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REVIEW ARTICLE

Emerging and New Treatment Options for Knee Osteoarthritis

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Abstract: Osteoarthritis (OA) is the most prevalent type of arthritis worldwide, resulting in pain and often chronic disability and a significant burden on healthcare systems globally. Non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, intra-articular corticosteroid injections are of little value in the long term, and opioids may have ominous consequences. Radiotherapy of knee OA has no added value. Physical therapy, exercises, weight loss, and lifestyle modifications may give pain relief, improve physical functioning and quality of life. However, none of them has articular cartilage regenerating potential. Due to a better understanding of osteoarthritis, innovative new treatment options have been developed. In this narrative review, we focus on emerging OA knee treatments, relieving symptoms, and regenerating damaged articular cartilage that includes intra-articular human serum albumin, conventional disease-modifying anti-rheumatic drugs (DMARDs), metformin, lipid-lowering agents (statin), nerve growth factors antagonists, bone morphogenetic protein, fibroblast growth factors, Platelet-Rich Plasma (PRP), Mesenchymal Stem Cells (MSC), exosomes, interleukin-1 blockers, gene-based therapy, and bisphosphonate.

Keywords: Anti-inflammatory agents, analgesics, cartilage, knee, nerve growth factors, osteoarthritis, pain, platelet-rich plasma.

1. INTRODUCTION

Until the 1990s, osteoarthritis (OA) was considered a "wear and tear" disease resulting in loss of cartilage [1]. New insights in molecular biology have profoundly modified this paradigm [1]. OA is a total joint disease characterized by loss of cartilage, subchondral bone changes, synovitis, and meniscus degeneration [2]. Chemical mediators like cytokines or prostaglandins yielded from synovial fluid and tissue due to increased production of Matrix Metalloproteinases (MMP) by chondrocytes, synoviocytes, and fibroblasts favor the "inflammatory" theory of OA [1, 2]. Over the last three decades, researchers' continuous efforts to unveil and understand the pathophysiology of Early OA (EOA) in greater detail have enabled us to understand more, recognize the condition, and intervene at its earlier stages. More treatment options are becoming available, slowing or halting disease progression, thereby minimizing disability attributed to the ailment [2].

OA is the most common rheumatic condition, classically associated with people over 65 years of age, but also those in the 5th and 6th decade of life often experience pain and loss of function in weight-bearing spinal and peripheral joints and non-weight-bearing small joints of the hands [3]. The disease burden for the OA patient is similar to that in rheumatoid arthritis (RA) at the initial visit to a rheumatology clinic and greater after six months [4], so diagnosing early cases can plunge disability prevalence.

Histologically, based on the *Osteoarthritis Research Society International (OARSI) scoring system*, EOA changes have been found only to affect the superficial and middle zones of articular cartilage [2]. Luyten *et al.* proposed classification criteria for knee EOA based on symptoms (pain: at least two episodes for ten days in the past year), radiological changes (Kellgren-Lawrence KL, grade 0 or 1-2 osteophytes only), and early degenerative changes detected by new imaging techniques and arthroscopy [5]. OA is not a joint disease of mere cartilage degeneration. OA also involves meniscus degeneration, subchondral bone change, and synovial membrane thickening [2, 5]. Magnetic Resonance Imaging (MRI) depicted hyperintense subchondral bone marrow also correlates with micro-damage of the trabecular bone histologically and contributes to bone pain. These lesions connect to the accelerated loss of the articular cartilage vicinity and contribute to joint pain and disability, as seen in early and advanced knee OA. Growing evidence suggests Knee OA is both cartilage and bone-based disease [6, 7]. Therefore, en-

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suring maximum benefit from any treatment strategy requires diagnosing and treating OA at its earliest stage, preferably at the modifiable "pre-osteoarthritis" stage [8].

Conventionally, OA is treated with non-pharmacological and pharmacological methods, and their appropriate use could reduce knee replacement incidence [9]. However, there is no uniform measure of success regarding how well different patients respond to treatment strategies. Comparative treatment outcomes are often unequal in terms of effectiveness across different subtypes of OA and or in various stages of the same OA. Perhaps most importantly, some of the treatments are currently not recommended by the National Institute for Health and Care Excellence (NICE) and the American College of Rheumatology (ACR) [10]; hence innovative new treatment options to more effectively managing the disease are warranted [10].

Over the last decades, effective new treatment options and strategies have become available for OA, primarily from pre-clinical and clinical trials [11]. However, one cannot recommend treatment strategies based on a single trial or very few trials only, specifically when the sample populations included in clinical trials are due to inclusion - and exclusion criteria, not truly reflecting patients encountered in routine practice. Therefore, reviewing and updating the evidence supporting effective treatment strategies is indicated. A further pitfall is that regression to the mean in not well-powered designs can bias study results in OA, where we know the placebo effect can be substantial [12]. On the other hand, sham interventions with negative connotations and unpleasant encounters with health care professionals may harm a phenomenon called the nocebo effect [13].

We researched the literature using PubMed and PubMed Central, Google with keywords: Osteoarthritis, knee, treatments, pharmacological, innovative, cartilage enhancement, and looked for specific topics as mentioned in the subheadings of the findings section. Only English language articles were included. Excluded were complementary medicine, alternative medicine, supplements, herbs, diets, surgery. No exclusion was applied based on publication dates; however, considerable emphasis was focused on the most relevant and up-to-date information available at the time of this review. This narrative review evaluates the current and emerging treatment options for OA knee. We aim to synthesize this information to benefit the science and healthcare community.

