Review Article

# The Future of Injectable Orthobiologic Substances for Knee Osteoarthritis: Options beyond Platelet-Rich Plasma

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## Abstract

The management of young arthritic knee and early grades of osteoarthritis (OA) aims to reduce morbidity and improve the quality of life for which newer modalities are emerging. Orthobiologics have emerged as a viable alternative option as they promote tissue regeneration and could be potential disease-modifying agents. Platelet-rich plasma (PRP) has been promising and is among the frontline treatment options in early OA knee; newer orthobiologic research is progressing beyond this and newer products are being tried. Various combinations of PRP with carriers and growth factor extracts from PRP are some new developments. Additional options beyond PRP include autologous conditioned serum, alpha-2 macroglobulin, adipose tissue derivative, bone marrow aspirate concentrate, and gene therapy. This review aims to shed light on the current literature and future potential of the use of these intra-articular orthobiologics in the 21st century.

**Keywords:** Adipose tissue derivative, alpha-2 macroglobulin, autologous conditioned serum, bone marrow aspirate concentrate, gene therapy, knee preservation, platelet-rich plasma, young arthritic knee

## Introduction

Osteoarthritis (OA) is a chronic and debilitating joint disease that affects the articular cartilage and underlying bone. Advanced and severe grades of OA warrant the need for joint replacement. However, the management of young arthritic knee and early grades of OA has seen much research in the early 21st century, and newer emerging modalities are allowing efficient management in this subgroup of patients.[1] The goal of treatment in the young arthritic knee is to reduce morbidity and improve the quality of life; delaying the progression of OA is a bonus. Modern thinking is focusing on "knee preservation," which is now emerging as a viable option for treatment.[2] The application of products from biological sources has been labeled as orthobiologics, and it has evolved significantly over the past 10 years.[3] The application of these products, though showing sufficient promise, needs thorough proper case identification, and thorough evaluation and identification of mechanical and biological factors contributing to the pathology. In the knee, mechanical factors found to be contributory need relevant management (corrective osteotomy for varus alignment, meniscal root repairs, and repair of ramp lesions). Nevertheless, the role of alteration of intra-articular biology is increasingly recognized, and various treatment options are currently practiced. Platelet-rich plasma (PRP) has emerged as the frontline option for the management of early OA knee,[4-7] and the research in the past 10 years has been promising. The success seen with PRP use has pushed scientists to try even newer modalities such as specific growth factors, interleukin-1 receptor antagonist protein (IRAP),[8,9] Alfa-2 macroglobulin (A2M),[10,11] and several other peptides. Gene therapy, which is focused on more sustained delivery of growth factors, is already in Phase 2[12-14] and Phase 3 trials.[15] This article discusses the recent modifications and trends in PRP use and introduce various other orthobiologics that have evolved for the management of OA [Figure 1].

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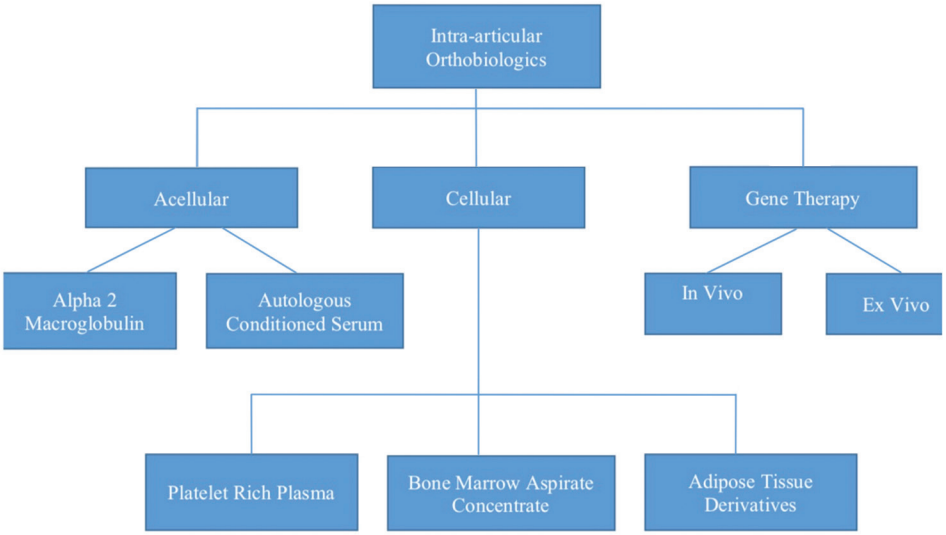


