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Review

Molecular Advances in Intra-Articular Injections for Knee Osteoarthritis

Juan M. Roman-Belmonte[1], Hortensia De la Corte-Rodriguez[2], E. Carlos Rodriguez-Merchan[3,*]

[1]Department of Physical Medicine and Rehabilitation, Hospital de la Cruz Roja San José y Santa Adela, 28003 Madrid, Spain
[2]Department of Physical Medicine and Rehabilitation, La Paz University Hospital-IdiPaz, 28046 Madrid, Spain
[3]Department of Orthopedic Surgery, La Paz University Hospital-IdiPaz, 28046 Madrid, Spain
*Correspondence: ecrmerchan@hotmail.com (E. Carlos Rodriguez-Merchan)
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Abstract

Knee osteoarthritis (KOA) is a common musculoskeletal condition characterized by progressive cartilage loss, subchondral bone alterations, and persistent, low-grade synovial inflammation. There is growing evidence indicates that KOA should be viewed not only as a degenerative disorder but also as a multifaceted inflammatory process driven by complex interactions among immune cells, cytokines, and cartilage-related molecular pathways. This review outlines recent molecular advances related to intra-articular injection therapies and their proposed mechanisms of action. Corticosteroid (CS) injections provide short-term pain relief by suppressing inflammatory activity; however, repeated administration raises concerns about cartilage integrity. Hyaluronic acid (HA) injections improve joint lubrication and restore viscoelasticity and modulate inflammatory signals, particularly in the early stages of the disease. Platelet-rich plasma (PRP) has gained attention as a biologically active therapy that modulates inflammatory cascades and support tissue repair by releasing diverse growth factors. Combined administration of PRP and HA may produce complementary biological effects; however, current clinical evidence is inconclusive. Regenerative modalities, such as fat-derived orthobiologics (FDO) and mesenchymal stem cell (MSC) therapies, show promise due to their paracrine actions on macrophage behavior and extracellular matrix regulation. Emerging evidence supports the investigation of exosomes, hyperosmolar dextrose, and botulinum toxin as novel intra-articular therapies, with exosomes representing a promising cell-free regenerative approach. Overall, intra-articular interventions play an important role in KOA management, though further studies are required to determine their long-term structural impact.

Keywords: osteoarthritis; knee; injections; intra-articular; platelet-rich plasma; hyaluronic acid; mesenchymal stem cells; exosomes

1. Introduction

Knee osteoarthritis (KOA) is one of the most common and disabling musculoskeletal disorders. It imposes a substantial burden on healthcare systems worldwide [1]. Patients typically experience persistent joint pain, swelling, increased tenderness, and progressive stiffness, all of which significantly compromise daily functioning. These symptoms often prompt individuals to seek care in primary settings. Contemporary analyses of musculoskeletal referrals indicate that KOA is the most frequent reason for referral from general practice to orthopedic services [2].

KOA follows a chronic and insidious course with considerable inter-individual variation in progression rate, though recurrent inflammatory exacerbations manifesting as morning stiffness, nocturnal pain, or joint effusion are common among affected patients [3].

KOA is characterized by progressive deterioration of the articular cartilage, structural changes in the subchondral bone, and low-grade synovial inflammation, although its precise etiopathogenesis has not been fully elucidated [4]. KOA is a whole joint disease, involving all joint tissues, including meniscal degeneration, and inflammation and biomechanical changes of the infrapatellar fat pad [5,6,7]. Traditional concepts portraying KOA solely as a degenerative mechanical process are now considered incomplete because accumulating evidence highlights its involvement in low-grade inflammation affecting the entire joint organ. This inflammation is mediated through multiple immune-related signaling pathways [8]. This persistent inflammatory environment disrupts the balance between catabolic and anabolic activities within the cartilage matrix, thereby sustaining a progressive cycle of cartilage degradation.

Current therapeutic strategies for KOA, including physical and pharmacological modalities, primarily aim to reduce pain and enhance functional capacity, but they lack the ability to halt disease progression. Consequently, intra-articular injections (IAI) have been proposed as a nonsurgical alternative for individuals who cannot tolerate oral pharmacotherapy, offering a potential means to postpone surgical intervention [8,9].

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2. Pathophysiology and Molecular Mechanisms of Osteoarthritis

The precise pathophysiological mechanisms underlying KOA are not fully understood, although substantial evidence supports characterizing the condition as an inflammatory disorder influenced by multiple immune cell subsets and their effector cytokines [10]. Throughout the progression of osteoarthritis, a distinct pattern of inflammatory cell infiltration becomes evident. This immunological profile varies considerably across the various clinical and structural stages of KOA.

The perceived symptoms are not only due to the deterioration of cartilage and subchondral bone; all structures are involved. A degenerated meniscus loses its biomechanical function and alters osteoarthritis-related gene expression in articular chondrocytes through paracrine mechanisms, promoting the production of cyclooxygenase-2 (COX-2) and matrix metalloproteinase-3 (MMP-3) [11,12]. Ligaments undergo changes in their extracellular matrix, as well as in chondrogenesis and ossification, particularly at the tibial insertion sites of the anterior cruciate ligament and collateral ligaments [13]. Synovitis triggers an immune response as degradation products of extracellular matrices of cartilage and other joint tissues activate Toll-like receptors and the complement cascade. This response leads to the synthesis and release of proinflammatory cytokines and chemokines [14]. Other structures, such as the capsule, express proinflammatory and profibrotic mediators [15], while the role of bursae is less well known [16]. The infrapatellar fat pad serves as a local source of inflammatory mediators within the joint, including neuropeptides and classical pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF) [4]. These changes affect the joint's stability and load-bearing capacity.

The nervous system also plays an important role in knee osteoarthritis through various mechanisms. First, peripheral sensitization occurs when joint nociceptors become sensitized by pro-inflammatory cytokines, nerve growth factors, and other mediators [17]. Secondly, KOA pain may become more constant through sensitization mechanisms, whereby neural pathways become over-responsive to both painful and non-painful stimuli [18]. Additionally, pathological innervation occurs when subchondral osteoclasts produce netrin 1, causing sensory nerve axons to grow abnormally within the bone [19].

The interplay between immune cells and cytokines is a highly dynamic phenomenon governed by the concurrent integration of pro- and anti-inflammatory signals, yielding a complex regulatory network involving multiple cellular subsets and soluble mediators [20]. Despite growing research, the specific contribution of each immune component to the initiation and progression of tissue damage in KOA remains only partially clarified. Among the relevant pathogenic mechanisms, an accelerated rate of extracellular matrix degradation is a key feature strongly linked to local inflammatory activity [21,22].

