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Effectiveness of intra-articular therapies in osteoarthritis: a literature review

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***Abstract*:** Osteoarthritis is a painful, chronic disease with widespread burden on patients, communities, health and social care systems. Conservative therapies, such as nonpharmacological interventions, systemic drug treatment and intra-articular therapies are used before resorting to surgery; nonetheless, disease control often remains inadequate. Recent advances in osteoarthritis management have aimed to provide greater variety of treatment options. Here, we summarize a targeted literature review evaluating efficacy and safety of intra-articular therapies for osteoarthritis.

Injections of intra-articular therapies directly into the joint avoid conventional barriers to joint entry, increase bioavailability and lower systemic toxicity. Intra-articular corticosteroids and hyaluronic acid are established United States Food and Drug Administration (US FDA)/European Medicines Agency (EMA)-approved treatments; however, concerns exist regarding effect duration, safety, effectiveness across populations and heterogeneity.

Newer therapies, such as autologous blood products and mesenchymal stem cells, are in development. Benefits of autologous blood products (e.g. platelet-rich plasma, autologous conditioned serum) include an expected improved safety profile and direct targeting of osteoarthritis-related pathophysiology. Autologous conditioned serum is cell-free and manufactured by a standardized process, whereas platelet-rich plasma composition and characteristics can vary. Currently, only limited efficacy comparisons between these biological treatments can be drawn; long-term clinical and safety studies are needed to increase the efficacy evidence base and earn consideration in treatment frameworks.

Keywords: autologous conditioned serum, conservative treatment, intra-articular injections, osteoarthritis management, platelet-rich plasma

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Introduction

Osteoarthritis (OA) is a chronic, disabling condition that affects 10–15% of adults over 60 years of age.[1] Joint inflammation, cartilage breakdown and bone remodeling contribute to a syndrome of chronic pain, stiffness and impaired movement. OA is the most common form of joint disease worldwide, whose prevalence is rising further alongside increases in life expectancy and risk factors, such as obesity.[1] The pain and decreased function associated with OA place a major burden on communities as well as health and social care systems;[1] hip and knee OA are leading causes of disability worldwide.[2]

Treatment modalities for OA can be broadly divided into conservative and surgical. Conservative therapies include supportive nonpharmacological therapy, systemic pharmacological therapy and localized intra-articular (IA) therapies delivered directly into the affected joint.[1] It is generally accepted that conservative treatment should precede the consideration of surgery,[1,3] however, management of OA patients should take into account multiple factors, such as anatomical distribution, disease phase and progression, comorbidities, as well as the patient's needs and expectations. Any OA treatment plan should be regularly reviewed and adjusted individually, depending on response and adherence.[1]

The field of OA management is experiencing an increase in the number and variety of available treatment options, only few of which are currently

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approved by the United States Food and Drug Administration (US FDA) or European Medicines Agency (EMA). Importantly, therapeutic options can be limited by complications arising from comorbidities, contraindications to surgery and long-term systemic medications, contributing to an increasing unmet clinical need for additional treatment modalities.[1]

A targeted *PubMed* literature search formed the basis of this review [search terms: osteoarthritis with: intra-articular, systemic, corticosteroid, hyaluronic acid, platelet-rich plasma, autologous conditioned serum, analgesic, anesthetic, protein therapy, biologic gene therapy, stem cell therapy (term group 1); efficacy, effectiveness, benefit safety, adverse event, side effect, cost, dosing, bioavailability, manufacturing, processing, pharmacokinetics, pharmacodynamics, administration, delivery (term group 2)].

The *MEDLINE* database was searched using *PubMed* to identify review articles and meta-analyses of IA therapies for OA published from June 2010 to January 2016. Articles evaluating the efficacy or safety of IA therapies for OA were considered, and hand-searching of reference lists identified further articles of interest. Included articles were reviewed to identify key results from meta-analyses and randomized controlled trials. Further hand-searching was then performed to identify additional publications, particularly those in known associated areas of interest. Treatment guidelines and recommendations issued in the last 5 years for IA therapies in OA were also reviewed.

This review focuses on current options for the conservative treatment of knee OA, discussing the role and potential advantages of various IA therapies over systemic therapy. In particular, the rationale and current evidence for the use of IA autologous blood products, which represent an emerging field that may present effective and safe therapeutic options for OA, will be considered.