**Figure 1:** Algorithm depicting intra-articular orthobiologics substances used for osteoarthritis knee in a simplified manner

## Role of Platelet-Rich Plasma in Knee Osteoarthritis

PRP, obtained by centrifugation of the patient's blood, contains biologically active proteins such as platelet-derived growth factor, tissue growth factor, fibroblast growth factor, and vascular endothelial growth factor, which reduce inflammation and cause cellular proliferation.[16] The role of PRP in alleviating pain and improving outcome scores has been established over the past decade.

Sánchez *et al*.,[17] in the first trial on PRP in 2008, showed that its intra-articular use is safe. Spaková *et al*.[18] established the safety and efficacy of PRP in early OA while comparing it with hyaluronic acid (HA) in a series of 120 patients. Patel *et al*.[4] showed its efficacy by comparing PRP with placebo (normal saline) and reported improved functional scores. This has been confirmed by many authors, and PRP is widely used as an intra-articular injection in the treatment of OA with excellent patient-reported outcomes.

## Modifications in Platelet-Rich Plasma for Intra-Articular Use

Despite its frequent use, there is much variability in PRP use in terms of its formulation (leucocyte-rich PRP or leucocyte-poor PRP),[19,20] use of activators,[21] number of injections administered,[22,23] and the platelet concentration used.[24] The future research should ideally focus on answering these questions and thereby define the ideal PRP formulation and its dose for use in OA Knee.

Studies have shown that PRP combined with HA has a synergistic action by promoting cartilage regeneration and inhibition of inflammation as both target different biological pathways. Saturveithan *et al*.[25] in their randomized clinical trial (RCT) showed that combining PRP with HA significantly reduced pain and improved functional outcomes as compared to HA alone at 1 year of follow-up. However, there are reports of loss of rheological properties of HA due to dilution with PRP.[26] Low-molecular weight HA is better than high-molecular weight for combining with PRP and enhances the synergistic effects better.[26] Suboptimal results may occur by loss of viscoelastic properties due to dilution or lower concentration of HA. It, therefore, seems more logical for using a combination of PRP and HA by administering them separately with spaced duration rather than combining them together.[27] The ideal combination, ratio, and sequence needs to be evaluated and could be a future research topic.

There is an increasing focus on delivering PRP with carriers to improve and sustain the delivery of growth factors at the target site. Some of the potential carriers being tried are chitosan and gelatin hydrogel. Saito *et al*.,[28] in their study on rabbits, demonstrated that gelatin hydrogel PRP suppressed OA both histologically and morphologically to a greater extent as compared to PRP alone. Chitosan has shown some role in improving PRP's efficacy and causes better platelet adhesion and aggregation. Dwivedi *et al*.,[29] in an animal study involving 2 groups (PRP and freeze-dried chitosan with PRP), observed better scores with chitosan + PRP at 8 weeks. They hypothesized that in contrast to PRP, which is quickly degraded, chitosan PRP persisted for several weeks *in vivo* with longer-lasting effects.

Another approach being tried to improve PRP is the use of photoactivated PRP (PA-PRP). Photoactivation of peripheral blood improves the inflammatory mediators and synergistic action of PRP. Paterson *et al*.[30] conducted a double-blind randomized trial in 23 patients using intra-articular PA-PRP and HA. They reported significant improvement in symptoms and visual analog scale (VAS) score and knee injury and osteoarthritis outcome (KOOS) pain scores at 4 and 12 weeks

with PA-PRP. However, no significant difference was found between the two groups (PA-PRP and HA) although PA-PRP did have improved symptoms and functional scores. Two patients had minor reactions of pain and swelling following PA-PRP. Despite promising results, there have not been any other trials reporting PA-PRP use in OA knees.

