Orthobiologics for Focal Articular Cartilage Defects

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KEYWORDS

• Cartilage restoration • Stem cells • Orthobiologics • PRP • Cartilage defect • Cartilage transplant

KEY POINTS

- Focal chondral defects of the knee are very common, and often result in pain, dysfunction, and in many cases, joint deterioration, and ultimately, the development of osteoarthritis.
- Because of the limitations of conventional treatments, biologic augmentation for the treatment of focal cartilage defects has recently become an area of interest.
- Orthobiologics for focal chondral defects can be applied in the clinical setting, as an isolated surgical procedure, or as an augment to cartilage restoration surgery.
- Orthobiologics used for cartilage defects include (but are not limited to) bone marrow aspirate concentrate, adipose-derived mesenchymal stem cells, platelet-rich plasma, and micronized allogeneic cartilage.

INTRODUCTION

Orthobiologics have become increasingly recognized as treatment options for a variety of orthopedic pathologies. Orthobiologics are currently being used as treatments for osteoarthritis (OA),[1–4] lateral epicondylitis,[5,6] fracture healing,[7] ligament reconstruction,[8] and focal articular cartilage defects.[9–13] Examples of orthobiologics include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), amniotic membrane–derived mesenchymal stem cells (MSC), and adipose-derived MSCs.

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There is a limited amount of literature assessing the efficacy of these techniques as treatment of focal articular cartilage defects. This article aims to discuss the current research and recommendations available on the use of orthobiologics for the treatment of focal articular cartilage defects.

BACKGROUND

Focal articular cartilage defects are common in the knee, and many times result in pain, swelling, and overall joint dysfunction. Widuchowski and colleagues[14] found the prevalence of chondral lesions in the knee to be 60% of those undergoing arthroscopies. Of these, 67% were classified as localized focal osteochondral lesions. Another study showed 63% of patients undergoing knee arthroscopies exhibited chondral lesions.[15] Although focal articular cartilage defects appear to be less prevalent in other joints such as the glenohumeral joint at 5% to 17%,[16] they can still be a substantial source of pain and discomfort. In addition, studies have suggested that focal cartilage lesions may progress to OA,[17] a major cause of morbidity in the United States.[18] Guettler and colleagues[19] examined the altered loading patterns and rim stress concentrations corresponding to different defect sizes and found that in lesions larger than 10 mm, the decreased contact area, increased rim stress, and increased stress on the surrounding cartilage are likely a few of the factors leading to degeneration of the remaining cartilage and, ultimately, arthritis.

Because of its aneural and avascular environment, articular cartilage lacks the ability to heal spontaneously. For this reason, combined with the symptomatic nature of the lesions and the predisposition for OA, early intervention is recommended to restore joint function and pressure distribution. The ultimate goal for treatment of chondral and osteochondral defects is to regenerate natural hyaline cartilage that is well integrated with the surrounding uninjured cartilage. Treatment of these lesions with orthobiologics can be performed either as an isolated injection-based treatment in the clinical or surgical setting, as described throughout the other articles in this text, or during surgery via augmentation of another cartilage restoration technique. Cartilage restoration surgery can be classified into 3 main categories. The first is palliative surgery, which consists of arthroscopic debridement, chondroplasty, and/or lavage. The second is reparative surgery, which includes marrow stimulation techniques, such as a microfracture, with or without biologic augmentation, and the third is restorative, which encompasses osteochondral grafting, including autograft or allograft, as well as autologous chondrocyte implantation (ACI) as well as matrix-induced ACI (MACI).[20]

Marrow stimulation techniques have traditionally been recommended for focal full-thickness chondral lesions less than 2 cm, or in patients with lesions greater than 3 cm and a modest level of physical demand.[20] This procedure functions to stimulate the subchondral bone marrow by creating a blood clot within the lesion rich with marrow elements, including MSCs for healing and fibrocartilage formation. Microfracture has shown its optimal results in patients who are less than 45 years old with lesions less than 2 cm, and a body mass index of less than 30,[21] suggesting it is not an effective treatment in older patients and those with larger lesions. In addition, microfracture leads to the growth of fibrocartilage, which is less durable than hyaline cartilage. Because of these limitations, biologic augmentation of microfracture for treatment of focal cartilage defects has recently become an area of interest.