Conservative management of knee osteoarthritis

The short-term goal of OA treatment is to relieve pain and stiffness to increase function and mobility. A longer-term goal of treatment is to stop or slow disease progression to avoid disability and prevent, or at least delay, the need for a total knee replacement (total knee arthroplasty). The generally accepted treatment hierarchy for OA utilizes nonpharmacological interventions initially (e.g. physiotherapy, weight management), followed by systemic pharmacological therapy [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, such as acetaminophen, and synthetic opioids]. The decision to administer IA therapies usually depends on the response to other conservative treatments (nonpharmacological and pharmacological). Surgery tends to be considered, if previous interventions have failed to achieve sufficient disease control.[1,3,4] The importance of conservative OA management is fundamental, especially as the effectiveness of some common surgical treatments has recently been questioned.[5,6] Standardized guidelines for the treatment of knee OA have been published by the AAOS (American Association of Orthopedic Surgeons), EULAR (European League Against Rheumatism), ACR (American College of Rheumatology) and OARSI (Osteoarthritis Research Society International).[7–10]

It is increasingly recognized that OA management must be optimized individually for each patient, and that treatment strategies need to be evaluated and adjusted regularly.[3,10] This is evident in the recently published OARSI guidelines for the nonsurgical management of knee OA, which provide evidence-based, internationally-recognized treatment recommendations (see Figure 1).[10] These guidelines, which aim to optimize conservative management and avoid or delay surgical intervention, were created following international consultation with global medical experts and patient representatives, consideration of previously published OA guidelines, and a systematic literature review.

Within the OARSI framework, treatment recommendations differentiate between patients with OA confined to the knee and those with multiple joints affected. The guidelines also recommend consideration of relevant comorbidities to optimize treatment strategy (Figure 1).[10]

Systemic versus intra-articular treatments

Alongside nonpharmacological supportive management strategies, systemic and IA therapies form the mainstay of conservative management. IA therapies have a number of physiological and practical advantages over systemic medications, including safety, especially when certain comorbidities are present (e.g. cardiovascular and

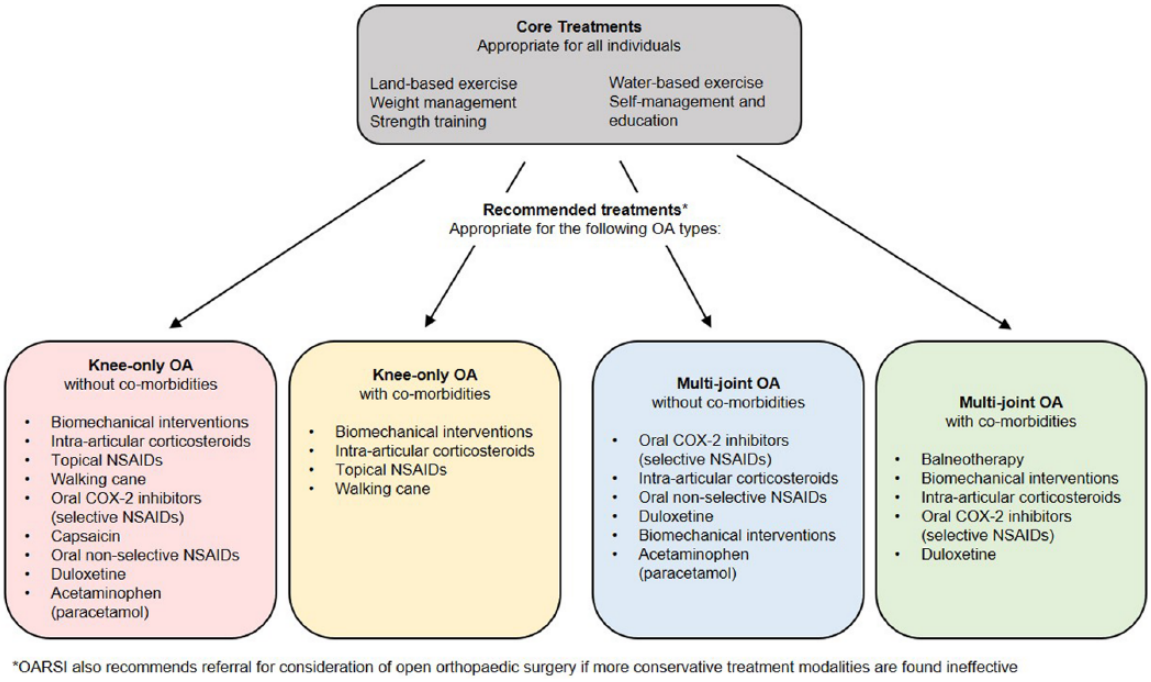

Figure 1. OARSI guidelines for the nonsurgical management of knee OA.
Adapted from McAlindon and colleagues.[10]
NSAID, nonsteroidal anti-inflammatory drug; OARSI, Osteoarthritis Research Society International; OA, osteoarthritis.

bleeding disorders), bioavailability, placebo benefit, and (for some) a novel mechanism of action more directly targeting the pathophysiology of OA. IA injection is a minimally invasive procedure, which can be performed easily in an outpatient setting, with a short recovery time. Joints commonly affected by OA are well-suited to an IA injection.[11]