Another emerging concept is a combination of intraosseous and intra-articular injections of PRP for severe OA knee.[31] The rationale behind this is that OA also affects the underlying subchondral bone apart from changes in the articular cartilage and synovial fluid. Subchondral bone is becoming the potential therapeutic target in OA knee, and efforts are focusing on stimulating its remodeling. Sanchez *et al*.[32] conducted a pilot study in 13 patients and reported a substantial reduction in pain and improved functional scores. They later conducted a study in 60 patients in which they compared the combination therapy with PRP alone and reported that the combination of intra-articular PRP with intraosseous infiltration of PRP was clinically superior at 6 and 12 months.[33] Similarly, Su *et al*.[34] in a series of 86 patients compared 3 groups: combination (Intra-articular PRP + intraosseous PRP), intra-articular PRP, and intra-articular HA. They reported a significant improvement in VAS and Western Ontario and McMaster Universities (WOMAC) OA Index score at 18 months of intervention in the combined group. Thus, the use of intraosseous PRP is potentially emerging as a useful adjunct in the treatment of advanced OA.

Homologous PRP is obtained from healthy blood donors and has been assessed for patients with poor general health, who are not candidates for autologous PRP.[35] These include anemic patients, those with platelet dysfunction, or hematological disorders. Bottegoni *et al.,*[35] in their pilot study, used homologous PRP in 60 patients and reported an excellent safety profile, but only a short-term clinical improvement. Functional scores improved at 2 months and 6 months from baseline. However, they reported poor results in patients aged over 80 years or in severe OA. They concluded that this could be considered in patients who are not suitable for autologous PRP. The study, however, did not have any controls and no randomization was done.

## Growth Factor Concentrate from Platelet-Rich Plasma

Another emerging concept is to extract the growth factors from PRP and inject the growth factor rich solution. This can be achieved using an activator to activate the PRP, which leads to degranulation and release of GFs, which can then be injected. The final products are acellular growth factor-rich concentrates.

This was first used and popularized by Anitua *et al.*[36] who used plasma rich in growth factors (PRGF-Endoret). They reported improvement in WOMAC and VAS scores as compared to HA. Vaquerizo *et al.*[37] showed improved results with 3 weekly injections of PRGF over one long-acting HA at 24 and 48 weeks. PRGF mediates anti-inflammatory effects and the growth factors aid in the repair of the injured cartilage. Raeissadat *et al.*[38] prepared PRGF by first producing PRP, followed by centrifugation of the upper 2 layers and addition of platelet-activating factor. This led to the release of growth factors by the platelets and subsequently a third spin, which made the platelets and attached fibrin stick to the bottom of the tube. The resultant fluid rich in growth factors was injected intra-articularly in 31 knees. They documented improvement in WOMAC and VAS scores compared to HA (36 knees). They believe that PRGF has the same effects as PRP without its side effects. All studies have reported no severe adverse reactions with only minor complications observed. Raeissadat *et al.*[38] reported swelling in 1 case and stiffness and heaviness of injection site in 6 cases of PGRF, while Vaquerizo *et al*.[37] reported pain at the infiltration site in 7 patients.

PRP has been consistently shown to be beneficial in the treatment of OA. However, research needs to be focused now on newer formulations, biomaterials, combinations, and newer modes of deliveries.

## Autologous Conditioned Serum

OA is associated with the upregulation of proinflammatory cytokines and matrix metalloproteinases (MMPs), including significant levels of interleukin-1 receptors on synovial fibroblasts and chondrocytes.[39] The interaction of IL-1 with its receptors triggers the inflammatory cascade responsible for OA knee pain and pathogenesis. This IL-1 receptor can be targeted by IL-1 receptor antagonist (IL-1Ra), thereby blocking its signaling activity.[40] Autologous conditioned serum (ACS) is rich in IRAP and hence used in OA Knee.