ACI uses a 2-step surgical procedure in order to implant the patient's own chondrocytes into the defect.[22] The first step is an arthroscopic biopsy of a nonarticulating area of the knee to obtain healthy chondrocytes for culture. The second surgery

involves the implantation of these cultured chondrocytes after about 3 to 12 weeks.[23] ACI has been found to have optimal outcomes in patients with lesions greater than 3 to 4 cm^2 without involvement of subchondral bone, young patients with greater than 2.5 cm^2 defects with high activity levels without involvement of subchondral bone, as well as some patients with large-diameter cartilage and subchondral bone defects.[24] Studies have found that 76% of patients treated with ACI were deemed to have successful treatment at 3-year follow-up,[25] and 71% of patients rated their outcomes as "good" or "excellent."[26] MACI is also known as third-generation ACI and was developed in an effort to improve traditional ACI technique outcomes while reducing complications.[27] In this technique, cultured autochondrocytes, as described above, are seeded onto a collagen bilayer matrix before implantation.[28,29] Zheng and colleagues[27] showed that in vitro MACI-regenerated cartilage-like tissue showed 75% hyaline-like cartilage. Ventura and colleagues[30] found that at 2-year follow-up 88% patients showed complete integration with surrounding endogenous cartilage on MRI. Second look arthroscopy and biopsy were performed in 6 patients and revealed full integration with surrounding cartilage as well as hyaline-like repair cartilage with type II cartilage. Augmentation with a collagen bilayer significantly improved cartilage regeneration in MACI, suggesting augmentation with biologics could further improve patient outcomes.

Osteochondral autografts and allografts are used to restore the natural architecture of the joint.[9] Autografts are used in patients with full-thickness osteochondral lesions less than 2.5 cm^2 as well as treatment of patients who have already failed previous cartilage restoration.[31,32] For lesions larger than 4 cm^2, osteochondral allograft (OCA) is often the procedure of choice. Although Frank and colleagues[33] found significant improvement in outcome scores at 5-year follow-up after OCA, a 32% reoperation rate was also noted. Levy and colleagues[34] found a reoperation rate of 47% by 10 years. In addition, 24% of knees had failed at a mean of 7.2 years. Predictors of allograft failure included 2 or more previous surgeries on the knee as well as age greater than 30 at the time of the operation.

Although these surgical treatments are effective for many patients, current research is focused on further improving outcome scores, reducing reoperation rates, and preventing the progression of these defects to OA through the use of biologics. The following sections describe how the senior author uses orthobiologics as an augmentation during the surgical management of focal chondral defects of the knee. Augmentation techniques, including BMAC, micronized allogeneic cartilage (MAC) matrix (BioCartilage), PRP, hyaluronic acid (HA), various scaffolds, growth factors, and cytokine modulation, have been described.

BONE MARROW ASPIRATE CONCENTRATE

The use of MSCs is currently being studied in many areas of orthopedics due to their regenerative potential. MSCs are able to be harvested from multiple sources, including bone marrow. Importantly, MSCs account for only 0.001% to 0.01% of nucleated cells in bone marrow.[35] Because of this, bone marrow aspirate can be harvested and processed via centrifuge to produce a more concentrated specimen. BMAC can then be used as a primary treatment or as adjunct to cartilage restoration surgery (**Fig. 1**). The utilization of BMAC stems from its extensive list of growth factors and cytokines, such as vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor-beta (TGF-β), and bone morphogenetic proteins (BMP) -2 and -7, all of which are present in higher quantities when compared with other biologic products such as platelet-rich plasma (PRP).[36,37] In

Fig. 1. BMAC.

addition, BMAC contains growth factors that are linked to chondrocyte proliferation, MSC differentiation, wound healing, and the suppression of proinflammatory cytokines.[38]

Early literature has been supportive of the use of BMAC as an adjunct to surgery for focal chondral defects. Saw and colleagues[39] augmented subchondral drilling with HA or BMAC + HA injections in a caprine model and found that at 24 weeks the BMAC + HA group's cartilage repair tissue was determined to have a significantly more hyaline-line structure as determined by the Gill score. Fortier and colleagues[40] used an equine model to compare microfracture augmented with BMAC and thrombin compared with microfracture alone in full-thickness, 15-mm defects and found that the BMAC group had significantly better International Cartilage Restoration Society (ICRS) scores with higher-quality repair tissue, increased type II collagen, and improved integration.

