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An Update on the Use of Orthobiologics: Use of Biologics for Osteoarthritis

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Osteoarthritis is a highly prevalent joint disorder affecting over 30 million adults in the United States. This debilitating disorder is associated with pain and decreased physical function. Though total joint arthroplasty is generally successful, this procedure has associated risk and many patients still have residual pain. Nonoperative treatments have been investigated to provide patients with durable pain relief with lower levels of associated risks. Orthobiologics, such as platelet-rich plasma, bone marrow aspirate concentrate, and amniotic products, contain cytokines and/or mesenchymal progenitor cells that have been demonstrated to modulate the pathogenesis of osteoarthritis in animal and basic science models and may provide clinical improvement in the clinical setting. This chapter will cover recent clinical trials involving orthobiologic injections in patients with hip or knee osteoarthritis.

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Introduction

Osteoarthritis (OA) is the most common joint disorder in the United States, affecting 10% of men and 13% of woman aged 60 or older.[1-4] The growing rate of obesity is likely to further increase the number of people affected by OA worldwide. OA has a significant economic and clinical burden on the orthopaedic and public health communities, as many patients with end-stage OA resort to arthroplasty as a final treatment option.[5] Many patients are seeking alternative, less-invasive treatment options to alleviate their arthritic pain.

The use of biologics in orthopaedic surgery has grown in popularity over the last decade, as preclinical trials have suggested their ability to augment osseous and soft tissue recovery and healing.[5] Biological therapies include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), adipose derived products, and other cell-based therapies. Some of these biologics have an additional benefit of containing growth factors or progenitor cells that may modify cartilage regeneration and improve recovery through anti-inflammatory pathways. Animal models of OA have suggested that these products may improve pain and decrease synovial inflammation, although the data remains heterogenous in part due to lack of standardization in how the biologics are prepared.[6,7] For example, the white blood cell (WBC) content in PRP (leukocyte poor vs leukocyte rich PRP) has been shown to influence clinical outcomes.[8] BMAC contains progenitor cells, platelets, growth factors, and cytokines. Similar to PRP, the anti-inflammatory and immunomodulatory components of bone marrow progenitor cells may aid in tissue regeneration.[9] The growing consumer interest initially had outpaced the evidence supporting the clinical use of biologics. However, an increasing number of studies are now appearing to help understand the mechanism and clinical efficacy of biologic treatments in arthritis. In this chapter we aim to review the current literature to evaluate the outcomes of using biologics to treat knee and hip OA.

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Knee Osteoarthritis

Platelet-Rich Plasma

PRP is the most commonly investigated orthobiologic for knee OA with over 15 randomized control trials performed. Preparation of PRP is simple to perform in the clinical setting by obtaining venous blood and then processing via centrifugation. PRP can be divided into 2 subtypes: leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP). These types are based upon whether the PRP injection has a neutrophil concentration above (LR-PRP) or below (LP-PRP) the concentration of neutrophils in peripheral blood. That being said, a preparation with 2x WBC concentration is in the same category as another with 10x WBC concentration. However, this differentiation is crucial when evaluating studies on PRP injections for knee OA, as LR-PRP is associated with increased levels of inflammatory cytokines such as interleukin-1B (IL-1B) and tumor necrosis factor-α (TNF-α), which may be associated with increased inflammatory and catabolic effects.[10,11] A network meta-analysis of 9 studies comparing LR-PRP to LP-PRP, found that LP-PRP provides increased clinical benefit compared to placebo, as described by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, while LR-PRP did not.[8] Many initial studies did not elaborate on the methodology of creating their PRP injection. In a systematic review of 105 studies, Chahla et al. reported that only 16% of the included studies provided quantitative results on the composition of the PRP used.[12] Variation also exists between manufacturers for PRP preparation systems. This heterogeneity limits comparison across studies as well as reproducibility of results. In addition, PRP is often compared to a hyaluronic acid (HA) control group. However, different types and preparations of HA exist, further complicating the ability to directly compare results between PRP studies. The following sections will evaluate the evidence available for LR-PRP and LP-PRP for the treatment of knee OA.