Meijer *et al*.[41] were the first to develop ACS branded as "Orthokine". The patient's whole blood was incubated with glass beads to produce an autologous cell-free serum that is administered intra-articularly twice weekly for 3 weeks. This therapy is available for humans in some European countries and has more widespread use in equine OA, where it improves clinical lameness in horses and has a suggested role of cartilage protection from degradation.[42] Weinberger[43] and Baselga García-Escudero *et al.*[44] have shown improved functional status with ACS use in animals. Baltzer *et al.*[8] conducted an RCT with 376 patients (3 groups) and compared ACS with HA and placebo. They reported improved functional outcome scores in the ACS group compared to the baseline and much larger improvement as compared to HA. They noted that the therapeutic effects persist for at least 2 years and noted an overall excellent safety profile. Auw Yang *et al*.[9] compared ACS with saline controls in 167 patients and observed significant improvement in functionality in both groups with a significant improvement in KOOS score compared with placebo. However, some studies, including Rutgers *et al.,*[45] have found no difference between placebo and ACS; they postulated that cytokines vanish quickly from the synovial fluid after intra-articular injection. They observed

that proinflammatory cytokines were also enhanced along with anti-inflammatory cytokines.

The major issue with ACS is that it is a prolonged process. Baltzer *et al*.[8] prepared ACS with an incubation period of 24 h and recommended 6 injections (2 mL weekly for 6 weeks). Tassara *et al*.,[45] in a retrospective series of 28 patients prepared ACS by incubation for 6 h, followed by centrifugation at 5000 rpm for 10 min. They reported a rapid decline in pain with a large improvement in knee range of motion. Woodell May *et al*.[46] followed a different protocol of ACS preparation, wherein they first prepared PRP from the blood by centrifugation and then incubated the PRP with glass beads. They noted similar desired results with a much shorter incubation period. They concluded that neither time nor temperature significantly increased IL-1Ra production. This was an important finding, as it paved the way for developing ACS in a much shorter time and making it easily available. Barreto *et al*.[47] centrifuged 60 ml blood for 15 min and then incubated it with medical grade beads for 30 min at ambient room temperature followed by a second spin for 3.5 min, which yielded ACS (Arthrokinex). They reported improvement in pain and functionality at 1 year of follow-up.

King *et al*.[48] observed that increased WBC concentration correlates with increased concentration of IL-1Ra in their product (nSTRIDE). This high concentration of WBC is achieved using the buffy coat layer after centrifuging blood (LR-PRP). Kon *et al*.[49] conducted a pilot double-blinded RCT in 46 patients and randomized it into 2 groups: APS group ($n$ = 31) and saline group ($n$ = 15). They reported improvement in functionality, and significant difference between groups was detected in a change in lesion size and central zone osteophytes of the lateral femoral condyle.

ACS has the potential to offer disease-modifying and chondroprotective effects for the management of mild and moderate OA. However, its potency is not validated, and large randomized control trials are required to evaluate its long-term benefits. Nevertheless, its effectiveness in short to medium term with minimal complications is fairly well documented.

## Alpha-2 Macroglobulin

A2M is a serum protease inhibitor, inhibiting all classes of endoproteases. These endoproteases include cartilage oligomeric matrix protein-cleaving proteinases (comp), MMP-13 and pro-inflammatory cytokines (IΛ-1 β and tumor necrosis factor-α).[50,51] It acts as a scavenger molecule by attaching to the proteinases, inducing conformational changes, and thereby scavenging them. They subsequently bind to macrophage receptors and result in clearance of the complex.[52] This resultant chondrogenic and chondroprotective effects have made A2M emerge as a potential therapeutic option for OA treatment. A2M is prepared by passing PRP through various filters, and by sequential filtration, small molecules escape out, and the resultant plasma is rich in A2M, which is a huge molecule.