2. DISCUSSION

Previously published works in the English language that addressed promising treatment options for OA knee (based on both clinical and preclinical trials), for example, Intra-Articular (IA) low-molecular-weight human serum albumin, Disease-Modifying Anti-Rheumatic Drugs (DMARDs), lipid-lowering agents (statin), Nerve Growth Factors (NGFs) antagonists, Bone Morphogenetic Proteins (BMPs), Fibroblast Growth Factors (FGFs), interleukin-1 (IL-1) inhibitors (Table **1**) are included in this new synthesis. The present article also focuses on regenerative therapies, including Mesenchymal Stem Cells (MSCs), Platelet-Rich Plasma (PRP), MSC-based exosomes, gene therapy, and bisphosphonate therapy to be useful in the disorder (Table **1**). As the purpose of the report is to provide a review, we aim to describe promising treatment options in OA-knee rather than focusing on determining a particular approach to managing the disorder.

For easy-going, we discuss the OA-knee emerging interventions into the following six categories: anti-catabolic, anabolic, anti-catabolic and anabolic, interleukin-1 inhibitors, gene therapy, and bisphosphonates. The RCTs, systematic reviews, cohort, and case-control studies included in the review satisfied the *Critical Appraisal Skills Program (CASP)* [14].

2.1. Anti-Catabolic (Agents Preventing Cartilage Degeneration)

2.1.1. Low-Molecular Weight Human Serum Albumin Fraction (LMWF-5A)

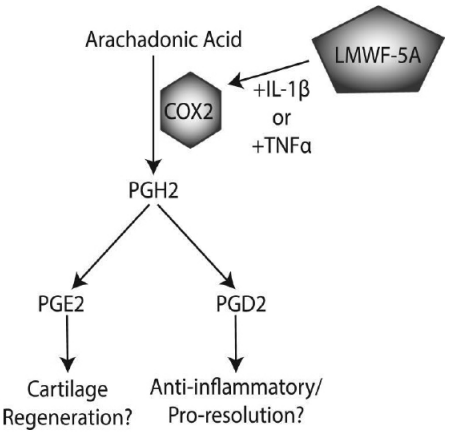
Cyclooxygenase-2 (COX2) has an established pro-inflammatory role; however, recent evidence suggests that COX2 is critical for the resolution after the initial activation phase of the immune response [15]. In culture media, fibroblast-like synoviocytes from OA-knee synovial membrane treated with LMWF-5A were found to release increased anti-inflammatory prostaglandin COX-2 mRNA/protein, prostaglandins (E2, D2), and promote resolution of inflammation and regeneration of damaged cartilage (Fig. **1**) [15].

IA - LMWF-5A injections also have immune-modulating potential and demonstrated to be safe compared to vehicle control (saline) at 12-week follow-up [15, 16]; IA serum albumin injection led to reduced pain and improved physical function in moderate to severe OA-knee as measured by Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index [16]. Schwappach *et al.* revealed that 2-weekly, 3-IA injections of 4-ml LMWF-5A, could be safe and effective in relieving OA-knee pain at 20-week follow-up [17]. In another clinical trial with 168 OA-knee cases, 71% of them received IA-LMWF-5A treatment, which led to significant improvement with the LMWF-5A arm compared with historical saline controls (65% *vs*. 43%, $p < 0.001$) [18]. IA-LMWF-5A could also reduce the incidence of total knee replacement (TKA) in severe OA [19]. IA - LMWF-5A is usually safe; however, mild-moderate adverse effects (AEs) common to any IA procedure could also happen. In a study, 34% of LMWF-5A intervention developed mild to moderate arthralgia. No severe AEs were recorded [18]. However, to assess the overall risk-benefit ratio of IA-LMWF in OA knee, long-term follow-up is required.

Table 1. Emerging treatment options for knee osteoarthritis.

Class of Interventions	Mechanism of Action	Mode of Application
Low-molecular weight human serum albumin fraction (LMWF-5A) [15-19].	Anti-inflammatory and immune modulating potential in knee osteoarthritis (OA)	Intra-articular (IA) injection
Disease modifying anti-rheumatic drugs (DMARDs), metformin and statins [20-35]	Methotrexate (MTX), hydroxychloroquine (HCQ), and statin cause a release in glycosaminoglycans, tumor necrosis factor-α (TNF-α), matrix metalloproteinase-13 (MMP-13), and O_2^- in treatment of OA, role of statin in OA knee progression or halt is yet to appear clear	MTX could be used both through route IA and orally; HCQ is given orally
Nerve growth factors inhibitors (NGFs) [36-45]	Monoclonal antibody antagonizing NGFs	tanezumab, fasinumab, fulranumab could be given IA
Bone morphogenetic protein (BMP) - 2, 7 [46-52]	BMP-7 has a strong anabolic effect on cartilage by stimulating synthesis of cartilage matrix components and increasing proteoglycan and collagen synthesis; BMP2 is an important protein component involved in the maintenance of the structure and function of articular cartilage	IA injection
Platelet rich plasma (PRP) [53-72]	PRP, a volume of plasma with higher platelet concentrate than that average in peripheral blood and causes tissue healing including degenerated joint cartilage releasing various growth factors	IA injection periodically
Mesenchymal stem cell (MSC) therapy [73-87]	Embryonic, fetal and adult stem cell, having differential potential to cartilage specific chondrocytes	IA injection of MSC, iPSC, ESC
Exosomes [84, 88-90]	Exosomes are cells secreted vesicles mediating cross talk between them with related biological processes such as chondrocyte homeostasis, cartilage healing, *etc*.	Transfection of purified exosomes from modified MSCs could be injected IA for cartilage healing in OA knee
Fibroblast growth factors (FGFs) [91-98]	FGF has shown the potential effects on the repair and regeneration of tissue. It is capable of promoting fibroblast proliferation and there are 22 members. They exert functions through FGF receptors activating Ras-MAPK pathway. With their potential biological functions, FGFs have been utilized for the regeneration of damaged tissues, including, articular cartilage.	IA injection
Interleukin (IL-1) blockers [99-108].	Blocking of interleukin-1	IA injection (Anakinra), SC (Canakinumab)
Gene therapy [109-111]	Genetically engineered chondrocytes overexpress TGF-b1 and promotes biological process required for healing of damaged cartilage	*in vivo* and *in vitro* approach of IA gene delivery
Bisphosphonate [112-116]	Altered bone turnover and preserve adjacent articular cartilage	Oral (daily, weekly, monthly, quarterly), and yearly injection

