The Role of Orthobiologics in the Management of Osteoarthritis and Focal Cartilage Defects

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abstract

Individuals with osteoarthritis have a diminished quality of life, and the condition is a major cause of disability. Newer biologic treatments have been developed that are believed to modify disease progression. These predominantly include hyaluronic acid, platelet-rich plasma, bone marrow aspirate concentrate, and adipose-derived mesenchymal stem cells. There is conflicting evidence regarding the use of orthobiologics for osteoarthritis and for focal chondral defects, although most studies indicate that injections of biologics are safe and without significant adverse effects. [*Orthopedics*. 2019; 42(2):66-73.]

Currently, 30 million Americans have osteoarthritis.[1] Quality of life is diminished for individuals with osteoarthritis compared with those without it, and osteoarthritis constitutes a major cause of disability in the United States.[2] The burden on the health care and financial systems increases as the prevalence of osteoarthritis increases. In 2003, the total cost of arthritis along with other rheumatic diseases topped $128 billion.[3] Current nonoperative treatments are primarily palliative and unable to slow or reverse disease progression. Many patients resort to total joint replacement to improve function and reduce pain. Recently, nonoperative, biologic treatments have been developed to provide patients with a more durable symptomatic relief. The predominant orthobiologic treatments available include hyaluronic acid (HA), platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and adipose-derived mesenchymal stem cells.

HYALURONIC ACID

Mechanism of Action

The concentration of HA is between 2.5 and 4.0 mg/mL in the healthy adult knee with no pathology, whereas it decreases by 33% to 50% in the arthritic knee.[4,5] In addition, the size of the HA molecules is reduced, resulting in less inter-molecular interaction and ultimately leading to decreased dynamic viscosity and elastic properties.[5] Intra-articular HA injections are believed to work through several mechanisms: viscoinduction, chondroprotection, and viscosupplementation. The injections induce the production of HA from chondrocytes and synoviocytes (viscoinduction) while preventing cartilage fragmentation (chondroprotection) and provide protection from mechanical stress (viscosupplementation).[4,6] The chondroprotective effect of HA injection is believed to be mediated through the interaction of HA with the cluster of differentiation 44 (CD44) receptors.[7] As HA binds to CD44, it causes an inhibitory effect on interleukin-1ß, which in turn decreases the production of matrix metalloproteinase and ultimately downregulates the catabolic effect on cartilage.[7]

Types and Processing

Several brands of HA injection are produced. Both high and low molecular weight concentrations are available (**Table 1**).[8-14] They may be given as a

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single injection or as multiple injections. High molecular weight HA is the form present in the extracellular matrix of the normal knee; it is converted into low molecular weight HA by hyaluronidase in response to injury.[15] The larger molecules in high molecular weight HA have a higher affinity for the CD44 receptor, which is believed to increase the inhibitory effect of high molecular weight HA on cartilage catabolism.[7] However, while in vitro studies support the superiority of high molecular weight HA, clinical studies have yet to show a significant difference in clinical outcomes between the 2 formulations.[16,17]

Table 1

Common Brands of High Molecular Weight Hyaluronic Acid and Their Characteristics

Brand	No. of Injections	Injection Amount, mL	Source
Euflexxa[8]	3	2	Bacteria
Synvisc[9]	3	2.25	Avian
Synvisc-One[10]	1	6	Avian
Supartz[11]	3 or 5	2.5	Avian
Durolane[12]	1	3	Bacteria
Hyalgan[13]	3 or 5	2	Avian
Orthovisc[14]	3 or 4	2	Bacteria

Adverse Effects

Another important point to consider when using HA is the safety profile of the injection. Altman et a1[18] recently analyzed the adverse effects in 17 studies examining multiple injection cycles of both low molecular weight and high molecular weight HA. No serious adverse reactions were reported, and the most common non-serious adverse reactions included arthralgias and joint swelling.[18] The rates of adverse reactions varied from 0% to 14.4%, and repeat injections did not have increased rates of adverse effects compared with single injections.[18]