BMAC has also been studied as an adjunct to scaffolds. Enea and colleagues[41] studied 9 patients in whom microfracture was supplemented with a collagen membrane soaked in BMAC as treatment of focal chondral lesions. The study found that at 1-year follow-up, of the 4 patients who underwent second-look arthroscopy and cartilage biopsy, hyaline-like cartilage was seen in one patient, a mixture of hyaline-like cartilage and fibrocartilage was seen in 2 patients, and fibrocartilage alone was seen in one patient, suggesting BMAC is a safe and effective adjunct treatment in creating a more hyaline-like cartilage repair tissue. In addition, Krych and

colleagues[42] showed that in patients with grade III or IV chondral lesions treated with a scaffold supplemented with BMAC, there was improved cartilage maturation and cartilage fill with mean quantitative T2 values closer to that of natural hyaline cartilage as compared with scaffold alone. Gobbi and colleagues[43] evaluated BMAC in combination with a collagen I/III matrix in focal cartilage defects with an average size of 8.3 cm and found a significant improvement in Tegner, Marx, Lysholm, VAS, IKDC subjective, and KOOS scores at 1, 2, and 3 years. The study also found complete filling of the defects on MRI in 80% of patients and less than 50% filling in 20% patients with complete integration of cartilage in 88% of patients. Gigante and colleagues[44] studied a 37-year-old man with a cartilage lesion on his medial femoral condyle treated with microfracture, BMAC, and a scaffold. The case report found the patient's MRI at 12 months showed substantial defect filling with tissue signal similar to that of surrounding tissue, and the patient remained asymptomatic throughout the 2-year follow-up.

In a study comparing BMAC in an HA scaffold (BMAC-HA) versus microfracture for full-thickness chondral defects, Gobbi and Whyte[45,46] found that all 50 patients significantly improved in IKDC scores, Lysholm, and Tegner at 2-year follow-up. In the microfracture group at 2-year follow-up, 64% of patients classified their functionality as "normal" and "nearly normal," whereas 100% of the BMAC-HA group classified their functionality as such. At 5-year follow-up, there was a significant decrease in the microfracture group, to 28%, in patients classifying their functionality as "normal" or "near normal," whereas the BMAC-HA group maintained their improvement across IKDC score, Lysholm, and Tegner.

In a prospective study, Gobbi and colleagues[47] compared MACI to the use of BMAC supplemented scaffolds in patellofemoral chondral lesions with a minimum follow-up of 3 years with average lesion sizes of 7.12 cm^2 and 5.54 cm^2, respectively. Both groups showed statistically significant improvements in IKDC score, KOOS score, VAS score, and Tegner. There was no significant difference between the improvements when both groups were compared with each other, except for IKDC scores, in which the BMAC group improved significantly more than the MACI patients.

Interestingly, Haleem and colleagues[48] studied expanded BMAC transplanted onto platelet-rich fibrin glue in 5 patients with full-thickness articular cartilage defects on either the lateral or the medial femoral condyle. Utilizing expanded BMAC involved a 2-step procedure as the MSCs underwent culture expansion for 2 weeks. All 5 of the patients experienced significant improvement in Lysholm and Revised Hospital for Special Surgery Knee Score at both 6 months and 1 year. MRI was completed at 1 year and showed complete defect fill with good integration of the repair tissue in 3 of the 5 patients. On second look arthroscopy at 1 year, one patient received an ICRS score of 11/12, denoting nearly normal cartilage.

Oladeji and colleagues[49] completed a cohort study to evaluate the effect of BMAC on integration of femoral condyle OCAs. In order to study this, grafts were saturated in BMAC for a minimum of 2 minutes before implantation (compared with no BMAC). Graft incorporation, as determined on radiographs, was significantly increased in the BMAC group at 6 weeks, 3 months, and 6 months. The BMAC group also showed significantly less sclerosis at 6 weeks and 3 months.

Taken together, these studies demonstrate that BMAC augmentation appears to play a role in regenerating a more hyaline-like repair tissue, improving patient-reported outcomes and improving radiographic evidence of healing. In addition, no major adverse events have been reported in these studies, suggesting that BMAC is a safe and efficacious adjunct treatment in cartilage defects.