LMWF-5A, Low-molecular weight human serum albumin fraction; IA, intra-articular; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate, MAPK, mitogen-activated protein kinase; HCQ, hydroxychloroquine; TNF-α, tumor necrosis factor-α; MMP-13, matrix metalloproteinase-13; NGFs, nerve growth factors inhibitors; BMP, bone morphogenetic protein; FGFs, fibroblast growth factors; PRP, platelet rich plasma; MSC, mesenchymal stem cell; iPSC, induced pluripotent stem cell, ESC, embryonic stem cell; SC, subcutaneous; IL-1, interleukin-1; TGF, transforming growth factor.



PGE2, prostaglandin E2, PGH2, prostaglandin H2, PGD2, prostaglandin D2, IL, interleukin, TNF, tumor necrotic factor, COX2, cyclooxygenase 2, LMWF-5A, low molecular weight human serum albumin fraction.

Fig. (1). LMWF-5A promotes regenerating damaged cartilage in OA [15].

2.1.2. Disease Modifications with DMARDS, Statins and Metformin

Unlike in inflammatory rheumatic diseases, DMARDs appeared ineffective in OA-knee [20]. However, three recent studies documented methotrexate (MTX)-mediated improvement of pain, WOMAC stiffness, physical function, and quality of life (QoL) scores after 3 and 6 months in OA-knee [21-23]. The analgesic effect of MTX was significant but of borderline clinical effect size [23]. DK226, a hyaluronic acid and methotrexate conjugate, exerts anti-arthritic effects in an animal model and could be a hope for inflammatory OA [24]. Hydroxychloroquine (HCQ) also appeared promising in the treatment of OA-knee [25]. But, a recent meta-analysis of RCT revealed that DMARDs (biologics and conventional) had neither statistical nor clinical significance in managing OA [20]. Further studies may shed light on the efficacy of DMARDs in OA-knees [20, 24]. Atorvastatin - HCQ combination trial in OA-knee is yet to be finished [26].

Metformin [27, 28] and statins [29, 30] appeared chondroprotective in preclinical and clinical OA-knee research. In an *in vivo* animal OA-knee model study, simvastatin caused Wnt *(Wnt is a portmanteau of int and Wg oncogenes and stands for "Wingless-related integration site)* / β-catenin signaling pathway inhibition and prevented intra-nuclear translocation of free cytosolic β-catenin that resulted in Wnt-dependent transcriptional activity inhibition for chondrocyte dedifferentiation and cartilage degeneration as confirmed by increased type II collagen expression and induced sulfated proteoglycan synthesis under Western blot technique [29]. Preclinical study with human OA articular cartilage-derived chondrocytes treated *in vitro* statin-rich (simvastatin) media reversed the pro-inflammatory cytokine (IL-1β) mediated effects on damaged cartilage, and the effects were statin dose-dependent reduced expression of mRNA of MMP-3, 13; increased expression of mRNA of aggrecan and collagen2a1 proteins [30]. In a population-based Dutch cohort study, OA-knees aged over 55 years were followed up. Overall radiological progression was reduced by more than 50% among statins users than non-statin users [31]. However, a West-European study documented worsening of tibiofemoral radiological joint space over three years among statin users [32]. Besides, a Swedish human study could not confirm the reduced incidence of OA-knee consultation or surgery among statin users [33].

In a longstanding cohort with US obese OA-knee patients, metformin appeared to preserve cartilage volume and reduce TKA [28]. A COX-2 inhibitor-metformin combination was also documented to reduce TKA incidence among Taiwanese [27]. Metformin stimulated adenosine monophosphate-activated protein kinase (AMPK), and adipose-tissue-derived MSC (ADMSC) showed a chondroprotective effect in animal OA-knee [34, 35]. Metformin caused up-regulation of phosphorylated and total AMPK expression in articular cartilage tissue with inhibition of synovial hyperplasia and osteophyte formation [34]. Metformin also halted OA progression in partial medial meniscectomy non-human primates [34]. As preclinical studies are promising and the findings of clinical studies are conflicting, an RCT to study the effect of oral statins in patients with knee OA still seems feasible [30, 31, 33]. As in animals, the impact of IA statins appears to be promising; a pilot phase-II clinical trial with a limited number of OA knee cases appears to be indicated. DMARD are found ineffective in OA knee [20]; the long-term follow-up outcomes of clinical research regarding the efficacy of metformin and statin could explore the safety profile with risk-benefit aspects of these agents for clinical use.