Role in Osteoarthritis

The role of HA injections in the management of osteoarthritis is controversial. In 2013, the American Academy of Orthopaedic Surgeons released its clinical practice guidelines for osteoarthritis, stating that the use of HA in osteoarthritis is not supported.[19] Notably, no stratification was performed on the outcomes based on the type of HA, which has since resulted in substantial controversy. The American Academy of Orthopaedic Surgeons' review of the literature found that although HA injections improved Western Ontario and McMaster Universities Osteoarthritis Index scores for pain, function, and stiffness, they failed to meet the clinically meaningful important difference.[19] Despite this fact, HA is still widely used by orthopedic surgeons, especially for moderate osteoarthritis (Kellgren–Lawrence grade II–III) as described in a recent survey by Carlson et al.[20] Since publication of the American Academy of Orthopaedic Surgeons guidelines in 2013, research has continued into the application of HA for knee osteoarthritis. In 2015, a systematic review by Campbell et al[21] indicated that when compared with nonsteroidal anti-inflammatory drugs, corticosteroid, PRP, and placebo, HA had the highest level of evidence supporting its use for early osteoarthritis, showing improvements in function and pain for up to 26 weeks. Higher-level clinical research is needed to elucidate the effects of HA in early osteoarthritis.

Role in Focal Cartilage Defects

There is limited evidence for the use of HA injections in isolation for focal cartilage defects of the knee. However, recent studies have increased interest in the application of HA in combination with surgical microfracture for promoting chondrocyte proliferation and differentiation in vitro.[22] Multiple animal studies have shown a positive effect of HA augmentation following microfracture through greater fill of defects and improved tissue quality.[22,23] Recent clinical studies using microfracture in combination with HA augmentation have shown similarly promising results. Görmeli et al[24] found that for patients treated with microfracture for osteochondral lesions of the talus, augmentation with HA improved American Orthopaedic Foot and Ankle Society outcome scores compared with those of the control group, and these scores were further improved when augmentation with PRP was used. A study by Gobbi and Whyte[25] indicated superiority of a combined HA and BMAC injection with arthroscopic debridement but without microfracture compared with arthroscopic microfracture at 5 years postoperatively in patients with cartilage lesions of the knee. Additional investigations have described techniques using HA with BMAC as an adjunct to osteochondral grafting in high-grade cartilage lesions of the knee. These studies found the development of hyaline-like cartilage where the previous defect had been and improvement in pain and functional outcome scores when compared with baseline measurements.[26,27] These studies indicate that HA may play an increasingly important role as an augment or scaffold in combination with other biologics for patients with focal cartilage defects.

Figure 1: Clinical photograph showing a standard venipuncture for collecting whole blood used in platelet-rich plasma.

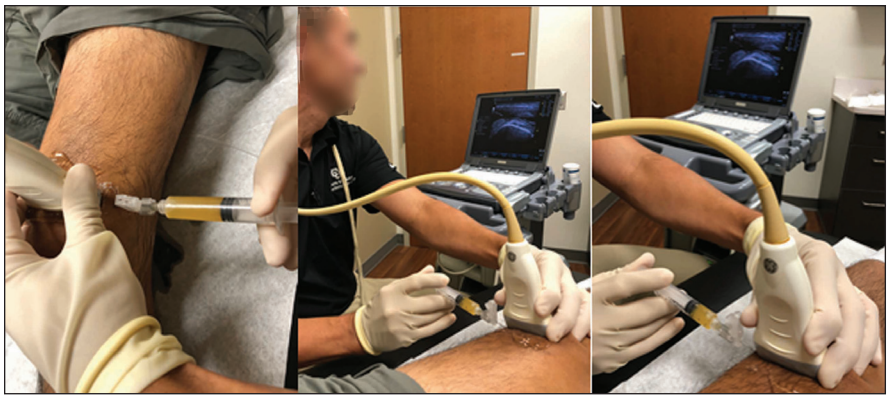

Figure 2: Clinical photographs showing an injection of platelet-rich plasma under ultrasound guidance.

Platelet-Rich Plasma

Mechanism of Action

Platelet-rich plasma contains supraphysiologic concentrations of platelets, which release cytokines and growth factors that are involved in the facilitation of tissue healing and regeneration.[28] In vivo studies have shown that when activated, PRP releases more than 300 proteins, including platelet-derived growth factors, insulin-like growth factor, transforming growth factor, and vascular endothelial growth factor.[29] The combination of these molecules has a strong chemotactic effect on chondrocytes and mesenchymal stem cells and shows a mitogenic benefit resulting in the increased production of proteoglycans and heterotopic cartilage.[30] In addition, PRP works to modify gene expression and inhibit the production of matrix metalloproteinase 13 and nuclear factor-kappa B, which ultimately decreases the inflammatory environment known to characterize the pathogenesis of osteoarthritis.[31]