Synovial fluid sampling during IAI procedures is a practical way to characterize biological events within the affected joint and provides insight into dynamic inflammatory changes [10]. In the early stages of osteoarthritis, this fluid is predominantly composed of macrophages (69%) and lymphocytes (18%), as well as elevated concentrations of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and interleukin-8 (IL-8). Neutrophils constitute a minor fraction of approximately 2%. Lymphocytes are primarily T cells (86%), while macrophages exhibit an M1/M2 distribution ratio of 6:4 [23]. In advanced KOA, synovial fluid [21], showed a mixed immune-cell profile, including macrophages, neutrophils and T cells, rather than a single dominant immune-cell population.

Macrophages and T cells also constitute prominent infiltrating populations in osteoarthritic joints, and their presence is clearly associated with enhanced production of inflammatory mediators. Functionally, macrophages are commonly divided into the pro-inflammatory M1 subset and the regulatory M2 counterpart. M1 macrophages secrete essential host defense cytokines, while M2 macrophages contribute to anti-inflammatory activity and tissue modulation [24]. Interestingly, an elevated M1/M2 ratio has been closely linked to pain severity and radiographic progression in individuals with KOA.

Synovial fluid IL-6 was associated with neutrophil numbers and may be produced by multiple OA synovial cell types, including macrophages and neutrophils, supporting its role in broad inflammatory pathways rather than as a specific marker of one immune cell subset [21]. Upregulation of IL-6 and IL-8 expression has also been implicated as a potential driver of disease progression [25,26].

The gene that encodes type II collagen (COL2A1) in cartilage is a key structural element of human hyaline cartilage that undergoes marked degradation in KOA. Additionally, SRY-Box Transcription Factor 9 (SOX9), a cartilage-specific transcription factor that regulates chondrogenesis, is required for cartilage formation during embryogenesis and for regulating type II collagen production [27,28].

The general concepts and pathophysiology of KOA are summarized in Table 1. The intra-articular treatments for KOA and their molecular mechanisms of action are outlined below.

3. Distribution and Pharmacodynamics of Intra-Articular Injections

Intra-articular drug distribution is characterized by poor cartilage penetration and rapid synovial clearance, creating significant challenges for achieving therapeutic concentrations at target sites. The dense, negatively charged cartilage extracellular matrix acts as a major barrier to drug delivery [29].

Table 1. General concepts and pathophysiology of knee osteoarthritis (KOA).

Category	Summary
Clinical and Epidemiological Relevance	KOA is one of the most common and disabling musculoskeletal disorders. It is a frequent cause of referral to orthopedics.
Main Symptoms	Persistent pain, swelling, increased tenderness, progressive stiffness, functional limitation. Flares with morning stiffness, night pain or effusion.
Clinical Course	Chronic, insidious and variable. Recurrent inflammatory episodes.
Current Concept of KOA	Low-grade inflammatory disorder, not purely degenerative. Involves the whole joint organ.
Structural Changes	Cartilage degradation, subchondral bone changes, persistent synovitis, Inflammation mediated by the infrapatellar fat pad. Infrapatellar fat pad and synovial membrane act as an anatomical-functional unit.
Inflammation in KOA	Network of pro- and anti-inflammatory signals. Disrupts anabolic–catabolic balance of cartilage matrix. Cytokines secreted by infrapatellar fat pad.
Role of Intra-Articular Injections	Alternative when oral drugs are not tolerated. Symptomatic relief but do not halt progression.
Synovial Fluid Composition (Early KOA)	Macrophages 69%, lymphocytes 18% (86% T cells), neutrophils 2%. High interleukin-6 (IL-6) and interleukin-8 (IL-8). M1/M2 ≈ 6:4.
Synovial Fluid in Advanced KOA	Approx. 30% macrophages, 30% neutrophils, 30% T cells.
Role of Neutrophils	Contribute to progression and increase in advanced stages.
Role of Macrophages	M1 pro-inflammatory, M2 regulatory. High M1/M2 ratio associated with pain and radiographic progression.
Key Cytokines	IL-6 and IL-8 involved in KOA inflammatory pathways.
Cartilage Molecular Regulation	Loss of COL2A1 (the gene that encodes type II collagen in cartilage) and reduced SRY-Box Transcription Factor 9 (SOX9) activity, essential for chondrogenesis.
Final Common Mechanism	Synovial inflammation → increased cytokines → matrix catabolism → progressive cartilage degradation.

Cartilage penetration barriers: The primary limitation is the difficulty of distributing drugs into cartilage, which is the main target tissue in osteoarthritis [29]. The dense cartilage extracellular matrix, which is composed of negatively charged glycosaminoglycans, creates a significant diffusion barrier that prevents most drugs from reaching the chondrocytes and the deeper layers of the cartilage [30].

Synovial membrane permeability: The synovium exhibits size-dependent permeability; larger molecules [>150 kilodaltons (kDa)] demonstrate slower trans-synovial permeation. In inflamed joints, synovitis increases permeability; 150-kDa molecules demonstrate approximately a 2.5-fold increase in flux in inflamed states, which alters distribution patterns [31].

In terms of pharmacodynamics, different drug classes have distinct effects, such as locally suppressing inflammatory mediators and cytokines within the joint space [32]. The pharmacodynamic response depends on achieving adequate local concentrations at cellular targets, such as chondrocytes, synoviocytes, and inflammatory cells [33]. Standard formulations provide a rapid onset of action, but the duration is short (weeks). Controlled-release systems, on the other hand, extend the therapeutic effects by maintaining sustained local drug concentrations [32]. Intra-articular delivery increases local bioavailability while reducing systemic exposure and minimizing adverse events compared to systemic administration [34].

4. Corticosteroid (CS) Injections

Osteoarthritic joints frequently exhibit synovitis, which is characterized by the infiltration of mononuclear cells and a proinflammatory environment that is rich in mediators that promote catabolic pathways. These pathways include the upregulation of aggrecanases and collagenases [35].

In this context, the pharmacological suppression of inflammation via corticosteroids may attenuate structural progression in KOA [36].

Immunohistochemical analyses in an in vivo osteoarthritis model showed that triamcinolone acetonide, particularly when combined with a hyaluronic acid–chitlac biopolymeric matrix, was associated with stronger type II collagen and aggrecan expression and reduced synovitis [37]. Similarly, experimental work with monocyte-derived macrophage cultures showed that triamcinolone acetonide modulates macrophage phenotype by suppressing CD80

expression and increasing CD163 expression, consistent with the induction an anti-inflammatory profile [38].