2.1.3. Nerve Growth Factors (NGFs) Antagonists

Nowadays, NGFs are considered promising as pain mediators and antagonists targeting NGFs mediated pain relief. Available anti-NGFs are tanezumab, fasinumab, and fulranumab, of which tanezumab is most widely studied in OA-knee [36-38]. Pain reduction had been documented in pre-clinical and clinical trials with various anti-NGFs in degenerative arthritis [38, 39]. A recent animal study showed further promise in OA-knee treatment with anti-NGF antibodies. Intra-peritoneal injection of anti-NGF antibody improved gait pattern in mice-induced OA-knee [40]. Similarly, active immunization (therapeutic and prophylactic) targeting NGF documented reversibly attenuated chronic pain behavior in murine OA-knee models [40].

However, osteonecrosis and rapidly progressive OA (RPOA) in target and non-target joints made the scientific societies alarmed about the safety profiles of this drug group, leading to a temporarily FDA imposed a ban on June 22, 2010, on all clinical trials with all anti-NGFs, though lifted later on March 12, 2012 [38, 41]. FDA-approved phase-III clinical trials with subcutaneous tanezumab in human OA-knees revealed a dose-dependent response: tanezumab 5 mg statistically significantly improved pain, physical function, and patient's global assessment of OA, whereas tanezumab 2.5 mg only improved WOMAC pain and physical function [42]. In an RCT, fasinumab significantly reduced WOMAC pain in moderate-severe OA-knee; further studies may unveil its minimum effective dose [43].

Trials concerning anti-NGFs safety were performed [42, 44]. Chen *et al.* reported that a reduced tanezumab dose (≤2.5 mg) not only caused OA pain relief but also caused fewer AEs [44]. Tanezumab could lead to primary osteonecrosis and subchondral insufficiency fracture. Some may require joint replacement therapy during and after the anti-NGF treatment [42]. Paraesthesia and hypoaesthesia with or without discontinuation could happen with the tanezumab 2.5-5 mg dose. Peripheral neuropathy, including carpal tunnel syndrome, could be a reported complication of anti-NGF therapy. Besides, infusion-related sympathetic nervous system function-related AEs such as bradycardia, orthostatic hypotension, and syncope could also happen with dose-dependent tanezumab therapy [42]. Patients also develop arthralgia, peripheral edema, and extremity pain [45].

Early clinical trials documented anti-NGFs mediated RPOA that addressed changes to the future related trial designs to minimize the RPOA risk and assess aspects of joint

safety. Careful monitoring of anti-NGFs associated AEs in clinical trials is needed to clarify this emerging OA medication class's overall risk-benefit ratio, particularly with long-term use [45].

2.2. Anabolic (Agents for Cartilage Regeneration)

2.2.1. Bone Morphogenetic Protein (BMP) Induced Cartilage Formation

BMP-7 profoundly affects chondrocyte metabolism, including synthesis, organization, and retention of matrix molecules but not chondrocyte proliferation [46]. Increased serum and SF - BMP-2 levels were found in patients with advanced OA-knee (grade-4 KL score) than in patients with early OA knees and healthy controls [47]. With increased age and progressive articular cartilage degeneration, the expression level of endogenous BMP - 2, 7 decreases gradually. A decrease in synovial fluid (SF) BMP - 2, 7 might play an essential role in the progression of cartilage degeneration, and patients could benefit from IA - BMP-2,7 injections [46, 48]. Exogenous BMP-2 stimulates recently isolated human articular cartilage chondrocytes and synthesis Col2A [46]. In a rabbit OA-knee model, IA or continuous pump of BMP-7 can stop articular cartilage degeneration without any significant AE [49]. In an RCT, in patients with symptomatic OA-knees, Hunter *et al.* found positive clinical outcomes following IA injection of BMP-7, without dose-limiting side effects [48].

As BMP is relatively short-lived, a single injection might not be effective in achieving the therapeutic outcome, and multiple injections or a sustained delivery system could be required. In an *in vivo* pre-clinical study, sustained delivery of BMP2 *via* a BMP2-coacervate effectively induced differentiation of muscle-derived stem cells to a chondrocyte lineage for cartilage regeneration [50]. The mRNA expression of aggrecan (AGC) and Col2A signifying chondrogenic differentiation was highest where sustained BMP2 is delivered *via* BMP-coacervate [50]. Both BMP - 2 and 7 appeared promising disease-modifying agents for OA patients and are currently under phase-II trial [51, 52]. Human MSC, including ADMSCs, treated with BMP-4, 6, and 9 modulate *in vitro* cartilage development [46]. Recently, in a case-control study, a significant association of rs1470527 and rs9382564 polymorphism of BMP - 5 gene with human OA-Knee has been demonstrated; this also may be a potential therapeutic target for OA [52].

IA-BMP injection is safe; in a study, David and colleagues demonstrated no significant difference between the BMP and placebo groups in terms of AEs documented following BMP-7 injection [48]. They were of mild category and limited to mild joint pain, swelling, injection site bruising, headache, nasopharyngitis, *etc*. [48]. There were no life-threatening AEs and death. No radiographic abnormalities consistent with ectopic bone formation were reported in follow-up. No patients developed anti-BMP-7 binding antibodies during the study [48]. However, further research to test the safety profile of IA-BMP is required.