Types and Processing

Platelet-rich plasma is produced by drawing a patient's blood via standard venipuncture (**Figure 1**) and using a centrifuge to separate the components into layers (differential centrifugation). After the initial centrifugation, the whole blood is separated into 3 layers. The red blood cells settle to the bottom, platelets and some white blood cells form the upper layer, and the middle layer or "buffy coat" is rich in white blood cells. If the goal is pure or leukocyte-poor PRP, the upper layer and superficial buffy coat are isolated and centrifuged a second time to remove residual white blood cells and red blood cells. If the goal is to produce leukocyte-rich PRP, after the initial centrifugation, part of the upper layer and the entire buffy coat are isolated and centrifuged a second time to remove residual red blood cells. The injection can then be performed with or without ultrasound (**Figure 2**). Although the centrifuge speed, time, and spins and the use of automatic or manual systems have been shown to impact the concentrations of cells and growth factors, they have not been standardized.[32-34]

The role of leukocytes in PRP is unclear and may differ based on the clinical condition being treated (ie, tendinopathy vs osteoarthritis). In general, leukocytes are thought to stimulate an early immune response following treatment. This immune response may be inflammatory due to the release of inflammatory cytokines such as interleukin 1-ß and tumor necrosis factor-α, which may be detrimental for the chondrocytes in osteoarthritis.[35,36] Conversely, leukocyte-poor PRP is believed to be superior for osteoarthritis because of the decrease in inflammatory effects.[37-39] A recent meta-analysis by Riboh et al[37] compared leukocyte-poor PRP, leukocyte-rich PRP, and HA for the treatment of osteoarthritis in 1055 patients and showed improved outcomes with leukocyte-poor PRP. The concentration of platelets in the injection is another important factor and varies significantly based on the method of production. Although in vitro studies have indicated that higher platelet concentrations release higher rates of growth factors,[40] it has also been reported that concentrations of greater than 1,000,000 platelets/µL may not provide additional benefit.[41]

Role in Osteoarthritis

The role of PRP for long-term pain relief for osteoarthritis remains controversial. Many orthopedic surgeons advocate the use of PRP injections to provide pain relief and functional improvements. A randomized, double-blind, placebo-controlled trial by Smith[42] showed that 3

weekly PRP injections into the knee significantly improved total Western Ontario and McMaster Universities Osteoarthritis Index scores by 78% at 12 months, compared with a 7% improvement with saline injections. Similarly, a randomized, double-blind trial by Forogh et al[43] compared a single PRP injection with a single corticosteroid injection in 41 patients with moderate knee osteoarthritis. They found that compared with corticosteroid, patients who received PRP had significantly greater pain relief and improved ability to perform activities of daily living and quality of life. Dai et al[39] recently analyzed 10 randomized controlled trials with a total of 1069 patients comparing PRP with HA and saline injections for knee osteoarthritis. They found that at 12 months, patients receiving PRP injections had significantly improved Western Ontario and McMaster Universities Osteoarthritis Index pain and function scores compared with patients receiving saline injections. Further, these differences exceeded the minimum clinically important differences, defined as the minimum improvement that is deemed clinically significant by the patient.[44] The study defined the minimum clinically important differences as an improvement in the Western Ontario and McMaster Universities Osteoarthritis Index pain score of 0.79 (scored 0-20) and the Western Ontario and McMaster Universities Osteoarthritis Index function score by 2.85 (scored 0-68). However, it was reported that 8 of 10 studies had a high risk of bias. Overall, the evidence suggests that PRP may have a role in the management of osteoarthritis and is a reasonable treatment for patients with failure of first-line treatments and who are not ready for arthroplasty.