However, potentially deleterious molecular effects associated with intra-articular CS administration have been reported, particularly regarding cartilage metabolism and extracellular matrix homeostasis [39]. In line with these concerns, a recent systematic review of 32 preclinical studies evaluating the effects of CS in animal models of osteoarthritis (1079 joints) demonstrated heterogeneous outcomes [39]. CS improved cartilage-related parameters in 68% of studies and synovial outcomes in 60%. However, adverse effects on cartilage and the synovium were documented in 11% and 20% of studies, respectively. These findings underscore the dual and context-dependent biological impact of CS in osteoarthritis and highlight the need for cautious interpretation of their molecular effects [40].

CS appears to be safe, with infrequent local complications and rare joint infections. However, other studies have shown that CS can cause cartilage damage, bone marrow lesions, and meniscus damage, as assessed by magnetic resonance imaging (MRI) [41].

A randomized trial evaluating sustained CS therapy did not detect differences in radiographic joint-space narrowing, though improvements in knee pain were observed in certain secondary outcomes, but not primary outcomes [42].

In contrast, a subsequent, higher-powered clinical trial revealed that administering 40 mg of triamcinolone every three months for two years resulted in significantly greater cartilage volume loss, without achieving clinically meaningful improvements in knee pain, compared with saline injections [43].

This study benefited from an MRI-based structural assessment, which enabled direct quantification of cartilage and soft-tissue morphology. MRI detected subtle yet clinically relevant changes in cartilage loss that would not have been observable using conventional radiography, a technique known for its inability to evaluate cartilage longitudinally [44].

Clearly, the effects of CS on cartilage at the molecular level and the outcomes at the structural level should be investigated in greater depth. Meanwhile, intra-articular glucocorticoid injections have been used clinically for over five decades. They have consistently demonstrated their ability to provide substantial pain relief and improve functional outcomes in individuals with osteoarthritis, with effects lasting at least 26 weeks [45].

CS are indicated for short-term pain relief and functional improvement [46], particularly in patients who do not respond to or cannot take oral medication [47]. The main advantage of CS is that they significantly improve pain and function for up to six weeks with a rapid onset of action [48]. The main drawback is that the effect diminishes over time: moderate after two weeks, mild after six weeks, and no evidence of an effect after 26 weeks. Therefore, there is a strong consensus between the American College of Rheumatology [49] and European Alliance of Associations for Rheumatology (EULAR) [50] in recommending intra-articular CS as an effective option for short-term symptomatic relief in KOA, particularly in the presence of acute flare-ups of knee pain, particularly if accompanied by effusion; however, their transient effect and uncertainties regarding their long-term structural impact limit their repeated use and necessitate a cautious and individualized approach. In addition to intra-articular treatment EULAR recommends individualized exercise as a core component of osteoarthritis management [51].

5. Hyaluronic Acid (HA) Injections

HA performs a broad spectrum of physiological and therapeutic functions, including lubricating articular cartilage, providing analgesia, modulating inflammatory pathways, and protecting cartilage. These effects arise from its capacity to interact with several cellular receptors, enzymatic systems, and multiple biomolecular networks [52].

The underlying mechanisms accounting for HA's therapeutic efficacy are partly unresolved. However, recent research demonstrates that HA engages in complex interactions with chondrocytes, synoviocytes, osteocytes, and immune cells. These interactions modulate cellular proliferation, differentiation, and migration while influencing key immune functions, such as attenuating lymphocyte and macrophage motility.

IAI of HA further promotes endogenous HA and proteoglycan synthesis by chondrocytes. This contributes to the attenuation of cartilage degradation and reduces levels of pro-inflammatory cytokines and MMPs within synovial fluid [53].

Dynamic alterations in synovial macrophage populations have been reported following HA IAI: M1 macrophages initially decline markedly and subsequently increase slightly, while M2 macrophages steadily rise. This pattern is consistent with an early immunosuppressive response. The shift from an M1 to an M2 phenotype correlates with pain relief. However, the trajectory of these subsets is not linear, which challenges the validity of a rigid M1/M2 polarization framework [23].

A modest rebound in M1 macrophages after multiple HA injections have also been described, potentially reflecting the development of immune tolerance. Consistent with this, a lack of clinical improvement after the first two HA injections often predict an inadequate response to subsequent treatments [54].

HA also modulates inflammatory mediators by reducing prostaglandins, leukotrienes, IL-1, and IL-6 [55].

IL-6 and IL-8 levels decline markedly after the first injection, with IL-6 showing the greatest variability. This reduction supports the anti-inflammatory role of HA and indicates that HA can substantially influence the synthesis of IL-6 and IL-8 by macrophages [23].

HA can be classified into three main categories based on its molecular weight. Low-molecular-weight HA, ranging from 500 to 1000 kDa, penetrates tissues more deeply and interacts more strongly with synovial cells [55]. However, its intra-articular half-life is shorter, meaning three to five injections are usually required [56]. Second, HA with an intermediate molecular weight (between 1000 and 2300 kDa) exhibits rheological properties closer to those of healthy synovial fluid. It occupies an intermediate position in tissue penetration and viscoelastic behavior compared to low- and high-molecular-weight formulations [57]. Third, high-molecular-weight HA, with a molecular weight exceeding 3000 kDa, is notable for its superior shock-absorbing and lubricating properties. it remains in the joint longer and typically allows for a treatment regimen involving a single injection [58]. It exhibits more pronounced anti-inflammatory and immunosuppressive effects and appears to provide superior clinical benefits compared with low-molecular -weight preparations [59].

HA infiltration has also been associated with meaningful pain reduction in mild osteoarthritis, with effects extending up to 24 weeks after treatment. However, several authors have suggested that IAI of HA may yield less favorable clinical outcomes than glucocorticoids in certain contexts. From a clinical perspective, the use of HA is the subject of considerable controversy. The EULAR [50] takes a more flexible stance in certain patients, whilst the American College of Rheumatology [49] opposes its routine use due to the limited magnitude of the benefits and the inconsistency of the evidence, which reflects the heterogeneity of the studies and the difficulty in identifying response subgroups.

6. Injections With Platelet-Rich Plasma (PRP)

The use of biological therapies has gained prominence as an approach to modulate the molecular mechanisms involved in the pathophysiology of KOA to slow structural disease progression [60,61,62]. Within this framework, the biological rationale supporting IAI of PRP as an alternative to IAI of CS is compelling.