Local delivery of an active drug to the joint space has the potential to result in fewer systemic effects and adverse events.[11] Reduced systemic drug exposure may be of particular relevance in patients with complex or severe comorbidities, including the elderly, and is pertinent for any long-term management strategy. Delivery of the active drug directly to the IA space bypasses the conventional barriers to entry to the joint following systemic delivery (Figure 2). Local delivery carries the advantage of increased bioavailability, and therefore, enables the administration of lower doses.[11] However, there are a number of risks associated with knee joint injections; pain or swelling at the site of injection may occur in up to 20% of patients.[12] Additionally, septic arthritis has been reported in patients treated with IA hyaluronic acid (HA)[13] and steroid injections.[14]

IA treatments, particularly newer therapies, have the potential to target the underlying pathological processes involved in OA, and may be more effective in combating disease progression than traditional systemic anti-inflammatory treatments.

While it is increasingly acknowledged that pain measurement in clinical trials is difficult and can contribute to the exaggeration of the observed effects of an intervention,[15] it has been demonstrated that the majority of treatment success of the different OA therapies can be attributed to a placebo effect, rather than then specific treatment modality. Its magnitude is influenced by the strength of the active treatment, the baseline disease severity, the route of delivery and the sample size of the study.[16–19]

Similarly, evidence is available that a considerable placebo effect is added to any intrinsic beneficial effects of IA therapies, which can provide a substantial and sustained reduction in joint pain. A recent meta-analysis of both oral and IA interventions reviewed 137 studies, with a total of 33,243 patients, and it was concluded that the placebo effect of IA injections on pain outcomes was significantly larger than that of oral placebo.[20] Notably,