Role in Focal Cartilage Defects

The role of PRP for focal cartilage defects is currently under investigation. It has shown promising results when used as an adjunct to enhance the results of surgical treatment. Lee et al[45] reported improved clinical results and tissue quality of patients treated with microfracture and a PRP injection compared with those treated with only microfracture for osteochondral lesions less than 4 cm^2 at 2 years. A study by Papalia et al[46] found that patients treated with microfracture and PRP either intraoperatively or postoperatively had greater improvement in clinical outcome scores and magnetic resonance imaging appearance compared with patients treated with only microfracture. In addition, a recent international consensus meeting on cartilage repair in the ankle recommended the use of PRP for osteochondral lesions after 4 to 6 weeks of conventional conservative treatment fails.[47]

Stem Cell Therapy

The interest in using stem cell therapy to regenerate cartilage has been present for many years; however, recent advances have provided clinicians with new ways to harvest and administer these cellular therapies. Stem cells may be classified into embryonic or adult stem cells. Embryonic stem cells are pluripotent cells derived from embryos and are not currently used in clinical orthopedic applications owing to safety and ethical concerns. Adult stem cells are multipotent and can be from the ectoderm, mesoderm, and endoderm. Mesenchymal stem cells, which originate from the mesoderm and have the potential to differentiate into chondrocytes, osteoblasts, myoblasts, and adipocytes as well as mediate cellular recruitment, immune system modulation, and regeneration, are of interest in orthopedics.[48,49]

Common sources of mesenchymal stem cells include bone marrow, adipose tissue, muscle tissue, synovial tissue, amniotic fluid, umbilical cord, and placenta tissue. In osteoarthritis, bone marrow aspirate and adipose-derived mesenchymal stem cells are among the most commonly used biologic agents for the administration of progenitor cells.

Bone Marrow Aspirate Concentrate

Bone marrow aspirate concentrate is most commonly harvested from the iliac crest, distal femur, proximal tibia, proximal humerus, and calcaneus. A study by Hyer et al[50] assessed the quantitative yield of osteoblastic progenitor cells in the BMAC from the iliac crest, distal tibia, and calcaneus in 40 patients. They showed the highest concentration of viable cells to be from the iliac crest when compared with the tibia and the calcaneus. There was no statistically significant difference in yield from the calcaneus and tibia. Another source for harvest is the proximal humerus or distal femur, and this harvesting may be performed during arthroscopic surgery. Beitzel et al[51] found that proximal humerus and distal femur aspiration during arthroscopy yielded high concentrations of mesenchymal stem cells. Harvest of mesenchymal stem cells from the femur using a reamer/irrigator/aspirator technique has also been suggested as a source of progenitor cells. Henrich et al[52] compared the method of harvest of femoral aspirate either through reamer/irrigator/aspirator or using a spoon and from the iliac crest using fine-needle aspiration or a spoon. They found that using a spoon to scrape out the bone marrow resulted in equivalent concentrations of progenitor cells in the iliac crest and the femur.[5]

Once the marrow aspirate is obtained, the sample is filtered and placed into a centrifuge. The time and revolutions per minute vary based on the system used. The preparation process then follows the same principles described above for PRP. Many systems are available for this purpose (**Table 2**).[53-57] A recent study by Gaul et al[58] compared many of the commercially available systems to assess their efficacy. They found that because there is no standardization in the reported data, the systems cannot be compared.[58]

Table 2

Commonly Used Systems to Concentrate Bone Marrow Aspirate and Their Characteristics

System	Input Volume, mL	BMAC Output, mL	Centrifuge Time, min	Centrifuge Speed, rpm
Angel[53]	40-180	Adjustable	15-26	3200
BioCUE[54]	30 or 60	3 or 6	15	3200
Arteriocyte Magellan[55]	30-60	3-10	12-17	2800 and 3800
ART BMC[56]	60	3.5-4	15	Not mentioned
Exactech[57]	60	6	10 or 12	2400 or 3600

Abbreviation: BMAC, bone marrow aspirate concentrate.

Role in Osteoarthritis

The role of BMAC in the management of osteoarthritis is still under investigation because little high-quality data are available. Chahla et al[59] recently analyzed the outcomes of BMAC in knee osteoarthritis. They found that the available data are heterogeneous regarding the reported benefits of BMAC injections, with many studies showing good to excellent degrees of improvement in pain and function with minimal adverse reactions, although there were no randomized trials included at the time of this review. Conversely, recent studies by Kim et al[60] and Shapiro et al[61] comparing BMAC with saline injections for patients with bilateral knee osteoarthritis did not show a statistically significant difference in patient outcomes through 12 months.

Role in Focal Cartilage Defects

Bone marrow aspirate concentrate for the treatment of focal chondral defects, either to augment healing after microfracture or as a separate therapy, is showing encouraging early results. A study by Hannon et al[62] found that, compared with microfracture alone, arthroscopic microfracture augmented with BMAC for talar osteochondral lesions led to improved outcome scores, overall outcome, and quality of repair tissue. As described earlier, Gobbi and Whyte[25] found that a combination of HA and BMAC injections with arthroscopic debridement but without microfracture was superior to microfracture alone at 5 years postoperatively in patients with cartilage lesions of 0.5 to 2.2 cm^2 in the knee.