At the molecular level, IAI of PRP reduces inflammatory biomarkers, enhances anti-inflammatory mediators, and downregulates key inflammatory enzymes within the joint microenvironment [63]. Furthermore, PRP has demonstrated beneficial effects on chondrogenesis and mesenchymal stem cell (MSC) proliferation, which further reinforces its therapeutic potential in managing osteoarthritis [64].

The early inflammatory response, which is characteristic of the initial stage of tissue repair, involves the active recruitment of neutrophils and macrophages to the site of injury. The macrophages play a crucial regulatory role in shaping the inflammatory environment by secreting cytokines and chemokines and by recruiting additional immune cells necessary for tissue healing [65]. Complementary findings derived from analyses of nuclear factor kappa B (NF-κB) signaling reveal a transient proinflammatory activation that ultimately transitions toward resolution of inflammation [66].

Considering that PRP contains both pro-inflammatory and anti-inflammatory cytokines, it is reasonable to infer that the pro-inflammatory components initiate an early tissue-clearing response while the anti-inflammatory cytokines and associated growth factors promote inflammation resolution and regenerative processes in the joint [67].

The bioactive proteins released from PRP are organized into functional groups based on their biological activities. This repertoire includes platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and a wide range of chemokines and cytokines that facilitate cellular proliferation, chemotactic recruitment, tissue healing, and angiogenesis. These processes contribute to an improved biological milieu in injured tissues [67].

Basic fibroblast growth factor has also been shown to enhance hyaline cartilage repair by upregulating various additional mediators, such as transforming growth factor (TGF), VEGF, and specific bone morphogenetic proteins, thereby stimulating multiple anabolic pathways [68].

PRP is produced by centrifuging autologous blood to achieve platelet concentrations ranging from two to five times higher than baseline values [69]. Platelets contain granules enriched with growth factors that play a central role in angiogenesis, tissue regeneration, chondrocyte proliferation, and extracellular cartilage matrix synthesis. Moreover, platelets help counteract the catabolic activity of interleukins that are intimately involved in the pathophysiology of osteoarthritis [70,71].

A considerable degree of heterogeneity exists among published studies regarding the number of intra-articular PRP injections administered. Some protocols rely on a single dose, while others employ multiple applications. This methodological variability complicates direct comparisons across studies and may account for the divergent clinical outcomes reported. In this context, some authors recommend three weekly injections, while others favor a single injection [72,73,74].

Standardizing the preparation of PRP is challenging due to the wide variation in protocols, commercial systems, and processing variables [75]. A Delphi consensus involving 35 experts concluded that PRP should be classified according to platelet count, white blood cell count, red blood cell count, activation method, and whether it is pure plasma or a fibrin matrix [76].

PRP preparations may contain varying leukocyte concentrations, stimulating ongoing debate about the advantages of leukocyte-rich PRP (LR-PRP) over leukocyte-poor PRP (LP-PRP) [77,78,79]. Additionally, higher platelet

concentrations have been associated with more pronounced effects on cellular migratory activity, highlighting the significant impact of preparation techniques on PRP composition. Likewise, analyses of 27 cytokines have shown that eight inflammatory cytokines, two growth factors, and one chemokine are significantly elevated in PRP compared to platelet-poor plasma (PPP). Regarding the involvement of growth factors in KOA, PDGF has been demonstrated to attenuate IL-1-induced inflammatory responses in chondrocytes by down-regulating NF-κB signaling and modulating pathways, including the Src/PI3K/AKT signaling axis, which includes the non-receptor tyrosine kinase Src, phosphoinositide 3-kinase (PI3K), and protein kinase B (AKT) [80].

Prior studies revealed that PRP has been administered using heterogeneous protocols across multiple disease contexts. Similarly, studies comparing platelet-rich fibrin (PRF), PRP, and plasma rich in growth factors (PRGF) emphasize the importance of standardized preparation protocols that clearly specify platelet and growth factor composition and incorporate long-term clinical monitoring [81,82].

Although comparative evidence between LR-PRP and LP-PRP remains limited, current findings suggest a more pronounced symptomatic effect with LR-PRP in this clinical setting.

A systematic review and meta-analysis showed that IAI of PRP were associated with superior clinical outcomes compared with CS injections, particularly with respect to pain reduction, decreased joint stiffness, and enhanced participation in physical activity and sports. This symptomatic improvement generally persisted for at least six months, and treatment regimens involving three weekly injections were more beneficial than a single administration [83].

Additionally, recent studies support the use of PRP as an alternative to HA for patients with mild KOA [84]. Although the combination of PRP and HA may offer complementary benefits, methodological heterogeneity limits comparisons between studies, highlighting the need for research involving larger sample sizes and standardized protocols [85].

However, variability in dosage, injection intervals, and therapy duration remains a central challenge that limits the clinical use of PRP. Furthermore, the biological mechanisms underlying the protective effects of PRP against progressive KOA have not been fully clarified. Several studies suggest that growth factors and cytokines stored in platelet alpha granules may have significant immunomodulatory effects, such as promoting anti-inflammatory macrophage polarization [86].

The use of intra-articular PRP remains highly controversial among expert groups. The American College of Rheumatology advises against its use due to a lack of standardization and variable results, whilst EULAR does not make a specific recommendation regarding PRP, highlighting the current uncertainty and the need for more robust studies to define its true role in the treatment of KOA [49,50].

7. Combining HA and PRP

Meta-analyses and reviews have shown that PRP and HA may exert complementary biological effects. Although the available evidence is limited, combined PRP and HA administration appears to be associated with clinical improvements in pain and functional status among KOA patients [87,88].

Experimental research in animal models demonstrating a synergistic biological interaction between HA and PRP supports this interpretation and has led to the hypothesis that their concomitant use may be more effective than either therapy alone. According to these investigations, both agents act through distinct physiological pathways and modulate cellular signaling related to inflammatory mediators, catabolic enzyme activity, cytokine release, and growth factor expression. These mechanisms may promote the repair of degenerated cartilage and slow the progression of osteoarthritis, thereby positively contributing to disease management. Furthermore, the described synergistic mechanism involves modulating inflammatory cytokines that are implicated in chondrocyte damage through specific mediators, including CD44 and the transforming growth factor beta receptor type II (TGF-βRII). TGF-βRII is a transmembrane serine/threonine kinase receptor that is involved in the transforming growth factor beta (TGF-β) signaling pathway. Ultimately, this enhances cartilage regeneration and attenuates inflammatory processes [89].