2.2.2. Orthobiologic (Platelet-Rich Plasma, PRP)

PRP enriched with growth factors like platelet-derived growth factor, insulin-like growth factor, vascular endothelial growth factor, and transforming growth factor (TGF) beta-1 is shown to be effective in healing injured cartilage [53]. It has a proliferative effect on autologous chondrocytes [53]. PRP supplemented chondrocytes cause glycosaminoglycan formation in tissue-engineered cartilage with greater compressive mechanical properties [54]. In an *in vitro* study with human OA-knee chondrocytes, PRP releasate (PRPr) was shown to have diminished IL-1 beta mediated inhibition of Col2A1 and AGC gene expression through *nuclear factor kappa B* (NFκB) pathway activation [55].

IA-PRP improves pain, overall QoL, synovitis, patellofemoral cartilage volume, and Whole-Organ MRI Score in OA-knee [56, 57]. It also improves joint stiffness, WOMAC overall scores, synovitis score, and ADL at 6- and 12-month in MRI defined EOA knees, compared with baseline in 73.3% and 83.3% cases, respectively at 1-year follow-up [57, 58], though without any qualitative MRI change in medial and lateral femoral compartments [57, 58]. In a recent trial with human OA-knee, both PRP and PRP with growth factors were more effective than ozone therapy [59]. Another study comparing the efficacy of IA-PRP and IA-HA in 192 OA-knee revealed that both treatments were equally effective, with sustained improvement up to 24 months; however, the re-intervention rate at 24 months was lower in PRP recipients [60]. A recent meta-analysis of RCT compared the efficacy of IA PRP-HA and IA-HA in symptomatic knee OA; the study depicted the remarkable improvement of WOMAC pain, stiffness, and function scores IA PRP-HA group as assessed 3-monthly for 12 months [61].

Sports personnel with OA-knee treated with PRP experienced pain relief and improved physical function; however, only 50% of them could successfully return to sports [62]. In a study, Su *et al*. demonstrated the superiority of IA plus intra-osseous PRP over IA-PRP and IA-HA in OA-knee with sustained lower VAS-pain scores, improved WOMAC, and QoL scores within the next 18 months [63]. Another RCT studied patients with mild-moderate OA-knee receiving IA-PRP had comparable outcomes with clinically significant functional improvement for at least 1-year [64]. IA injections of HA, PRP, and corticosteroid combination is found an effective and safe at least for short-term in relieving WOMAC pain and physical function and QoL scores, especially in younger patients and mild-moderate OA cases [65]; positive outcomes were sustained for at least 25 months, particularly in EOA-knee patients [65]. PRP also appeared effective in combination with biocompatible carriers/scaffolds like gelatin hydrogel, chitosan, polylactic-co-glycolic acid mesh, and β-tricalcium phosphate scaffolds in OA-knee [66]. Photo-activated PRP (10-minute exposure to monochromatic light) improved pain, stiffness, and function in mild-moderate OA-knees [67]. PRP supplemented with home-based strengthening and stretching exercises addressing calf and hamstring muscles provided better pain relief, improved joint ROM, and WOMAC scores than only PRP or

only therapeutic exercise intervention for OA-knees [68].

PRP therapy is a simple, minimally invasive, and cost-effective intervention for OA-knee. We are yet to have precise data regarding PRP's accurate composition, intrinsic and extrinsic factors modifying its efficacy, optimal dosage, duration between injections, injection frequency, when to inject after preparing PRP, therapeutic effectiveness, cost-effectiveness, and post-injection rehabilitation [59, 69, 70]. PRP could be more effective in early OA-knee [64, 65]; nevertheless, recent works documented its cartilage regenerating potential regardless of cartilage damage level [56]. In their recent annual congresses, NICE and the European Congress of Rheumatology (EULAR) recommended PRP as the second--line treatment option in OA-knee [70, 71].

IA-PRP is usually safe [65]. However, published research reported the following complications after PRP injection: dizziness, headaches, nausea, gastritis, sweating, tachycardia, and all they said self-limiting. In addition, there could be post-injection pain, swelling, and limited daily activities and could resolve within 3-4 days [53, 65, 72]. No study documented the long-term AEs of PRP; hence, a time--to- event prospective survey could be the answer.

PRP shows promise in the OA trials; however, some studies depicted PRP as not the answer to articular cartilage degeneration. RCTs favor PRP use over other IA treatments for the short and medium-term; however, most evidence was of the poor level of evidence. They were further biased regarding PRP preparation methods, platelet concentration, platelet activation before injecting, indications, injection frequency, precautions, and instructions to follow after injecting. At the moment, without further standardization of PRP protocol, the therapeutic aspects (risk and benefit) of PRP will remain an issue of open debate [53]. PRP's risk-benefit issue regarding its clinical applicability depends on these topics; we hope scientists' future endeavors will mitigate them.

2.2.3. Orthobiologic (Mesenchymal Stem Cell, MSC)

The American Society of Interventional Pain Physicians endorsed homologous bone marrow concentrate (BMC) in musculoskeletal disorders [73]. Early phase clinical trials with MSC injections unveiled beneficial effects on articular cartilage and subchondral bone [74]. Multi-potent MSC can be isolated from adipose tissue, blood, and bone marrow; their immune-modulatory, reparative, and anti-inflammatory properties were depicted in pre-clinical and clinical research [75, 76].