Adipose-Derived Mesenchymal Stem Cells

Adipose-derived mesenchymal stem cells are a form of minimally manipulated cell therapy used to treat a variety of orthopedic conditions. Adipose-derived products are of particular interest given their abundance of progenitor cells, with high concentrations of nucleated cells extracted per harvest.[63,64] Adipose-derived mesenchymal stem cells are harvested via a lipoaspirate technique using subcutaneous fat[65] (ie, from abdomen, flank, or buttocks) or arthroscopically from the infrapatellar fat pad.[66] Once the adipose tissue is harvested, there are a variety of techniques available aimed at isolating the adipose-derived mesenchymal stem cells from the adipocytes and extracellular tissues. Although different processing systems use different techniques, the ultimate goal is to isolate the stromal vascular fraction, which is thought to contain the majority of the progenitor cells. Techniques for processing and isolating the stromal vascular fraction use microfragmentation and cleansing, vibrational energy, and/or enzymatic digestion, along with differential centrifugation to form the ultimate product. Of note, enzymatic processing of the adipose tissue, although used internationally, is not currently approved by the US Food and Drug Administration, as it falls beyond the classification of minimally manipulated. The final product is then typically placed into the joint via an intra-articular injection or otherwise arthroscopically. This process can be completed in the clinic or operating room and processed as a point of care therapy to be used during the same surgical anesthesia.

Role in Osteoarthritis

Currently, no randomized, placebo-controlled clinical trials exist evaluating the use of stromal vascular fraction or adipose-derived mesenchymal stem cells in osteoarthritis. Phase I clinical trials have shown the safety of adipose-derived mesenchymal stem cells, with only minor local adverse effects.[67] Russo et al[68] investigated the effects of stromal vascular fraction on knee osteoarthritis in 30 patients. At 3-year follow-up, they reported improvements in clinical outcome scores when compared with baseline. A recent systematic review by Hurley et al[69] evaluated the available clinical evidence on the use of adipose-derived mesenchymal stem cells in the treatment of osteoarthritis. Sixteen studies were included, which all showed improvement in clinical outcome scores when compared with baseline measurements. Notably, there was a 5% incidence of adverse reactions, consisting predominantly of pain and swelling. Overall, evidence has indicated that the use of adipose-derived mesenchymal stem cells and stromal vascular fraction is safe, with minimal adverse reactions. However, research supporting the use of adipose-derived mesenchymal stem cells and stromal vascular fraction in osteoarthritis is limited to small studies and case series. Further large clinical trials

are needed to better elucidate the role of adipose-derived mesenchymal stem cells and stromal vascular fraction in osteoarthritis.

Role in Focal Cartilage Defects

Limited evidence exists regarding the use of adipose-derived mesenchymal stem cells as an adjunctive treatment for focal cartilage defects. A study by Koh et al[70] explored the role of adipose-derived mesenchymal stem cell injections in combination with microfracture in 80 patients with focal defects of 3 cm^2 or larger. At 2-year follow-up, they reported improved magnetic resonance imaging appearance of the lesions in the cohort treated with microfracture and adipose-derived mesenchymal stem cells when compared with the cohort treated with only microfracture. Importantly, their study failed to show any difference in outcome scores or tissue quality during second-look arthroscopy. Certainly, additional work examining the role of adipose-derived mesenchymal stem cells and stromal vascular fraction therapy in the treatment of focal cartilage defects is warranted.

Conclusion

Overall, given the lack of high-level evidence, the role of biologics in the treatment of both osteoarthritis and focal cartilage defects remains controversial. However, most studies examining the use of biologics have reported a good safety profile without significant adverse effects. The available research regarding the use of biologics for focal cartilage defects holds promise and appears to support augmenting traditional microfracture surgery with biologics to improve tissue healing, cartilage quality, and clinical outcomes. As pressure increases for physicians to find alternative, minimally invasive techniques to combat osteoarthritis and focal defects, the role of biologics seems posed to expand. Further research is needed to elucidate the role biologics should play in the management of focal and diffuse articular cartilage disease, including the type, frequency, and amount of product needed for a given clinical condition.

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