Nevertheless, the topic remains controversial. Although the combination of PRP and HA may offer additional benefits, methodological heterogeneity limits comparisons between studies, highlighting the need for further research involving larger sample sizes and standardized protocols [85].

8. Autologous Fat-Derived Orthobiologics (FDO)

IAI of FDO has emerged as a promising therapeutic alternative for individuals with KOA, offering sustained mid-term clinical benefits, such as symptom reduction and anatomic joint preservation. This treatment has the potential to postpone the need for arthroplasty.

In 1999, investigators successfully isolated MSCs from human bone marrow and demonstrated their ability to differentiate into adipocytes, osteoblasts, and chondrocytes. This marked a pivotal step in understanding the biological plasticity of these cells [90].

Since then, MSCs have been extensively studied and are now known to be obtainable from various tissue sources, including the umbilical cord, adipose tissue, the synovial membrane, the placenta, cartilage, and skeletal muscle [71].

Although subcutaneous adipose tissue is the initial source material, subsequent processing of lipoaspirate determines the final cellular composition and regenerative

characteristics of the resulting preparations. Several studies have shown that the choice of liposuction technique influences the cellular profile and quality of the resulting MSCs [91].

In 2001, Zuk and her colleagues [92] first characterized adipose-derived stromal/stem cells (ASCs) obtained from autologous subcutaneous fat. This milestone significantly advanced the development of cell-based therapeutic strategies [92].

Later, in 2011, Pak and colleagues [93] reported the first human case series in which ASCs were used to treat knee and hip osteoarthritis. This approach was supported by previous experimental models that had shown ASCs' promising reparative properties [93].

The clinical application of adipose-derived injectable preparations for cartilage regeneration is encompassed by the term "FDO". However, there is considerable procedural heterogeneity in the processing of lipoaspirate for intra-articular use. To mitigate terminological inconsistencies, the product obtained through enzymatic digestion, originally described by Zuk et al. [92], has been designated the cellular stromal vascular fraction (cSVF).

When the cellular fraction in the cSVF undergoes *in vitro* expansion in specific culture media, the resulting preparation is referred to as ASC therapy. This approach is garnering increasing interest in regenerative engineering [94]. ASCs possess a robust capacity for chondrogenic differentiation, particularly under hydrostatic pressure conditions, as demonstrated in three-dimensional induction models.

Reliable differentiation between cSVF cellular populations and ASCs requires that each preparation meet specific viability and functional thresholds: at least 70% viable cells and at least 90% viable cells, respectively, as well as a minimum frequency of 1% or 5% fibroblastoid colony-forming units [95,96]. In contrast, when lipoaspirate undergoes mechanical treatment alone, the resulting material is defined as a tissue stromal vascular fraction (tSVF) [95,96,97].

Regarding the therapeutic profile of FDO, accumulating evidence indicates that the paracrine activity of ASCs—driven by the release of a broad spectrum of bioactive mediators—may play a more significant role than their differentiation into parenchymal phenotypes [98]. The collective influence of ASC-derived cytokines and soluble factors mediating anti-apoptotic, pro-angiogenic, and immunomodulatory effects supports the maturation and proliferation of resident stem and progenitor cells, induces chemotactic responses, and mitigates scar formation. This influence is encompassed within the "secretome" paradigm [99]. *In vitro* data also show that synovial fluid can initiate macrophage differentiation. Consequently, it is conceivable that the paracrine mechanisms associated with FDO influence synovial fluid by modulating macrophage polarization and the subsequent inflammatory cascade [100,101].

A recent systematic review found that 28 out of 29 studies documented improvements in pain and functional outcomes following intra-articular FDO treatment [101]. The review analyzed 1234 patients treated with tSVF, 884 with cSVF, and 387 with ASCs. tSVF appeared to have a greater regenerative effect than cSVF; it had surface markers twice as high, though cSVF had a higher cell count and density. tSVF has several distinguishing characteristics: it requires less processing, preserves the matrix, and improves structural integrity, as seen on MRI. cSVF appears to have a greater analgesic effect. ASC yields a more homogeneous cell population and appears to have a greater long-term clinical effect (12 months). However, more clinical trials and additional evidence are required before this therapy can be implemented in daily practice.

It appears that the infrapatellar fat pad is a rich source of MSCs, which may offer important advantages over other sources in terms of ease of isolation, safety of harvesting, expansion potential, and chondrogenic differentiation capacity, making it a promising regenerative therapy [102].

9. Human Bone Marrow–Derived MSCs

MSCs are widely acknowledged for their robust proliferative capacity and for exhibiting immunomodulatory activities closely linked to their ability to promote cartilage regeneration and enhance knee joint function. These therapeutic benefits are partly attributable to the well-established role of an intra-articular inflammatory milieu, particularly when synovitis is present, in driving the onset and progression of osteoarthritis and subsequent joint degeneration [103].

Human bone marrow–derived MSCs include **autologous** (from the same patient) and **allogeneic** (from a donor) MSCs.

9.1 Autologous Bone Marrow-Derived Cells

For KOA fall into two main categories: Bone marrow aspirate concentrate (BMAC), which is a minimally processed product obtained by centrifugation on the same day; and cultured bone marrow-derived MSCs (BM-MSCs), which are cells expanded *in vitro* and require several weeks [104]. The different products are:

• Bone Marrow Aspirate (BMA). This unprocessed product is obtained directly from aspiration and contains a very low proportion of MSCs compared to other cell types [105].

• BMAC: This is a minimally processed product obtained by centrifuging bone marrow aspirate. It has a cell viability of approximately 90%, and it can be prepared on the same day [106].

• Cultured (Expanded) BM-MSCs: These are cells isolated from bone marrow and expanded *in vitro*, yielding a higher number of MSCs and a more homogeneous population [107].

They are obtained by aspirating bone marrow, usually from the posterior iliac crest, though the proximal tibia may also be used. BMAC consists of a heterogeneous population of total nucleated cells (TNCs), MSCs, colony-forming units-fibroblasts (CFU-F), platelets, monocytes, lymphocytes, and hematopoietic progenitor cells [108,109].

The therapeutic effect is primarily paracrine, rather than through direct differentiation, involving: (1) Inflammatory modulation, including inhibition of NF-κB and mitogen-activated protein kinase (MAPK), reduction of IL-1β, TNF-α, and IL-6, and increase in TGF-β and IL-10; (2) Cartilage protection: increased SOX9, aggrecan, and collagen II; inhibited MMP-13 and ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motifs 5), and (3) action of extracellular vesicles carrying microRNAs (miRNAs), mRNAs, and proteins that promote regeneration, reduce chondrocyte apoptosis, and modulate macrophages (M1 to M2). Additionally, two mechanisms produce early (MMP13+) and late tissue inhibitor of metalloproteinases-1 (TIMP1+) MSCs with chondrogenic differentiation and a trophic effect, respectively [110,111].