MICRONIZED ALLOGRAFT ARTICULAR CARTILAGE AND PLATELET-RICH PLASMA

Another biologic option for patients with focal chondral defects involves the combination of particulated (or micronized) allograft articular cartilage with PRP. This technique is used most often as an augment to microfracture in an effort to form a more durable, hyaline-like cartilage rather than fibrocartilage.[21,50,51] BioCartilage Extracellular Matrix (Arthrex Inc, Naples, FL, USA) is one such product that is developed from allograft cartilage and contains the extracullular matrix that is found in normal articular cartilage. The application of BioCartilage and PRP can be done in a one-stage procedure unlike ACI. After preparation of the defect bed, typically using marrow stimulation techniques, the BioCartilage and PRP mixture is placed into the lesion and is then covered with a fibrin glue sealant to help it incorporate into surrounding cartilage and prevent expulsion.[50,51] In a study by Fortier and colleagues,[52] BioCartilage was used to fill 10-mm full-thickness cartilage defects at the trochlear ridge after microfracture in an equine model. The ICRS Score was significantly better in the BioCartilage augmentation group when compared with microfracture alone, as was the T2 relaxation time on MRI. Although there are multiple technique articles illustrating the implantation of BioCartilage in the knee, shoulder, and elbow[53] after microfracture, unfortunately, there is a paucity of data with regard to treatment outcomes of microfracture augmented with micronized allograft articular cartilage and PRP. Although future studies are required to determine if this technique is able to improve cartilage repair in vivo as well as to determine if it is able to provide patients with long-term pain relief, preliminary results suggest it is a safe and effective treatment for improving cartilage restoration techniques.

Notably, because these studies discuss the application of PRP in conjunction with BioCartilage, it is difficult to determine if the results are from the PRP or the MAC. PRP has shown promising results in vitro and in vivo for knee OA,[2,54–56] but its use is much less prevalent in the treatment of focal osteochondral defects, and results thus far have been mixed. Milano and colleagues[57] evaluated PRP in an ovine model as an adjunct to microfracture in the treatment of 8-mm^2 full-thickness chondral defects. The study compared microfracture alone, microfracture with PRP and fibrin placed within the microfracture holes, and an intra-articular injection of PRP after closure. At 6 months, the PRP + fibrin glue group showed well-integrated hyaline-like repair tissue that completely covered the defect, whereas the microfracture-alone group revealed continued exposure of subchondral bone with thin repair cartilage partially covering the defect. In the PRP injection group, repair tissue covered almost the entire defect. Although microfracture holes were no longer evident and cartilage repair tissue did have good integration with the surrounding tissue, it was thin and irregular in the central aspect of the defect. Smyth and colleagues[58] evaluated the use of leukocyte-rich PRP as an intra-articular injection in a rabbit model immediately after creating 3-mm^2 focal chondral defects in bilateral femoral condyles. In each rabbit, one defect was randomized to receive PRP and the other to receive saline. This study found that mean ICRS macroscopic score of the donor site was greater in the PRP-treated knees but did not reach statistical significance. However, microscopic assessment of the defect suggested increased tissue regeneration in the PRP group with greater glycosaminoglycan deposition and more type II collagen immunoreactivity throughout the repair tissue.

Van Bergen and colleagues[59] used a caprine model to analyze the use of PRP in adjunct to a demineralized bone matrix for the treatment of a 6-mm^2 osteochondral defect in the ankle. After 24 weeks, all of the defects were covered with fibrocartilage, and no significant differences were noted between the demineralized bone matrix

group versus the adjunctive PRP group with regard to bone volume fraction, macroscopy, histomorphology, or fluorescent microscopy. Sun and colleagues[60] studied the effect of PRP as adjunctive treatment to polylactic glycolic carrier (PLGA) versus PLGA alone on 5-mm^2 osteochondral defects in a rabbit model. This study found that the group with the addition of PRP showed improved cartilage regeneration and integration of the hyaline-like cartilage. In a separate trial, Smyth and colleagues[61] analyzed the effect of PRP on the bony integration of osteochondral autografts in a rabbit model. The autografts were soaked in either PRP or saline for 10 minutes before implantation in the 2.7-mm^2 defect. The mean modified ICRS histologic score was significantly higher for the PRP group as compared with the control group. In addition, the mean score for graft integration was significantly higher in the PRP group as compared with the control group. As in the previous study, there was also an increase in glycosaminoglycan content and type II collagen immunoreactivity in the PRP group.

As stated above, PRP has shown promising results in the treatment of knee OA, suggesting it may have a similar effect in osteochondral defects. There is currently no standardized preparation technique for PRP, which has led to different concentrations of leukocytes and other factors in the final PRP preparation and may be the reason for conflicting results in numerous studies.[54,62–65] Studies have shown that higher concentrations of leukocytes are correlated with higher concentrations of proinflammatory molecules and that leukocyte-poor PRP is associated with improved bone marrow MSC proliferation, improved chondrogenesis, and decreased synoviocyte death.[66,67] The senior author's preferred technique of preparation of leukocyte-poor PRP is as follows. Venous blood is drawn from the patient, and the sample is centrifuged at 1500 rpm for 7 minutes. Centrifuge separates the sample into a bottom layer of red blood cells, an intermediate buffy layer filled with leukocytes and platelets, and a top layer of plasma (**Fig. 2**). This system uses a double syringe system (Arthrex Inc) so that after the initial centrifuge, the second syringe within the outer syringe fills with only the top layer of PRP.

