased studies, and a paucity of robust Level I evidence[25]. Consistent with this, the largest placebo-controlled trials have been disappointing: the ADIPOA2 phase 2b trial of adipose-derived stromal cells found no benefit over saline at its six-month primary endpoint[26].

This is also the area of greatest concern over direct-to-consumer marketing where claims often outstrip the evidence[27]. Professional standards on informed consent, transparency and shared decision-making should be applied, particularly where patients pay substantial sums for unproven treatments.

Injectable polyacrylamide hydrogels

Injectable polyacrylamide hydrogel (Arthrosamid®) has attracted considerable recent attention. It is a synthetic, non-biodegradable hydrogel that integrates with the synovium and is intended to act as a durable viscoelastic cushion; the manufacturer additionally proposes a local, macrophage-mediated anti-inflammatory effect, although this mechanism remains unproven. The supporting literature is limited: lower order evidence suggests favourable short-term outcomes[28,29], and the available randomised data show it to be broadly comparable to HA over one year[30], but there is no placebo-controlled Level I evidence and efficacy has not been convincingly demonstrated. The main practical concern is that the gel is permanent: being non-biodegradable, it cannot reliably be removed from the joint, even at arthroplasty, and the long-term implications are unknown. It is also worth emphasising that Arthrosamid is regulated as a medical device rather than as a licensed medicine; device approval requires evidence of safety and performance but not the efficacy standard expected of a drug, so its availability should not be taken as proof of clinical effectiveness. Routine use therefore appears premature until high-quality placebo-controlled trials establish efficacy, safety and cost-effectiveness.

Emerging therapies and future directions

Several newer preparations are emerging. Amniotic and placental-derived products (for example amniotic suspension allograft) have anti-inflammatory and putative regenerative properties; one single-blind RCT reported superiority over HA and saline at six months, although replication and long-term data are awaited[31]. Disease modifying agents such as the Wnt-pathway modulator lorecivivint aim, with mixed trial results to date, for structural modification rather than symptom relief but remain investigational.

Heterogeneity is common to every class, both in the preparations and in the patients. Response likely depends on OA phenotype; those with an inflammatory picture (synovitis, effusion) appear more likely to benefit from corticosteroid, whereas those with advanced structural damage respond less well. Better characterisation of responders and non-responders is an important direction for future research, allowing more rational targeting of therapy.

UK guideline positions are summarised in Table 2. NICE guidance (NG226, 2022) is the most recent authoritative synthesis but pre-dates some evidence discussed here. International guidelines (OARSI, ACR and the American Academy of Orthopaedic Surgeons) differ in emphasis: all support corticosteroid for short-term relief, but they diverge on HA, which is recommended against by ACR and AAOS but conditionally supported by OARSI, and on PRP, which is recommended against by ACR but given a 'limited' recommendation by AAOS[6,7,32].

Injectable Therapy	Proposed Mechanism	NICE recommendation
Corticosteroids	Potent suppression of synovial inflammation	**Consider** when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise. Explain that benefit is short-term only (2 to 10 weeks)
HA (viscosupplementation)	Restores viscoelastic properties of synovial fluid	**Do not offer** for osteoarthritis
Autologous blood products	Delivery of concentrated platelets and growth factors, and modulation of inflammatory cytokines, using autologous blood-derived factors	**Not recommended** for routine use. NICE HealthTech guidance HTG497 (formerly IPG637) advises use of PRP only with special arrangements for clinical governance, consent, and audit or research
Cell-based therapies	Paracrine immunomodulation and potential tissue repair	**Not recommended outside research.** NG226's evidence review concluded that stem cell injection should be limited to clinical trials
Injectable polyacrylamide hydrogels	Permanent synthetic hydrogel integrates with synovium to provide durable cushioning	No NICE recommendation

HA; hyaluronic acid, NICE; National Institute for Health and Care Excellence, PRP; platelet-rich plasma. Adapted from NICE NG226 (2022) and NICE HealthTech guidance HTG497 (formerly IPG637).

Table 2: Summary of NICE guideline positions for emerging therapies. Guidelines from https://www.nice.org.uk/guidance/ng226/chapter/Rationale-and-impact.

Conclusion

Injectable therapies for OA are a rapidly developing field addressing a genuine unmet need, particularly in early- to moderate-stage disease unsuitable for arthroplasty. Innovation should be welcomed but held to a consistent, evidence-based standard. Crucially, no injectable has yet been shown to modify the underlying disease or slow its structural progression. Corticosteroids retain a role for short-term relief but warrant caution over chondrotoxicity; viscosupplementation offers, at best, a small inconsistent benefit; PRP has the most encouraging evidence among the biologics, although the single highest-quality randomised trial was negative and preparation variability limits interpretation; and cell-based therapies and permanent hydrogels need robust, long-term placebo-controlled trials before adoption. Above all clinicians must ground recommendations in high-quality evidence, with transparent communication, informed consent, and appropriate governance.

Key learning points

- OA carries a large and rising global burden, yet proven options for early-to-moderate disease are scarce, fuelling rapid growth in the injectables market.
- No injectable has been shown to modify the underlying disease or slow structural progression; all are used for symptom relief only.
- Corticosteroids provide short-term symptom relief only; repeated use adds little and raises chondrotoxicity concerns.
- Viscosupplementation comprises heterogeneous products; pooled benefit falls below clinically important thresholds, and NICE does not currently recommend its use.
- PRP has the strongest emerging evidence among biologics, but preparation heterogeneity limits interpretation; at present cell-based therapies and permanent hydrogels lack robust Level I data.
- Where injectables are offered privately and at cost, evidence, transparency, informed consent, and governance must come first. ■

References

References can be found online at www.boa.ac.uk/publications/JTO.