The evidence shows that it improves clinical outcomes in 94.4% of cases, but does not demonstrate superiority over other biologics and has a longer-lasting effect than HA in mild osteoarthritis. There is no difference at 24 months compared with PRP and a higher response rate than with corticosteroid administration [112].

9.2 Allogeneic Mesenchymal Stem Cells

Allogeneic mesenchymal stem cells (AMSCs) are used for their ability to alleviate pain, improve knee function, facilitate cartilage repair and exert an immunomodulatory effect. However, the collection of these cells is an invasive procedure, and when obtained from older patients, they have a reduced capacity to exert their regenerative effect. Obtaining bone marrow cells from young, healthy donors results in a greater immunomodulatory capacity [113]. Administering them may slow the progression of cartilage degeneration at 12 months, as assessed by MRI with T2 mapping [114].

The injections primarily exert their effects through paracrine action by facilitating the synthesis of new cartilage via MMP13+ or releasing factors that stimulate endogenous repair processes via TIMP1+ [111]. Furthermore, they modulate cytokines by reducing pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, and MMP-13) and promoting anti-inflammatory cytokines [TGF-β1, IL-10, hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), and chemokine (C-C motif) ligand 2 (CCL-2)] [114,115].

Clinically, MSCs have been associated with improvements in pain (4.08 points) and function, as measured by the IKDC (2.88 points), the Western Ontario and McMaster Universities Arthritis (WOMAC) Index (–11.05 points), the Lequesne index (5.32 points), the Lysholm score (5.07 points), and the Tegner activity scale (0.44 points). The maximum therapeutic benefits were reached at 24 months [116].

10. Exosomes Derived From Different Stem Cells in Animal Models

As mentioned earlier, cell-based therapeutic approaches, particularly those employing MSCs, have emerged as a promising avenue for managing osteoarthritis [117]. Although MSCs were initially considered agents capable of direct tissue repair, substantial evidence now suggests that their primary mechanisms are mediated by the secretion of cytokines and trophic factors. However, most cells are rapidly cleared from the organism before they can effectively interact with the target microenvironment [118].

Over the past decade, exosomes have gained considerable prominence due to their involvement in the pathophysiology of diverse biological systems and their expanding diagnostic and therapeutic potential. This has driven rapid growth in biomedical research in this field [119].

These nanovesicles facilitate intercellular signaling and are recognized as key contributors to multiple physiological and pathological processes, as supported by an increasing body of scientific evidence. Exosomes typically exhibit diameters ranging from 30 to 150 nm and flotation densities between 1.13 and 1.19 g/mL [120].

In osteoarthritis research, exosomes have been identified in many intra-articular sources, including tissue-specific MSCs, osteoblasts, chondrocytes, synovial fibroblasts, tendon cells, adipocytes of the infrapatellar fat pad, and PRP. Their molecular features have been shown to change as the disease progresses [121,122].

Exosomes intended for intra-articular delivery are most commonly isolated by ultracentrifugation. This procedure enables the recovery of relatively large quantities, but it also results in higher levels of contaminants and requires specialized equipment. A variety of commercial isolation kits offer alternative approaches [123].

Current evidence suggests that stem cells primarily exert their effects through paracrine mechanisms, with exosomes acting as the main mediators of these biological actions [124]. An early study describing membrane-derived vesicles with potential physiological roles was instrumental in recognizing the biological significance of exosomes [125].

Available preclinical studies suggest that exosomes may reverse osteoarthritic alterations in experimental animal models, highlighting their potential as therapeutic agents. However, extensive and rigorous research is required before these preliminary findings can be translated into human clinical applications [126].

Exosomes derived from MSCs primarily exert their effects by transferring miRNAs that modulate key signaling pathways, resulting in anti-inflammatory, chondroprotective, anti-apoptotic, and antioxidant effects [127].

Table 2. Intra-articular therapies for knee osteoarthritis (KOA).

Therapy	Mechanisms	Structural effects	Clinical evidence	Limitations / Risks
Corticosteroids (CS) [37,38,39,40,41,42,43,44,45,46,47,48]	Reduce inflammatory mediators; increase chondrogenic markers; shift macrophages toward M2.	Heterogeneous: improvement in 60%–68%, adverse effects in 11–20%.	Pain relief up to 26 weeks; some studies show greater cartilage loss.	Concerns about structural safety; temporary relief.
Hyaluronic acid (HA) [23,52,53,54,55,56,57,58,59]	Lubrication; anti-inflammatory modulation; stimulates HA synthesis; M1→M2 transition.	Reduces degradation; stronger effect with >3000 kDa formulations.	Improves pain and function up to 24 weeks; good safety.	Variable response; reduced benefit in advanced KOA.
Platelet-rich plasma (PRP) [60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,149]	Anti-inflammatory; increases MSC activity; growth factors (PDGF, bFGF, VEGF).	Stimulates extracellular matrix; protocol-dependent effects.	An alternative to CS and HA; 3 injections better than 1.	High variability; lack of standardization.
PRP + HA [85,86,87,88,89]	Molecular synergy; modulates cytokines and growth factors.	Synergistic biological interaction in animals	Improvements in pain and functional status.	Inconsistent results; limited evidence.
Fat-derived orthobiologics (FDO) [71,90,92,93,94,95,96,97,98,99,100,101]	Paracrine anti-inflammatory and pro-angiogenic effects.	Improves joint microenvironment and supports regeneration.	28/29 studies show improvement.	Heterogeneous processing; requires liposuction.
Bone marrow mesenchymal stem cells (MSCs) [103,104,105,106,108,110,111,112,113,114,115,116,150]	Local immunomodulation; cartilage protection (T2 mapping).	Reduces degeneration markers.	Improves pain and function; best results with young donors.	Invasive harvesting; reduced quality in older patients.
Exosomes [117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133]	Regenerative signalling vesicles.	Reverse osteoarthritis features in animal studies.	Preclinical evidence only.	No human trials; isolation variability.
Ozone therapy [134,135,136,137,138,139]	Increases reactive oxygen species; reduces cytokines.	Short-lived due to fast clearance.	Short-term improvement (up to 6 months).	Uncertain long-term efficacy; limited evidence.
Prolotherapy [140,141,142,143,144]	Dextrose induces growth factors; promotes proliferation, collagen maturation	Enhances fibrous tissue; possible chondrogenic effect reported	Improves pain and function in knee osteoarthritis	Limited evidence; insufficient support for widespread use
Botulinum toxin [145,146,147,148]	Inhibits neuropeptides and cytokines; reduces peripheral and central sensitization	No clear structural modification demonstrated	Short-term analgesia; improved function, especially with sensitization	Short duration; limited evidence; indications still unclear

PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor.