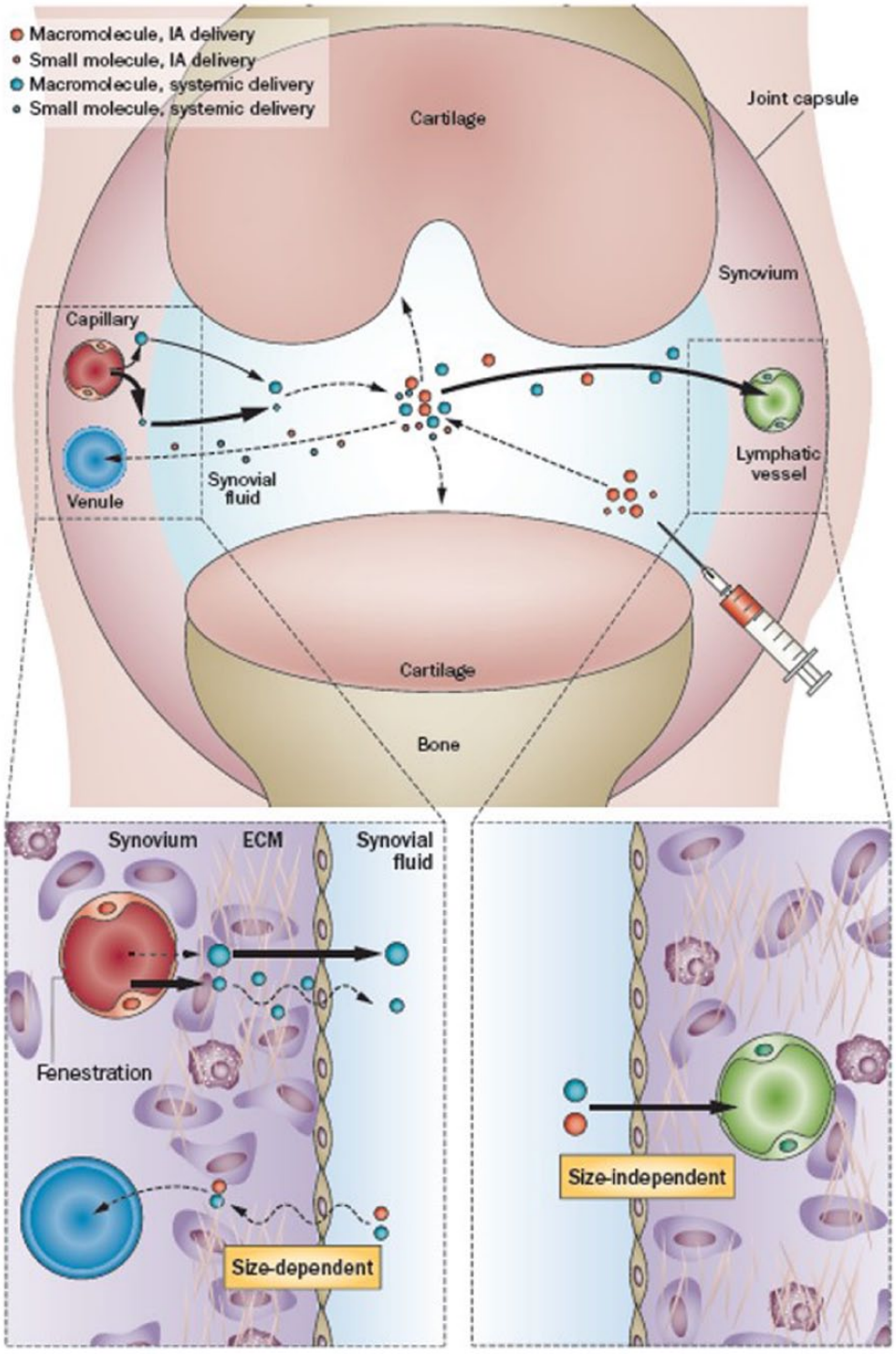

Figure 2. Entry elimination of soluble molecules from the joint space.
Macromolecules in the circulation enter the joint *via* the synovial capillaries and are sieved by the fenestrated endothelium of the capillaries. Small molecules also enter *via* the capillaries, but in this case the major resistance to entry is provided by the ECM of the synovial interstitium. IA injection bypasses both of these barriers to entry. However, both large and small molecules rapidly exit the joint, *via* the lymphatic system and small blood vessels, respectively.
ECM, extracellular matrix; IA, intra-articular.
Adapted from Evans and colleagues.[11]

no oral NSAID was superior to IA placebo injections with respect to pain reduction outcomes. A similarly marked difference in effect size between IA and oral placebos was reproduced in a network meta-analysis of OA placebo treatments.[21]

The importance of the placebo effect has been increasingly acknowledged in medicine, and the role of mood and psychology in chronic, painful conditions is significant. Far from being ineffective or insignificant, the placebo effect is a useful neurological phenomenon to be employed and utilized clinically, and perception is shifting to acknowledge that the placebo effect may be recognized as an OA treatment modality in itself.[17] The practical reality is that the placebo effect associated with IA injection can contribute to the overall benefit of the IA treatment administered in clinical practice.[20]

Intra-articular treatment options

IA corticosteroids and HA are established, popular OA treatments with known limitations. Within recent years, interest in newer IA therapies, such as autologous blood products and mesenchymal stem cell therapy, have emerged (Table 1). Unlike corticosteroids and HA, these therapies are not yet approved by the US FDA or EMA and thus are not currently considered in current treatment frameworks: further research is needed to establish their efficacy and safety, and their position within the context of guidelines for OA care.

Corticosteroids

IA corticosteroids have been widely used for over 5 decades in the treatment of knee OA, with the rationale to reduce joint inflammation and pain by the local delivery of a potent anti-inflammatory agent. Triamcinolone preparations are used most frequently and are approved by the US FDA and in Europe as crystalloid suspensions.[11] However, major limitations of IA corticosteroids include a short duration of effect and safety concerns that limit the frequency of use.

A 2009 Cochrane review of IA corticosteroids for the treatment of knee OA concluded that IA corticosteroids were more effective than placebo in reducing pain at 1–2 weeks' post-injection, with few side effects; however, at 4–24 weeks' post-injection, little evidence of an effect was observed.[42] This is likely to be related to the short half-lives of IA corticosteroids.[11] Further meta-analyses have supported short-term improvements in OA symptoms with IA corticosteroids; however, less evidence is available for long-term benefits (post-4 weeks after injection).[22,43–45] In addition, concerns have been expressed that prolonged exposure to IA corticosteroids may have an adverse effect on articular cartilage and accelerate the progression of OA. In a recent study, corticosteroids were shown to cause significantly greater cartilage volume loss when compared with intra-articular saline.[23] A recent systematic review of the effect of corticosteroids on articular cartilage confirmed that, at higher doses and for longer treatment durations, IA corticosteroids were associated with chondrotoxicity.[46] For this reason, many physicians limit the use of corticosteroids to 3–4 IA injections annually into any given joint.[11]

It has been suggested that corticosteroids may be more efficacious in certain patient subpopulations, such as patients with joint effusion, or resting rather than mobile patients, although there is no clinical consensus on these findings or on the reservation of corticosteroids for these cases.[11,47]

These concerns and limitations are reflected in a lack of consensus across national and international guideline frameworks. The OARSI guidelines recommend IA corticosteroid use as an appropriate treatment modality for all considered patient subgroups; however, this recommendation recognizes that IA corticosteroids are indicated for short-term analgesia, but that physicians should consider other treatments for long-term pain management.[10]

The AAOS was unable to recommend for or against treatment with corticosteroids for OA of the knee, due to 'a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm'.[7] In contrast, the ACR guidelines recommend IA corticosteroid treatment when appropriate, on the basis that the potential benefits may outweigh associated risks in certain clinical scenarios.[9] Similarly, the 2014 UK National Institute of Care Excellence (NICE) recommendations state that IA corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate-to-severe pain in patients with OA.[48]

Thus, although no consensus exists between guideline frameworks on corticosteroid use, the indications given are limited to short-term symptom relief, with considerable caution regarding frequency and duration of use.