Autologous BMMSCs therapy in OA-knee appeared safe, improved pain and symptoms, and reduced synovial inflammation at 12-months [75]. Autologous ADMSCs (adipose-tissue derived MSC) also improved pain, function, and MRI - OA scores in symptomatic OA-knee at 12-month follow-up without serious AEs [76]. Full-thickness injured knee cartilage treated with HA and BMC-MSC provides good-excellent clinical outcomes at long-term follow-up irrespective of the extent of the injury, number of lesions, and joint compartments involved, specifically in younger cases [77]. Similarly, in advanced OA-knee, a single IA injection of 1, 10, or 50 million BMMSCs revealed significant overall improvements of pain, QoL, WOMAC stiffness score, dose-dependent improvement of ROM, cartilage catabolic biomarkers, and MRI synovitis scores in a phase I/IIa trial [73, 75].

Irrespective of ADMSCs cell dosage, improvements of sustained pain score, functional (WOMAC), and structural (MRI-based) improvements lasted a maximum of 24 months [76]. There were no treatment-related AEs. A statistically significant improvement in higher dose groups was found, and clinical outcomes tended to deteriorate after one year in the low- and medium-dose groups [78]. Besides, OA-knee receiving subchondral BMC treatment could postpone TKA for a period of a mean of ten years [79].

In patients with deformed OA-knees treated with distal femoral osteotomy and human umbilical cord blood-derived (hUCB)-MSCs, improved pain and WOMAC scores were seen, and modified two-dimensional MRI showed cartilage repair [80]. Repeated hUCB-MSC treatment is found safe with superior efficacy over IA-HA in symptomatic OA-knee at 1-year follow-up [81]. In OA-knee rat models, a single IA injection of hUCB-MSCs temporarily decelerates cartilage degeneration [82]. In another animal study, transfected hUCB-MSCs with miR-140-5p mimics and miR-140-5p lentivirus over-expressing miR-140-5p (microRNAs) in rat OA-knee models signified its cartilage healing potential [83]. Induced MSC exosomes also showed a more significant cartilage regeneration potential in collagenase-induced mouse OA-knee [84].

In a rat OA-knee model study, extracorporeal shock-wave therapy (ESWT) and ultrasonogram guided injection of autologous ADMSC showed a greater chondroprotective effect over ESWT and human umbilical cord Wharton's jelly-derived mesenchymal stem cells [85]. MSCs or stromal vascular fraction (SVF) seem to produce promising good-excellent clinical and pre-clinical results for knee-OA treatment; however, we still lack RCT considering the large sample size [75].

MSC therapy may have few AEs. Most of them are limited to mild joint pain and swelling that improve with analgesic and NSAIDs like ibuprofen; sometimes, overnight observation relieves the pain [86]. In a patient, incidental unstable angina was documented three months after injection. No clinical evidence suggests that treatment with MSCs of any type increased the cancer risk [86].

MSC is proved safe in human OA [75-79]. MSCs will be widely used in clinical OA with the gradual improvement of related technologies and processes. It is yet to appear clear to know which molecular pathways and chemicals of MSC contribute to cartilage regeneration. Furthermore, injection quantity, source, and preservation technique, and combining MSC with sodium hyaluronate, steroid, PRP are worth exploring its risk and benefits aspects [87].

2.2.4. Exosomes

Exosomes are secreted vesicles; they mediate cell cross-talk and related biological processes [88]. In OA, exosomes releasing from chondrocytes accelerate IL-1β-mediated synovial inflammation, reducing anabolic and increasing catabolic chondrocyte gene expression [88, 89]. However, human-induced pluripotent stem cell-derived MSC (hiPSC-MSCs) released exosome (iMSC-Exos) and synovial membrane MSC exosome (SMMSC-Exos) could attenuate OA-knee progression; chondrocyte migration and proliferation; the inhibition of progression is greater with autologous iMSC-Exos over SMMSC-Exos [84]. PRP, bone marrow, adipose tissue, and embryonic tissue-derived MSC-Exos also maintain chondrocyte homeostasis and ameliorate the OA severity [84, 88, 90]. Both *in vitro* and *in vivo* studies of transfection of exosomes from modified MSCs loaded with miRNA (miR-92a-3p, miR-140-5p, miR-320c), long non-coding RNA (lncRNA-KLF3-AS1) appear to be promising for OA-knee treatment [89]. Genetically engineered primary chondrocytes can repair injured cartilage in OA-knee [89]. As we are unsure of several aspects of exosomes, further studies addressing its mechanism of action, isolation techniques, diagnostic, and therapeutic potentials in OA are required. Advanced technology may clarify these questions regarding exosome-based therapy in the treatment of OA-knees in the future [88].

Limited preclinical evidence explored the aspects of exosomes to be helpful in OA. We don't have direct proof of transferring endogenous exosomes from cell to cell in the joint *in vivo*, limited further studies. Further clarification on exosomes sources, how they work on their targets, or how they penetrate deeper parts of degenerated cartilage are required. We are yet to learn in-depth the chondroprotective miRNA profile of exosomes. We hope the coming days' research will address these aspects of exosomes therapy to help us understand its risk-benefit in clinical OA knee [88].