Clinical trials in humans are underway and yet to be published.[53] However, many studies have reported therapeutic benefits in animal studies. Wang *et al*.[10] showed rats that underwent anterior cruciate ligament (ACL) transection and received intra-articular A2M had decreased MMP-13 levels and a slower rate of progression of OA. They suggested that supplemental intra-articular A2M provides chondral protection for posttraumatic OA on OA cartilage samples. Cuellar *et al*.[11] used New Zealand white rabbits and gave intra-articular injections on days 1, 4, and 14 post-ACL transection and showed less joint degeneration and supportive role of A2M in cartilage preservation.

It is postulated that the major beneficial role of A2M may be in the acute flare of OA. This is because the acute flare is associated with the upregulation of proteases, which are inflammatory proteins. A2M inhibits these proteases and neutralizes cartilage degradation and joint destruction. A2M has been referred to as the master inhibitory molecule by Wang *et al*.[10]

Nevertheless, clinical studies are needed to assess its true potential benefits for knee OA. In this regard, a phase 1 RCT clinical trial is underway in 75 patients to assess the ability of A2M in reducing proinflammatory synovial fluid biomarkers.[53]

## Bone Marrow Aspirate Concentrate

Bone marrow aspirate concentrate (BMAC) injections have recently been used for OA knee, owing to the regenerative potential of progenitor cells in marrow.[54] Bone marrow aspiration is percutaneous, safe, and commonly performed from the iliac crest; this is centrifuged to isolate its cellular components in distinct layers. BMAC is rich in mesenchymal stem cells (MSCs), which are capable of differentiation toward cells of a mesodermal lineage. It also has high concentrations of IL-1Ra and IL-1 beta, which are anti-inflammatory growth factors.[55,56] Although MSCs comprise only 0.001%–0.01% of the cells in BMAC, these have homing abilities, which recruit more cells to the desired site.[57] There is an ongoing discussion to rename MSCs as medicinal signaling cells from its earlier nomenclature of MSCs due to its autocrine and paracrine functions.

One important aspect of BMAC preparation is to obtain a large population of progenitor cells; hence, a good technique of bone marrow aspiration is vital. Hernigou *et al*.[58] described an improved output with aspiration at multiple locations with a small syringe; however, Oliver *et al*.[59] found no significant difference in single versus multiple location aspirations. On the other hand, they reported increased procedural pain with multiple site aspiration. Either way, it is important to maintain low aspiration volumes, as the first 2 ml collects the bone marrow-derived cells, and this is diluted by blood volume subsequently.

Few studies have assessed the use of BMAC in OA knees. Kim *et al*.,[60] in a series of 75 patients, reported increased functional scores (IKDC, KOOS, and SF-36) compared to preoperative

scores, although this was not statistically significant. They reported that a higher grade of OA was associated with poorer outcomes. Centeno *et al*.[61] compared the efficacy of BMAC with adipose tissue derivative (ATD) cells but reported no improvement in efficacy. Shapiro *et al*.[62] conducted a placebo (saline) controlled pilot study in 25 patients. They reported that BMAC and saline caused similar pain relief and improvement in activity level at 6 months of follow-up. Themistocleous *et al*.[63] retrospectively analyzed intra-articular BMAC in a series of 121 patients and concluded that it is a safe procedure causing clinical improvement in OA. Anz *et al*.[64] compared BMAC with PRP in their RCT involving 90 patients and they reported similar improvements in both groups. There was no superiority of BMAC over PRP.

Chahla *et al*.,[65] in a systemic review, reported good outcomes; however, they highlighted the lack of high-quality studies. Although studies have shown the benefits of BMAC, evidence supporting its superiority to PRP has not been established. Moreover, the morbidity associated with the technique of BMAC aspiration from iliac crest compared to a much simpler PRP preparation technique does not justify BMAC use for OA Knee at present.

BMAC is thus a promising option for OA knee in terms of feasibility and ability to concentrate MSCs for safe use. However, longer follow-up studies and large clinical trials are required to assess the effect of cell count, frequency of treatment, and cell types. It is also important to establish if there is any added supremacy over PRP as BMAC includes cellular components as well.