Table 1. Summary of IA therapies.

	Corticosteroids	HA	Platelet-rich plasma	Autologous conditioned serum	Mesenchymal stem cells
Components	Glucocorticoid (usually triamcinolone), in suspension	Hyaluronic acid or its sodium salt (sodium hyaluronate)	Plasma containing cells and coagulation factors, plus additives [anticoagulants, fibrinogen, activator (Ca^2+)]. Cell concentration varies depending on manufacturers' processing recommendations	Cell-free serum without platelets, white or red blood cells or additives. Standardized manufacturing process	Suspension of multipotent adult stem cells
Mechanism of action	Anti-inflammatory agent	Lubricating component of synovial fluid	Growth factor release, including TGF-β, PDGF, IGF, VEGFs, EGF and FGF-2	Elevated concentration of anti-inflammatory cytokines (including IL-1Ra, IL-4 and IL-10) and regenerative growth factors	Stem cell-secreted factors including cytokines and growth factors
Preparation and administration	Product injection directly into the joint	Product injection directly into the joint	Platelet enrichment in device from anticoagulated blood by centrifugation and elimination of superfluous plasma. Platelet yield is usually 50–75%. PRP may be activated with Ca^2+, and then injected directly (single injection). Sterile filtration not possible	Serum conditioning by incubation of whole blood in a pyrogen-free device at 37°C. Conditioning stimulates production of cytokines including IL-1Ra. Serum is separated by centrifugation and extracted/stored at −18°C for ⩽7 months. Injection 3–6 times per visit, given twice a week for 3 weeks, 1–3 times, sterile filtration possible	MSCs can be isolated from several organs and tissues (e.g. bone marrow) and grown using various cell culture techniques
Efficacy	Evidence for short-term efficacy over placebo. Long-term benefits less well substantiated[11,22]	Incongruous literature regarding efficacy and safety: some indicating a good efficacy,[24] others suggesting HA provides little or no benefit over placebo.[25,26]	Most reviews provide evidence of clinical benefits,[27,28] some remain equivocal.[29]	Limited data due to less expanded use and nonconsideration in guidelines. Clinical studies indicate significant improvements over placebo and saline.[30]	Efficacy data are very limited, albeit encouraging.[31–37] Further studies are ongoing.
Safety	Prolonged exposure may adversely affect articular cartilage or be associated with chondrotoxicity	Incongruous literature, some meta-analyses concluding HA to have a low risk of harm,[26] others identifying concerning safety signals, albeit with unclear causal mechanisms.[25]	Perceived favorable safety profile due to autologous nature. Limited evidence available from long-term safety studies. Some evidence that PRP injections may lead to an increase in adverse events.[28,38]	Perceived favorable safety profile due to autologous nature. Limited data are available, but no serious side effects have been observed in published trials.[30,39]	Based on limited data available to date, IA MSC therapy appears to be relatively safe.[40,41]
Treatment recommendations	OARSI recommend corticosteroids, but recognize that other treatments may be more appropriate for long-term analgesia.[10]	OARSI do not recommend HA in multi-joint OA and cite uncertainty in the use of HA to treat knee OA.[10]	Not considered by OARSI in OA treatment recommendations	Not considered by OARSI in OA treatment recommendations	Not considered by OARSI in OA treatment recommendations

ACS, autologous conditioned serum; CS, corticosteroid; EGF, epidermal growth factor; FGF-2, basic fibroblast growth factor; HA, hyaluronic acid; IA, intra-articular; IGF, insulin-like growth factor; IL-1Ra, interleukin-1 receptor antagonist; IL-4, interleukin-4; IL-10, interleukin-10; MSC, mesenchymal stem cell; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; PDGF, platelet-derived growth factor; PRP, platelet-rich plasma; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

Hyaluronic acid

IA HA has been widely used in knee OA since it received US FDA approval in 2001. HA is found intrinsically within the knee joint and provides viscoelastic properties to synovial fluid. The onset of OA causes natural HA concentration and average molecular weight to decrease, leading to a decline in mechanical properties of the joint. By increasing HA levels through IA injection, the viscoelasticity of the synovial fluid is restored, aiding shock absorption, lubrication and protection of the joint. In addition, HA has been reported to increase chondrocyte proliferation and decrease chondrocyte apoptosis, which decelerates the progressive joint space narrowing associated with osteoarthritis (chondroprotection).[49] Anti-inflammatory and analgesic effects have also been reported. Clinical trials, systematic reviews and meta-analyses have provided discordant results regarding HA efficacy compared with placebo. Assessment of clinical efficacy is further complicated by considerable heterogeneity between marketed products, which can vary regarding molecular weight, HA concentration, elasticity, viscosity, and administration schedule. Concerns regarding industry bias in the reporting of studies of HA in OA have also been highlighted.[50]