Growth Factors

The 2 main growth factors used in microfracture supplementation are BMP-4 and -7, members of the TGF-β superfamily, because they have been shown to induce bone and cartilage formation as well as regulate cell proliferation and differentiation.[68] BMP-7 is also known as osteogenic protein-1 and is found in normal articular cartilage. Klein-Nulend and colleagues[69,70] showed that BMP-7 stimulates differentiation of cartilage from perichondrium tissue, which suggests BMP-7 is an important factor in cartilage regeneration and restoration.

Kuo and colleagues[71] studied the effect of microfracture augmented with BMP-7 in rabbits with patellar groove articular cartilage full-thickness defects as compared with microfracture alone and BMP-7 alone. The study found that when compared with the control group without treatment, microfracture alone increased the quantity of repair tissue present and improved the surface smoothness of the repair tissue. BMP-7 alone was found to increase the amount of repair tissue as well; however, it did not increase the quality of the repair cartilage. When combined, microfracture and BMP-7 were found to further increase the quantity of cartilage repair tissue as well as quality of the cartilage repair tissue. The investigators hypothesized that BMP-7 is acting directly on the MSCs released by the microfracture procedure. Similarly, Zhang and colleagues[72] studied BMP-4 as adjunct treatment to microfracture and decalcified cortical bone matrix in full-thickness defects in the trochlear groove in rabbits. This study found that animals that underwent microfracture with a scaffold and BMP-4 supplementation exhibited hyaline articular cartilage at 6 weeks and complete repair

Fig. 2. Preparation of leukocyte-poor PRP.

of articular cartilage and subchondral bone at 12 weeks. In the microfracture-only group, the defects displayed concave fibrocartilage at 24 weeks, suggesting scaffold + BMP-4 improves regeneration of hyaline articular cartilage.

ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

Another way MSCs can be derived is through adipose tissue, offering easy accessibility. Adipose-derived stem cells (ASCs) are obtained as lipoaspirate via liposuction. Next, the sample is purified and processed to isolate the ASCs via collagenase digestion, centrifugation, and culture. ASCs have anti-inflammatory effects and potential for regeneration of new cartilage in a defect. The senior author's preference is as follows: using the Lipogems technique (Lipogems International, Milan, Italy), the surgeon can harvest and process lipoaspirate intraoperatively, creating a single-step procedure with biologic adjunct. ASCs have been shown to have more stem cells per unit volume than BMAC,[73] and furthermore, have been shown have anti-inflammatory and chondroprotective effects intra-articularly.[74]

Bosetti and colleagues[75] analyzed ASC chondroinductive properties in vitro and showed that ASCs induce chondrocyte proliferation and extracelluar matrix production. The investigators demonstrated that microfragmented lipoaspirate clusters can give rise to spontaneous cell outgrowth in both floating culture conditions and in a 3-dimensional collagen matrix. Jo and colleagues[76] performed a randomized controlled trial and reported that intra-articular ASC injections resulted in a significant improvement in WOMAC scores at 6-month follow-up in patients with knee OA, a significant decrease in the size of the defect, and a significant increase in the amount of cartilage present in the joint. This study suggests ASCs would be a viable treatment option for focal cartilage defects because it would allow for a single-stage procedure for cartilage regeneration within the defect. However, more clinical data are needed to evaluate the safety and efficacy in vivo in treating these focal defects.

SUMMARY OF TREATMENT OPTIONS

There are many emerging options in the use of orthobiologics for the treatment of articular cartilage lesions. Although many studies show promising results of improvement in patient-reported outcomes as well as formation of a more hyaline-like cartilage repair tissue, additional high-level randomized controlled trials must be completed to further ensure safety, evaluate efficacy in different patient populations, and determine the appropriate protocol for preparation and administration of these biologics. There is no one treatment that is appropriate for each cartilage defect, but future research will help build a systematic algorithm based on the patient's defect size, age, activity level, and motivation to return to baseline in order to determine which biologic is the best fit.

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