## Adipose-Derived Stromal Cell Therapy

ATDs are considered to be one of the greatest sources of adult stem cells, which have the ability to differentiate into chondrocytes or tenocytes.[66] These are also postulated to contain supportive cells that modulate the microenvironment and aid in regeneration and repair.[67]

Use of ATD is becoming popular as bone marrow harvesting is relatively invasive and associated with donor site morbidity and risk of wound infections.[68] Adipose tissue is abundant and an easily accessible cell source and has characteristics similar to that of bone marrow-derived MSCs.[69] Moreover, MSCs derived from adipose tissue have been suggested to have the highest chondrogenic potential.[70]

These are collected from the lipoaspirate of the abdomen, thigh, or buttock using handheld syringes or machine-generated vacuum pressure and a liposuction cannula. The aspirated adipose tissue undergoes a serial stepwise processing and leads to the extraction of stromal vascular fraction (SVF). The process involved in preparation is more than minimal manipulation and hence faces regulatory issues in some countries. The procedure is done as a single outpatient visit and hence is desirable to the patient. ATD used to treat knee OA includes microfragmented adipose (MFAT) tissue and an SVF. MFAT is generated by mechanically breaking up the adipose tissue by passing it through a size reduction filter.[71] SVF is obtained by centrifugation followed by a-enzymatic digestion (usually collagenase), b-enzymatic digestion, and size reduction filter or c-filter alone.[72] However, it is believed that filter alone lacks the efficiency and yield of enzymatic separation.

There are many studies, which have shown the positive effects of ATDs in OA models in animals. Toghraie *et al*.[73] induced OA in 20 New Zealand white rabbits and showed that ATD decreased the amount of joint space narrowing, subchondral sclerosis, and osteophyte formation. Mei *et al*.[74] demonstrated that ASC therapy in a rat model of OA decreased cartilage degeneration grossly and histologically by 8–12 weeks after treatment when compared with a placebo.

Some studies in the literature have reported positive results with the use of ATDs. Spasovski *et al*.,[75] in their series of 9 patients, reported improvement in all clinical scores and substantial pain relief at 18 months of follow-up. Koh *et al*.[76] used adipose MSCs in 35 patients and reported good to excellent results in 33 patients. Jo *et al*.[77] reported that clinical outcomes improved in all 18 patients with the use of intra-articular ATDs. They also studied the relation of three doses of cells with the duration of relief. The clinical scores deteriorated after 1 year in low- ($1 \times 10^7$) and medium-dose groups ($5 \times 10^7$), while the scores plateaued and persisted until 2 years in the high-dose group ($1 \times 10^8$). Adverse effects were minimal in all the above studies, consisting of pain and swelling limited to 24 h.

Culture expansion is not required with ATD use as these already contain a substantially high number of MSCs. Koga *et al*.[78] used $5 \times 10^7$ cells/ml and Wakitani *et al*.[79] used $1 \times 10^6$ cells/ml of culture-expanded MSCs for the treatment of cartilage defects. However, studies using ATDs were able to extract a similar number of cells without culture expansion (Spasovski *et al*.[75] 0.5–$1 \times 10^7$; Koh *et al*.[76] $3.8 \times 10^6$ cells/mL).

ATD use has shown early success and acceptable safety profile, but the evidence is low with few studies with small sample sizes available so far. Larger clinical trials are required focusing on aspects of the most effective processing method, cell source, and effective dose. They need further evaluation to arrive at some conclusions.

## Gene Therapy

The major challenge with the treatment of OA is that it is an ongoing disease and requires sustained supply and delivery of therapeutic agents (growth factors, IRAP) in order to have sustained benefits; this is where gene therapy could play a major role. Gene therapy aims at the presence of a long-term therapeutic agent to protect and rebuild the damaged articular cartilage. Gene therapy is a promising therapeutic approach for structural modification of OA. All current treatments available are unable to

regenerate the entire joint structures completely. However, from the structural aspect, targeting the early stages of OA appears beneficial, as the entire articular cartilage is not yet eroded.