A systematic review of meta-analyses comparing IA HA treatment with other IA therapies and oral NSAIDs concluded HA to be a viable treatment option for knee OA, producing improvements in pain and function that can persist for up to 26 weeks, and demonstrating a good safety profile.[24]

In contrast, a separate, recent systematic review and meta-analysis concluded that IA HA use should be discouraged, given its poor efficacy and safety profile. The authors noted discordant results of previous systematic reviews of HA in knee OA: of six reviews, three concluded that HA was more effective than placebo, whereas the other three were more tempered, concluding either no difference in effect, or only small, short-term benefits.[25,26] The authors suggested that deficiencies in review methods could underlie these discordances, and, after analysis with more stringent criteria, found the effect of HA to be clinically insignificant, noting concerning safety signals in comparison to placebo.

Recommendation of IA HA for knee OA within the OARSI guidelines is uncertain, and was judged to be an inappropriate treatment option for multi-joint OA. OARSI estimations of effect sizes of HA for pain range from 0.37 [95% Confidence Interval, (CI) 0.28–0.46] to 0.46 (95% CI 0.28–0.65). For physical function, effect sizes range from 0.31 (95% CI 0.11–0.51) to 0.33 (95% CI 0.22–0.43). These results contrast with a recent meta-analysis by Bannuru and colleagues, which estimated an effect size for pain of 0.63 (95% CI 0.39–0.88).[20] Within this meta-analysis, HA had the greatest effect size of any considered treatment on pain outcomes, providing an analgesic benefit superior to oral NSAIDs. The more conclusive effect observed in this meta-analysis is understood to be due to a difference in methodology: by comparing with oral treatments, this meta-analysis allowed estimation of the effect size of the placebo effect of an IA injection. The authors suggest that this is more comparable with the effect in clinical practice. It should be noted that in this review, the effect of HA on stiffness and function was less marked, although still significantly better than IA placebo.

Other national and international treatment guidelines reflect the uncertainty in the literature. The AAOS guidelines recommend against the use of HA for knee OA, as do the NICE 2014 guidelines for OA, which state that IA HA injections should not be offered for the management of OA.[7] The ACR stated that they had no recommendations for the use of HA in either hip or knee OA.[9] However, the Cochrane Collaboration concluded that evidence was sufficient to support the use of HA in the treatment of knee OA, with comparable efficacy with systemic interventions.[51]

Autologous blood product therapies

One of the main issues undermining OA drug trials to date is the inability to demonstrate structural improvements of the affected areas, rather than improvement of pain management,[4,52–55] which has contributed to the marked increase in interest in autologous blood product therapies that has occurred in recent years. The rationale of autologous blood-based therapies is to exploit and utilize the body's own capacity for controlling inflammation, healing and repair. The two main categories of IA autologous blood therapies are as follows: platelet-rich plasma (PRP) and autologous conditioned serum (ACS).

PRP is obtained by centrifuging an anticoagulated sample of the patient's venous blood once or twice to produce a plasma fraction containing an increased concentration of platelets and decreased

concentration of erythrocytes. Upon IA injection of plasma coagulates, the platelets are activated and undergo degranulation, releasing a range of growth factors, including transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor, vascular endothelial growth factors, epidermal growth factors and basic fibroblast growth factor 2.[56] These growth factors are thought to activate a variety of signaling pathways, which promote healing of bone and soft tissue.

ACS is a cell-free treatment, obtained by incubating venous blood for 6–9 h in a specialized modified syringe. Exposure of blood to the syringe's internal surfaces induces blood cells to produce increased amounts of several anti-inflammatory cytokines [including interleukin (IL)-1 receptor antagonist (IL-1Ra), IL-4 and IL-10] and regenerative growth factors (including TGF-β)].[57] The post-incubation serum is recovered by a single centrifugation step and injected into affected joints, usually in a series of 3–6 IA injections, given twice a week for 3 weeks.

No standardized method or device for PRP production exists yet, and injection volume and frequency vary widely among published knee OA studies. Variables include platelet concentration, leukocyte concentration, use of anticoagulants, use of platelet pre-activation factors and injection volume/frequency.[58] The number of centrifugations and centrifuge speed/timing has a major influence on the final PRP concentration of platelets and leukocytes, and therefore, small variations can yield PRP products with significantly different compositions and characteristics, contributing to variable patient responses.[58] To generate PRP, blood must be withdrawn on each occasion, as PRP cannot be stored or frozen. This may also contribute to variability in composition between blood withdrawals and the desired outcomes.[56]

The production of ACS is a standardized process, as ACS-processing devices are available to ensure consistency for the generation of ACS. ACS contains no additives, such as anticoagulants (e.g. citrate), or platelet-activating agents, (e.g. thrombin or calcium chloride), which are frequently used in PRP preparations. In contrast with PRP, preparation of ACS involves a single withdrawal of patient blood; the serum is then aliquoted for reinjections and can be frozen for future use.