The main signaling pathways involved are:

• The mTOR (mechanistic target of rapamycin)/autophagy pathway. Exosomes rich in miR-100-5p inhibit mTOR, promoting autophagy in chondrocytes and maintaining cartilage homeostasis. This process reduces apoptosis and increases extracellular matrix synthesis [128].

• The WNT/β-catenin pathway: miR-376c-3p, carried by adipose-derived stem cell (ADSC) exosomes, inhibits WNT3 and WNT9a, thereby suppressing the WNT/β-

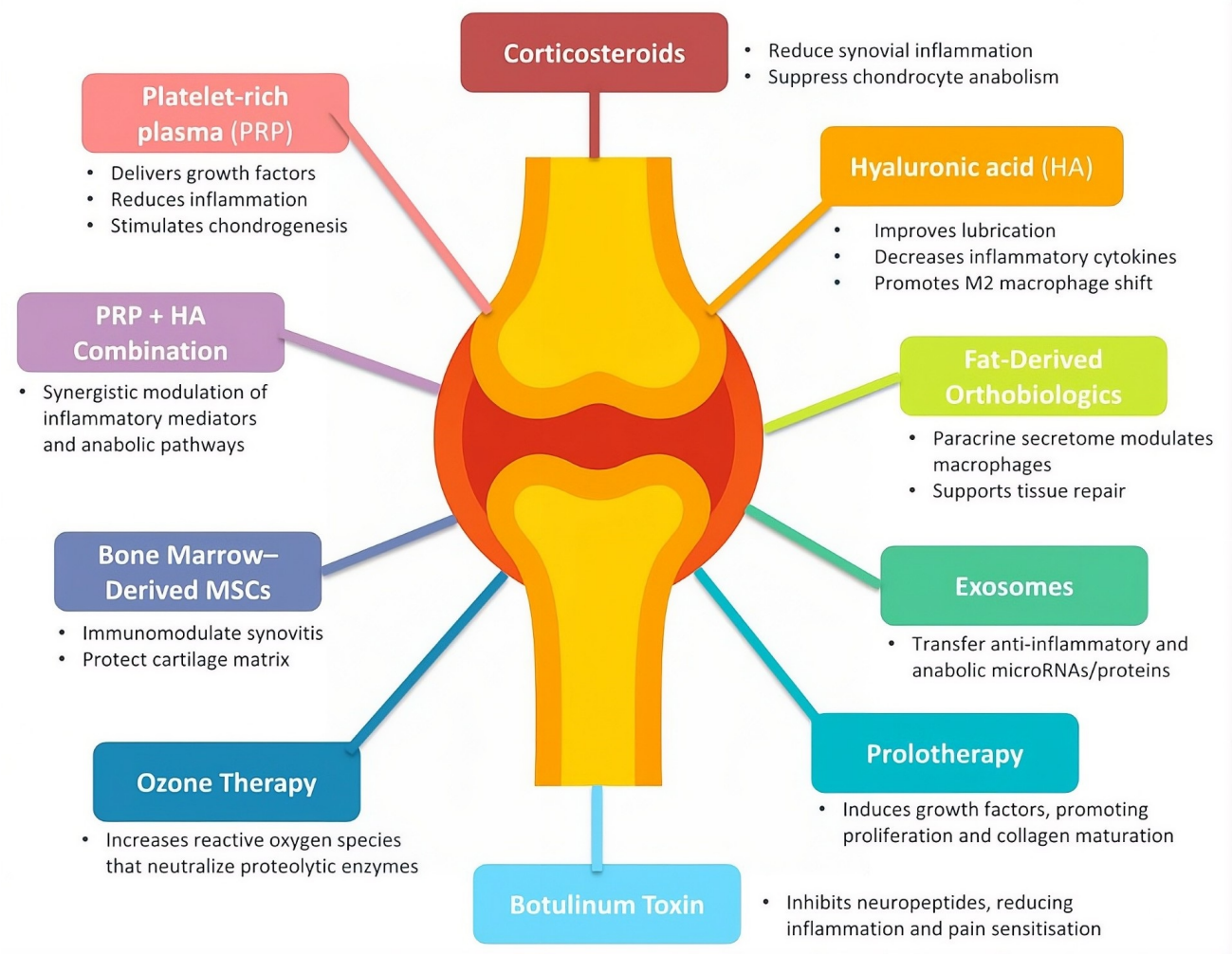

Fig. 1. Intra-articular injections described for knee osteoarthritis (KOA) and their molecular mechanisms of action. MSCs, mesenchymal stem cells.

catenin pathway and attenuating chondrocyte degradation and synovial fibrosis [129].

• Via the NF-κB pathway. Multiple miRNAs, including miR-146a, miR-326, and miR-361-5p, act together to inhibit NF-κB. This reduces the expression of proinflammatory cytokines (IL-1β, TNF-α, and IL-6), MMPs, and pyroptosis mediators (NLRP3, Caspase-1, and GSDMD) [130].

• Via PINK1/Parkin: ADSC exosomes activate mitochondrial autophagy by upregulating PINK1/Parkin, thereby protecting mitochondrial function, increasing membrane potential, and reducing reactive oxygen species (ROS) [131].

• Via the GAS6-MERTK-PI3K/AKT pathway: NMN-primed exosomes activate the GAS6-MERTK-PI3K/AKT pathway, which suppresses catabolic factors (MMP2, MMP9, and VEGF) and upregulates anabolic markers (COL2A1) [132].

• Via the AMPK-SIRT3 pathway: IFN-γ-induced exosomes carry Hsp70, which maintains AMPK-SIRT3-mediated mitochondrial homeostasis and attenuates chondrocyte senescence [133].

11. Ozone Therapy

Intra-articular administration of ozone has been proposed as a treatment that can enhance the production of reactive oxygen species in the inflamed joint microenvironment. These reactive species may neutralize active proteolytic enzymes and downregulate the secretion of proinflammatory cytokines, potentially leading to symptomatic improvement. However, since dissolved ozone is rapidly cleared from the synovial fluid, its therapeutic impact may diminish quickly. Consequently, repeated dosing has been suggested as a potentially advantageous approach that could be incorporated into established therapeutic regimens for KOA [134].