Gene transfer techniques are used to suppress inflammatory factors or to overexpress therapeutic factors (growth factors and transcription factors). Gene delivery is vector based which uses nonviral or viral vectors.[80] Gene transfer is done by an *in vivo* or *ex vivo* approach. *In vivo*, the gene of interest is directly introduced into the patient's own cells within the knee by injection of the viral vector carrying the desired gene. *Ex vivo* is modification of target cell outside the patient's body and subsequent injection of the same into the knees to express the desired gene. Recombinant adeno-associated virus has emerged as the most promising candidate for both *ex vivo* and *in vivo* gene therapy. It is used for *in vivo* therapy due to its possible long-term clinical benefits.[81]

*Ex vivo* approach by targeting transforming growth factor beta (TGF-β1) expression is currently the popular gene therapy option for OA knee. It is supported by animal studies as well as Phase 2,[12-14] Phase 3 clinical trials.[15] In this technique, allogeneic chondrocytes are genetically modified using selective genes (TGF-β1 expression related), which are introduced within them and these allogeneic chondrocytes are available as over-the-counter products for injection.

Noh *et al*.[82] first described the potential positive effects of chondrocytes expressing TGF-β1 in a preclinical evaluation in animal models with articular damage. They reported new foci of hyaline cartilage matrix with staining characteristics consistent with articular cartilage. Ha *et al*.[83] conducted the first clinical trial (Phase 1) in patients with 12 end-stage knee OA using a retroviral mediated gene transfer to cause overexpression of TGF β1. They observed minor local reactions, most common being knee effusion but no serious adverse events. This was followed by a multicenter, single-blind Phase 2 trial in which patients were randomized to receive TGF β1 at doses $6 \times 10^6$ or $1.8 \times 10^7$ cells at a 1:1 ratio.[12] No significant adverse events occurred and both groups showed improvement in functional scores (IKDC and WOMAC) and VAS score. Lee *et al*.[13] conducted a placebo RCT and reported significantly improved IKDC and VAS score in the gene therapy group as compared to placebo. Cherian *et al*.[14] conducted a Phase 2 randomized study of genetically engineered allogeneic human chondrocytes expressing TGF β1 in patients with grade 3 OA in 102 patients and reported a more positive response in IKDC evaluation, VAS, and less likely use of analgesics.

Kim *et al*.[15] conducted a Phase 3 clinical trial using retrovirally transduced chondrocytes to overexpress TGF β1. They reported significant improvement in IKDC and VAS scores and trends toward thicker cartilage on MRI. In fact, South Korea approved the world's first gene therapy (*Invossa*), which encodes transforming growth factor-β1 in 2018.[84,85]

Research exploring *in vivo* pathways of gene therapy is usually directed toward IL-1 pathway and is still in its infancy stages with few *in vivo* studies available. Nixon *et al*.[86] conducted a study on mouse and horse models expressing the IL-1Ra gene. They noted improvement in the cartilage volume and surface in mice and improved lameness parameters in horses. Currently, clinical trials are underway for IL1Ra based gene therapy.[87]

Gene therapy strategies, thus, enable targeted gene delivery and bear promise for the future to alleviate symptoms in early OA as it has the potential for sustained delivery of the drug. It may prove to be the option that may reverse or at least halt the disease process by structural disease modifications. Research into region-specific editing of genes related to OA is ongoing and may allow controlled therapeutic gene expression for OA treatment.

## Conclusion

The success and safety of PRP use in OA Knee have been encouraging and have prompted research into newer Orthobiologics substitutes for intra-articular use. Orthobiologics are encouraging as they are believed to be disease-modifying therapy strategies. Trends are focused on using specific growth factor extracts, cellular therapy (MSCs from BMAC and ATD). Gene therapy is in Phase 3 clinical trials with early promising results. The debate is ongoing regarding the benefit of these orthobiologics and further studies are needed to clarify their role.

### Ethical approval

The authors confirm that this review had been prepared in accordance to COPE roles and regulation. Given the nature of the review, IRB review was not required.

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### Conflicts of interest

There are no conflicts of interest.

### Authors contribution

SP analyzed data and reviewed the initial draft and provided logistic support. KJ wrote initial and final draft. MD Conceived and designed the study and provided research material. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

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