Although ACS and PRP are both blood-derived products, they are differentiated by several significant biochemical and clinical differences. It should be noted that ACS and PRP have different cytokine profiles, which impacts their respective mechanisms of action. ACS contains high concentrations of IL-1Ra,[57] which contributes to the anti-inflammatory effect of ACS in a clinical setting.[58] IL-1Ra, alongside other anti-inflammatory cytokines, is thought to have a beneficial effect on the development of degenerative articular changes in OA, following the results of several animal studies.[60–62] Direct comparison of cytokine profiles between ACS and PRP is difficult, given the lack of standardization in PRP production. However, in a study comparing ACS with a different autologous blood product, autologous plasma, the beneficial cytokine concentrations in ACS were all substantially higher than in autologous plasma, with large differences in IL-1Ra concentrations.[59]

As ACS is a newer treatment method, only limited clinical data are available so far, restricting comparison of the clinical efficacy of PRP and ACS. Recently published systematic reviews and meta-analyses draw variable conclusions regarding the clinical efficacy of PRP, some equivocal, and some positive. Of three recent systematic reviews, two concluded significant clinical benefits of PRP up to 12 months post-injection,[27, 28] whereas the other recognized that current studies are at best inconclusive regarding efficacy PRP.[29] A recent meta-analysis concluded some limited evidence suggesting short-term clinical benefits of PRP for symptomatic knee OA,[63] although it also concluded that the majority of studies were of poor quality and at high risk of bias. Others have come to firmer conclusions that PRP is associated with improved efficacy compared with HA and placebo.[38]

However, concerns exist regarding the quality of published studies and the high risk of bias.[63] Similar to HA preparations, the heterogeneity of PRP preparation and composition between studies is a major limitation when assessing results for PRP, as the different preparation methods may impact clinical outcomes. This limits the generalizability of published efficacy results for PRP in knee OA.

To obviate the problem of preparation variability, a recent systematic review focused on trials using

only one type of PRP preparation, named 'plasma rich in growth factors' (PRGF), a pure PRP containing few white blood cells.[64] This review concluded that PRGF was more effective than HA or leukocyte-enriched PRP in knee OA. It should, however, be noted that only two of the five trials included were randomized controlled trials, and three studies were identified to have a high risk of bias.[64] The use of PRP has increased in sports medicine and also for treatment of tendinopathies and musculoskeletal soft tissue injuries, but while short-term improvements appear to be common, conclusive evidence regarding its benefits is still lacking.[27–29,65,66] Given its relatively recent evidence base and difficulties with generalization of evidence, PRP is not considered in the current ACR and OARSI guidelines, and AAOS was unable to recommend for or against PRP treatment for knee OA.[7]

To date, only two randomized controlled trials of ACS have been conducted in patients with knee OA. In the first, 376 patients with knee OA were randomized to ACS, HA, or an IA placebo saline solution and were assessed using the Western Ontario and McMaster Universities OA (WOMAC) index, global patient assessment and a visual analog scale after 7, 13 and 26 weeks (with a follow up after 104 weeks). ACS was shown to be significantly more efficacious, compared with HA and saline for all efficacy outcome measures and time points, and improvements were clinically relevant.[30]

In the second trial, 182 patients with knee OA were randomized to receive either ACS or placebo saline solution, with a primary endpoint of 30% superiority in ACS WOMAC score compared with that of placebo at 3, 6, 9 and 12 months' post-treatment. ACS treatment was associated with statistically significant improvements in multiple clinical outcomes, including Knee Injury and Osteoarthritis Outcome Score symptom and sport parameters, but the primary endpoint of the study was not met. However, methodological limitations, including the unrecorded use of analgesics during the study and low disease severity at enrolment, complicate the interpretation.[39] Lower levels of improvement in WOMAC score were 16.5% in the placebo group, compared with 16.8% in the ACS group. Recent network meta-analysis found IA placebo effect sizes of 0.29 (95% CI 0.09–0.49).[21] A placebo effect roughly half that size raises questions about study design and performance.

A recent open-label study observed knee OA patients with chronic pain whose disease severity made them eligible for surgical treatment, but who chose treatment with ACS in combination with physiotherapy. By 24 months, only one out of 118 patients receiving this treatment opted for a knee replacement; all other patients experienced >60–80% improvement in pain, indicating long-term efficacy of ACS.[67] Furthermore, a subgroup analysis within this study showed that effective pain reduction was effective irrespective of age, sex, weight and disease grade, which supports the hypothesis that ACS could represent a suitable treatment for a large number of different patient populations.