Medical ozone, composed of three oxygen atoms, exhibits analgesic, anti-inflammatory, and antioxidant properties that support its musculoskeletal applications. Intra-

articular infiltration has demonstrated significant benefits in reducing pain and improving function among individuals with KOA during the initial follow-up period, typically within the first six months. However, substantial knowledge gaps persist regarding its long-term effectiveness and the most appropriate dosing protocol. Both topics warrant further systematic investigation [135].

Ozone's fundamental mechanism of action is oxidative preconditioning, or adaptation to oxidative stress, which stimulates the body's own antioxidant system, thereby reducing tissue damage [136]. At the molecular level, ozone significantly modulates the inflammatory response. It is associated with a reduction in pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) [137]. Furthermore, ozone promotes an increase in anti-inflammatory mediators, particularly IL-10. Additionally, ozone interacts with key intracellular signaling pathways, notably through its effect on the NF-κB/Nrf2 axis. Activation of Nrf2 promotes expression of antioxidant enzymes, while crosstalk with the NF-κB pathway helps modulate the inflammatory response. This balance, among other effects, inhibits macrophage polarization towards the pro-inflammatory M1 phenotype and promotes the M2 phenotype, which is associated with anti-inflammatory and tissue repair functions [138,139].

12. Prolotherapy

Prolotherapy is an interventional treatment involving the injection of small amounts of an irritant solution, typically dextrose, into joints, ligaments, and entheses over a variable number of sessions. The goal is to promote tissue regeneration [140]. The dextrose concentration used in prolotherapy typically ranges from 12.5% to 25%. Dextrose administration induces the release of various growth factors, including PDGF, TGF-β, epidermal growth factor (EGF), bFGF, and insulin-like growth factor (IGF). These mediators promote cell proliferation and collagen precursor maturation. Furthermore, a potential chondrogenic effect has been reported [141,142].

Dextrose can also modulate the peripheral nerves, reducing pain and promoting increased strength in tendons and ligaments by stimulating fibrous tissue formation [143]. Currently, prolotherapy is mainly used to improve pain and function in patients with KOA. However, the available evidence is insufficient to support its use for other musculoskeletal conditions [144].

13. Botulinum Toxin

Botulinum toxin is a neurotoxic protein complex produced by the anaerobic bacterium Clostridium botulinum. Intra-articular administration of botulinum toxin type A inhibits the release of inflammatory mediators and neuropeptides by nociceptors, which helps reduce pain and neurogenic inflammation associated with osteoarthritis. Botulinum toxin type A reduces peripheral and central sensitization processes, alleviating pain in osteoarthritis. At the peripheral level, botulinum toxin type A inhibits the release of neuropeptides involved in nociceptive transmission, such as substance P. It may also reduce the expression of pro-inflammatory mediators, including cytokines such as IL-1β, IL-6, and TNF-α [145,146].

It has also been suggested that botulinum toxin type A undergoes retrograde axonal transport, which allows modulation of neuronal activity in the central nervous system. This effect could be mediated, at least in part, by interaction with inhibitory systems, such as GABAA receptors and μ-opioid receptors, in the spinal cord [147]

Botulinum toxin appears to have a short-term analgesic effect on KOA, especially in patients with central or peripheral pain sensitization. This effect is associated with improved motor function and quality of life. It may be particularly indicated for patients with moderate osteoarthritis [148].

The intra-articular treatments described for KOA and their molecular mechanisms of action are summarized in Table 2 (Ref. [23,37,38,39,40,41,42,43,44,45,46,47,48,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,92,93,94,95,96,97,98,99,100,101,103,104,105,106,108,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150]) and Fig. 1.

14. Conclusions

Intra-articular treatment strategies for KOA are advancing alongside growing insights into the disease's immunological and molecular mechanisms. Accumulating data indicate that KOA should no longer be regarded solely as a passive degenerative process but rather as a multifactorial, low-grade inflammatory disorder characterized by complex crosstalk among immune cell populations, cytokine networks, and cartilage-specific molecular pathways. This evolving paradigm establishes a biologically plausible rationale for targeted intra-articular approaches aimed at attenuating synovial inflammation, altering the catabolic-anabolic balance, and influencing structural disease progression.

Intra-articular CS remains valuable for short-term analgesic benefits. However, concerns about potential adverse effects on cartilage integrity highlight the importance of careful patient selection and limited use. HA has a favorable safety profile and modest clinical benefits, particularly in the early stages of the disease. These benefits are likely due to the restoration of viscoelastic properties and modulation of inflammatory signaling. PRP has gained increasing attention as a biologic therapy, with consistent evidence supporting symptomatic improvement and potential molecular modulation. However, heterogeneity in prepara-

tion techniques, cellular composition, and dosing regimens limits cross-study comparability and standardization. Combined PRP and HA formulations may have additive or synergistic effects, but the available evidence is insufficient to draw definitive conclusions.

FDO- and MSC-based interventions represent the emerging frontier of regenerative intra-articular therapeutics. Their predominantly paracrine mechanisms, which impact macrophage polarization, inflammatory mediator expression, and extracellular matrix turnover, suggest regenerative capabilities that extend beyond providing symptomatic relief. However, challenges related to reproducibility, regulatory frameworks, manufacturing consistency, and long-term safety must be addressed before these interventions can be widely implemented in clinical practice. Emerging research on exosome-based therapies offers an exciting, cell-free alternative; however, translation into clinical practice will require substantial preclinical and clinical validation. Finally, ozone therapy may provide short-term symptomatic improvement, though its ability to affect structural disease progression is unclear.

Overall, intra-articular therapies are a cornerstone of contemporary KOA management, particularly for patients aiming to postpone surgical intervention. Future research efforts must prioritize protocol standardization, biomarker-driven patient stratification, and rigorous, longitudinal assessment to determine which therapeutic strategies offer true disease-modifying potential.

For mild osteoarthritis, the initial treatment option would be HA. If the response is insufficient, the next option would be CS injections. For moderate or severe osteoarthritis, the initial treatment would be PRP, and if there is no improvement, HA or CS can be considered. Other therapies with promising results, such as FDO and MSCs, are not yet sufficiently validated to establish their place in treatment recommendations. Therefore, as with ozone therapy or botulinum toxin, their use should be assessed on a case-by-case basis.

Author Contributions

JMR-B, HDLC-R, and ECR-M conducted the literature search and planned the review. JMR-B wrote the first draft of the manuscript. All authors read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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