2.3. Anabolic and Anti-Catabolic (Agents Cause Cartilage Regeneration and Stop Cartilage Degeneration)

2.3.1. Fibroblast Growth Factor (FGF) - Mediated Cartilage Regeneration (Anabolic and Anti-Catabolic)

Basic fibroblast growth factor (bFGF) or FGF-2 is a polypeptide that plays an essential role in tissue regeneration [91, 92]. Nummenmaa *et al.* demonstrated that FGF-2 induced catabolic and anti-anabolic effects in OA-knee patients by up-regulating the production of matrix-degrading MMP-1, 13 enzymes, and down-regulating the *de novo* synthesis of aggrecan and collagen II in articular cartilage. An FGF-2 receptor antagonist appeared to be promising in OA-knee treatment [91]. Li *et al.* documented increased SF - FGF-1/FGF in patients with advanced OA than controls [92]. Increased plasma bFGF/FGF-23 levels are associated with both clinical and radiological severity of human primary OA and may be potential biomarkers for diagnosing and monitoring knee OA [91-93]. Higher plasma FGF-23 levels in patients with OA-knee were found in joint effusion cases and bilateral OA. Increased serum- and SF FGF-21 concentrations were also associated with radiographic progression in knee OA, making it a potential biomarker to predict cartilage damage and a therapeutic target in OA patients [94].

S100B, a 21 kilodaltons (kDa) EF hand-type cytosolic calcium-binding protein, causes FGFR1 signaling-mediated inflammatory response. In diseased human cartilage, S100B is up-regulated, and extra-cellular S100B promotes cartilage degradation. A recent study in rabbit OA-knee models revealed higher S100B expression associated with increased SF - TNF-α and IL-1β levels [95]. Besides, S100B-mediated fibroblast stimulation in synovial tissue resulted in FGFR1 signaling-mediated inflammatory response (increased expression of FGF1 mRNA, FGFR1 mRNA, and respective proteins and decreased type-II collagen), making it a potential therapeutic target as well for OA [95].

Sprifermin (recombinant human fibroblast growth factor 18; rhFGF18) promotes chondrogenesis and cartilage matrix production activating fibroblast growth factor receptor 3 (FGFR-3) in cartilage as tested *in vivo* and *in vitro* studies [96, 97]. Among patients with symptomatic, radiographic OA-knee and KL grade - 2 or 3, IA administration of 100 μg of FGF-18 (sprifermin) every 6 or 12 months *versus* placebo resulted in a significantly increased total femorotibial joint cartilage thickness after two years, but no clear clinical effect; a significant difference was also found with 30 μg sprifermin every 6 or 12 months over placebo; however, the durability of the response was uncertain [96]. Dose-dependent response in terms of medial tibiofemoral thickness has not been achieved with any sprifermin dose [96].

Sprifermin was not associated with any significant local or systemic safety concerns [96, 97]. No deaths were reported. There was no statistically significant dose-response relationship between increasing occurrences of acute inflammatory reactions and increasing doses. Treatment-emergent AEs mainly mild, including arthralgia and joint swelling, injection site pain, nasopharyngitis, hypertension, and headache. Acute inflammatory responses could also be reported. AEs led to treatment discontinuation, or trial withdrawal is infrequent. Severe AEs considered unrelated to the treatment or unlikely to be related to the study, for example, bacterial arthritis [96, 97].

In a recent meta-analysis, IA sprifermin was also reported safe in KOA without any specific AEs. Injection sprifermin may lead to cartilage thickness, volume, and surface morphology improvement; however, it proved no positive impact on symptom alleviation. More evidence is still required for its efficacy and safety to be regarded as a disease-modifying OA agent [98].

2.4. Inhibition of Interleukin-1 (IL-1)

Several human studies report that members of the IL-1 family are found in both SF and synovial membranes of OA knees. Blocking various members of the IL-1 family in murine models showed cartilage protective effects [99]. In

early OA, infiltrating myeloid cells are a major source of IL-1 locally; as the disease progresses, there are fewer infiltrating myeloid cells, and the role for IL-1 may be gone. IL-1β, more than any other cytokines, has been linked to the pathogenesis of destructive OA. In OA, synovial cells induce COX2 enzyme and PGE2 synthesis through IL-1; hence, the widespread use of oral COX-2 inhibitors could well target pain and cartilage degradation [100]. A reduction in IL-1β in OA is chondroprotective, which is echoed in RA patients treated with anakinra [100, 101]. In a clinical study, no uniform association was found between IL-1β / TNF-alpha production and radiographic OA in either sex [102]. However, a possible association could exist between the highest levels of IL-1β production and knee osteophytes (OR=2.0, 1.2-3.5) and joint space narrowing (OR=1.7, 1.1-2.8) in women [102]. Parenteral administration of IL1R1 (AMG108, a fully human immunoglobulin subclass G2 monoclonal antibody binding the human IL-1 receptor type 1, IL-1a and IL-1b), ABT-981, and canakinumab [103-105] were all promising in OA. Based on a recent clinical trial, subcutaneous canakinumab (50-300 mg) was effective in reducing the incidence of total TKA, preferably in primary OA; however, further study was suggested [106]. Other oral small molecules such as selective NLRP3 inflammasome inhibitors are considered promising in this respect [107].

The safety profile of AMG 108 and placebo injection are comparable in human OA knee trials [103]. Injection site pain was the most common AE. SAEs' profile of patients receiving IV and SC anti-IL1 (100 and 300 mg) included hemorrhagic diarrhea, unstable angina, lobar pneumonia, respiratory failure, multi-organ failure, sepsis, neutropenia, and leukopenia in the other, pancreatitis, and supraventricular tachycardia [103]. Early studies using therapeutic approaches in large animal models offered benefits, but IL-1α/β, IL-1-converting enzyme, and IL-1 receptor knocked out murine failed to stop developing OA [108]. Recent RCTs regarding the usefulness of IL-1 inhibitors in human knee OA concluded a lack of efficacy [108]. Hope future study could explore risk-benefit aspects of IL inhibitors in OA knee.