The autologous nature of PRP and ACS implies a favorable safety profile for both treatments; however, conclusions are limited by the lack of safety studies and long-term clinical trials. Data available from randomized controlled trials suggest that ACS treatment is well tolerated, and tolerance to IA PRP and short-term safety also appears acceptable.

However, Crnogaca and colleagues have suggested that ACS treatment should be avoided in patients with elevated C-reactive protein (CRP).[68] They hypothesize that if a patient has any kind of preexisting systemic inflammation at the time of blood sampling, this could shift levels of cytokines in favor of proinflammatory factors in the resulting ACS, which in turn might initiate or enhance an inflammatory response, thus potentially contributing to disease progression.[68] Although it has been demonstrated that ACS composition can be influenced by the host's systemic state in animals,[69] these concerns have not yet been substantiated by robust clinical evidence from human studies.

A meta-analysis of PRP studies found that an increased incidence of nonspecific adverse events among patients treated with PRP, compared with HA and placebo,[38] and one systematic review noted increased local adverse reactions with multiple PRP injections.[28] Similarly, concerns have also been raised over the safety of PRP preparations, which contain leukocytes. Increasing the concentration of leukocytes in the IA space may cause inflammation, increasing patient discomfort.[64] In particular, polymorphonuclear neutrophils may have a negative effect on cartilage, exacerbating existing tissue damage. In a study comparing PRGF (leukocyte-free) with leukocyte-enriched PRP, the incidence of adverse

events related to pain and swelling was increased in the leukocyte-enriched PRP group.[70]

Mesenchymal stem cells

Interest in mesenchymal stem cells (MSCs) as a treatment strategy for OA is increasing considerably, although this research is still in early stages. MSCs are multipotent adult stem cells with the capacity to mediate tissue regeneration following damage. These cells have the ability to differentiate *in vitro* along multiple cell lineages of connective tissue, including chondrogenic and osteogenic lineages.[71] MSCs also secrete a range of mediators, such as trophic factors, cytokines and neuroregulatory peptides, which play a role in tissue repair and regulate inflammatory and immune responses.[40,72,73] IA injection of MSCs has been hypothesized as a novel therapy approach for OA, with the capacity to stimulate local repair and regeneration of damaged joint tissues, and to reduce inflammation and associated pain.

Although preclinical data for the use of MSC therapy in OA are encouraging, only a small number of human clinical studies have been published so far. Data on efficacy data are limited, and involve relatively low numbers of patients. However, encouraging preliminary results have been reported when MSCs are used to treat knee OA,[31–37] in particular, as adjunctive therapy alongside surgical or arthroscopic procedures.[74,75] A recent systematic review and meta-analysis drew positive conclusions about the potential for MSCs to treat pain and decreased function in knee OA, but also brought attention to the need for rigorous and adequately powered clinical trials.[76] It is important to acknowledge that the conclusions drawn from this analysis were ultimately based on data from only two trials (94 patients), as the quality of the other trials under investigation was considered to be inadequate. In addition, both trials included in the analysis compared MSCs with HA as a control measure and did not use a standard placebo. It should be noted that no consensus on the most appropriate source of MSCs has been established yet, as well as the optimal conditions for culture, the optimal stage of differentiation at time of injection or the appropriate dose per injection, and the expected length of effect.[72,73,77] Preparation of autologous MSCs for injection requires *ex vivo* culture in a good manufacturing practice facility, which makes the process laborious and expensive. It is not known whether allogeneic MSCs are effective.

Based on the available evidence to date, including a recent systematic literature review by Peeters and colleagues, IA stem cell therapy appears to be relatively well tolerated.[40,41] Possible concerns about risk of malignant transformation have not yet been supported by clinical evidence,[40] and long-term safety in a greater number of patients needs to be monitored further.

Conclusions

The rising prevalence and high burden of disease of OA drive a need for effective and coherent treatment strategies, which is further emphasized by the complexity of available conservative OA treatment options.

IA therapies have many intrinsic features, which might provide advantages over systemic therapies: increased safety, lower drug dose, and a positive placebo benefit. In addition, IA injection is a relatively simple and well tolerated procedure associated with minimal recovery time.

In particular, randomized controlled trials have demonstrated the safety and efficacy of ACS in the treatment of knee OA, and it is expected that the results of ongoing clinical trials will add to the evidence base for efficacy of biological IA treatments.

The further development of well tolerated and effective IA therapies could potentially provide alternative treatment options to complement the current strategies. However, recognition of their capabilities by OARSI and other guidelines is still limited, and larger and longer-term studies are therefore needed to confirm initial positive results and substantiate the applicability of IA therapies.

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Conflict of interest statement

Peter Wehling is CEO and founder of Orthogen AG; William Maixner is a board member and consultant for Orthogen AG; Jana Wehling is an employee of Zentrum für Molekulare Medizin und Orthopädie; Christopher Evans is a supervisory board member for Orthogen AG and scientific advisory board member for TissueGene Inc.

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