2.5. Gene Therapy (Genetically Engineered Chondrocytes)

The arthritis gene therapy concept was first published in 1992 [109]. In 2015, a phase-II trial unveiled genetically engineered chondrocytes virally transduced with TGF-β1 applicable in OA-knee [109]. Later in 2017, South Korea first approved gene therapy for OA treatment [110]. In a phase-III trial, IA TissueGene-C (TG-C) was shown to improve VAS pain and WOMAC (pain, stiffness, and physical function) scores in OA-knee [110]. In another phase-III trial, INVOSSA (cell and gene therapy, allogeneic non-transformed and retrovirally transduced chondrocytes to over-express TGF-b1) caused improved pain and function [111]. Both INVOSSA and TG-C have OA disease-modifying potentials [110, 111]. The most frequent AEs in the TG-C group were peripheral edema, arthralgia, joint swelling, and injection site pain. The SAEs were not observed [110]. Gene therapy is at its infancy regarding OA knee treatment; we are yet to have more data regarding the outcomes of gene therapy in OA knee.

2.6. Drugs Affect Bone Turnover and Prevent Cartilage Degeneration

Increased evidence suggests that high bone turnover plays an essential role in the initiation and progression of cartilage degeneration in OA, leading to an increased interest in drugs affecting bone metabolism, such as bisphosphonate. In a recent prospective open-label trial in Italy, eighteen consecutive patients with painful knee prosthesis and OA received parenteral (IV or IM) clodronate (CLO) (induction dose was 2.0-2.1g, followed by a weekly dose of 200 mg IM for six months) and knee rehabilitation (knee physiotherapy and walking). Following the intervention, VAS pain (8.1±1.8 to 5.6±2.6, $p<0.05$) and Tegner Lysholm Score (TLS, a patient-reported outcome tool following knee ligament surgery) (40.4±20.3 to 62.7±24.1, $p<0.05$) improved significantly at six months. BMI was also seen positively correlated with VAS (r=0.73, p=0.004) and lower TLS at one month (r= -0.62, P=0.006). Administration of a high dose (induction dose) of CLO every three months appeared to be the most effective regimen compared to a weekly regimen [112]. In another recent cohort with radiographic OA knee, bisphosphonates were found to stop radiographic progression in non-overweight OA cases. Propensity-matched results indicated that bisphosphonate users (69% alendronate) with KL grade <2 were protected against progression than bisphosphonate users with KL grade ≥2. This effect is more substantial among those with lower BMI (<25 kg/m2); however, the duration of bisphosphonate exposure did not affect OA knee progression [113]. An earlier meta-analysis of 15 RCTs by Xing *et al*. also indicated that bisphosphonates therapy could relieve pain and stiffness and accelerate functional recovery for OA but can't stop OA progression [114].

However, in a meta-analysis of seven RCTs, including 3013 patients Vaysabrot and colleagues demonstrated no promising bisphosphonate's effects on OA knee - it neither provided symptomatic pain relief nor improved physical function or radiographic progression; only a small RCT suggested high subchondral bone turnover was reduced with Bisphosphonates (alendronate 70 mg/week) at six months, though the overall risk of study bias was high [115]. Bisphosphonates displayed good tolerability, with no statistically significant differences in AE outcomes over placebo [115]. Effects of IV zoledronic acid (5 mg in a 100-mL saline solution) on knee cartilage volume loss in symptomatic KOA with MRI-detected subchondral bone marrow lesions further studied in multiple Australian centers over two years period; however, the outcomes were not promising [116]. The study demonstrated no significant difference between the zoledronic acid and placebo groups in terms of cartilage volume (p=.50), VAS knee pain (p = .17), WOMAC physical function scores (p = .21), and bone marrow lesion sizes (p = .60). AEs were more common with zoledronic acid than placebo (96% *versus* 83%, respectively) and consisted mainly of acute reactions within three days of infusion administration; 87% *versus* 56%) [115]. Study outcomes regarding the effi-

cacy of bisphosphonate intervention in OA knee are inconsistent and inconclusive; further study is required to document its usefulness in OA knee, safety profile, and risk-benefit ratio.

CONCLUSION

Osteoarthritis may lead to chronic disability if left untreated for a long-time. Even the most prudent healthcare facility cannot provide a complete cure for the disorder following state-of-the-art approaches. Some of the reported emerging interventions are found helpful in joint degeneration, especially in early osteoarthritis. However, the outcomes of some other interventions are inconclusive, and they are based on low-quality evidence-based studies and warrant further research.

KEY MESSAGES

1. Intra-articular human serum albumin, nerve growth factors antagonists, bone morphogenetic proteins, fibroblast growth factors, orthobiologics, exosomes, interleukin-1 blockers, gene-based therapy, and bisphosphonate appear promising in OA knee treatment.

2. The role of conventional disease-modifying anti-rheumatic drugs (DMARDs), lipid-lowering agents (statin), and metformin in OA knee management is unclear.

3. Further research addressing OA knee treatment should be done.

DISCLOSURES

The authors have nothing to disclose regarding this study

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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