Leukocyte Rich Platelet-Rich Plasma

Several randomized control trials have been conducted on LR-PRP and have found that although LR-PRP improved outcomes compared to baseline, it failed to show improvement compared to control injections. A clinical trial was performed by Filardo et al. on 192 patients with Kellgren-Lawrence (K-L) < III knee OA. Patients were randomized to a LR-PRP or hyaluronic (HA) injection group.[11] Each injection group received 3 weekly injections. Significant improvements in patient reported outcomes (PROs) were reported in both the LR-PRP treatment group and HA control group. In the LR-PRP group, the International Knee Documentation Committee (IKDC) improved from 52.4 ± 14.1 at baseline to 63.2 ± 16.6 at 2 months and 66.2 ± 16.7 at 12 months. Similar improvements were observed in the HA group and no significant differences on any PRO were observed between the 2 study arms. A recently published randomized control trial investigated long-term (5-year follow-up) outcomes in 192 patients randomized to receive LR-PRP or HA injection.[13] Significant improvements in the PRP group in IKDC, Euro Quality of life Visual Analog Scale (EQ-VAS), and Tegner score were observed at 2 months compared to baseline ($P < 0.0005$) and these were maintained at 2 years ($P < 0.001$ vs baseline) but decreased at final follow-up at 5 years postintervention. Similar improvement in PROs was observed in the HA group. No significant differences between these groups were observed at any time point for any PRO. An additional randomized control trial of 54 patients comparing LR-PRP to HA injection was performed by Louis et al.[14] This study found that patients who underwent either LR-PRP or HA injection had significantly improved WOMAC scores at 1, 3, and 6 months postintervention. However, no differences between the 2 groups were noted at any time point. Furthermore, the authors observed a correlation between platelet derived growth factor-AB (PDGF-AB) and transforming growth factor-β1 (TGF- β1) levels and change in WOMAC scores with lower growth factor levels associated with nonresponders (PDGF-AB: $P = 0.009$, TGF- β1: $P = 0.003$).

Leukocyte Poor Platelet-Rich Plasma

Randomized control trials have also been performed to investigate outcomes after LP-PRP. A recent randomized control trial by Huang et al. investigated the effects of LP-PRP injections compared to corticosteroid and HA injections in knee OA in 120 patients.[15] They found that WOMAC and VAS significantly improved in all 3 groups and that there were no differences between the groups at earliest follow-up (3 months). However, the LP-PRP group showed significantly lower WOMAC scores at 6, 9, and 12 months after treatment and significantly lower VAS scores at 12 months. This study suggests that LP-PRP provided clinical improvement in pain compared to HA and steroid injections. A randomized control trial on patients with K-L grade I-III knee OA was performed by Montanez-Heredia et al. and randomized 55 patients into a LP-PRP or HA injection group.[16] At 3- and 6-month follow-up, both groups had improvement in pain based on VAS and Knee Injury and Osteoarthritis Outcome Score (KOOS). No significant differences were observed between groups, although the LP-PRP group with lower K-L scores (< III) was observed to have a greater improvement in function scores ($P = 0.012$-0.04). A randomized control trial by Lin et al. randomized 87 knees into 3 groups: LP-PRP, normal saline, or HA injection.[17] They observed that all groups had significantly lower WOMAC and IKDC scores at 1 month, however, only the LP-PRP group-maintained improvement in WOAMC and IKDC scores at 12 months. Furthermore, patients in the LP-PRP group were the only patients to reach minimal clinically important differences in WOMAC scores at each time point. Finally, a randomized control trial of 99 patients performed by Cole et al. compared 3 weekly LP-PRP to HA injections.[18] Although they did not find a significant difference in the primary outcome, the WOMAC score, significant improvements were observed in VAS and IKDC scores at 24- and 52-week postintervention in the LP-PRP group compared to controls. The outcome data from these randomized control trials on LP-PRP and LR-PRP is heterogeneous but suggests that LP-PRP may provide superior clinical benefit over HA or saline. Future randomized control trials are needed to clarify the degree of knee OA

that will benefit most from PRP injection, to directly compare LP-PRP to LR-PRP injections, and to investigate how many PRP injections are needed for patients to receive the greatest clinical benefit.

Autologous Adipose and Adipose-Derived Products

Adipose treatments include adipose-derived mesenchymal cell injections and minimally manipulated autologous adipose injections, which contain mesenchymal cells, albeit at lower concentrations.[19] Autologous uncultured stromal vascular fraction (SVF), which is separated from mature adipocytes via centrifuge, has a lower percentage of viable progenitor cells, and has differing positive cell markers and distribution of cell markers than adipose-derived mesenchymal cells.[20] Adipose-derived mesenchymal cells (AD-MSCs), which are the result of culturing SVF and are more homogenous in nature, are proposed to aid in the regeneration of diseased arthritic tissue and also may provide a paracrine anti-inflammatory effect.[21] AD-MSCs have demonstrated the ability to differentiate into multiple cell types, including chondrocytes and adipocytes.[22] How this compares to the differentiation ability and effect on the progression of OA compared to bone marrow-derived mesenchymal cells remains unclear.[23-25] Due to this basic science research, promising preclinical trials, and safety and efficacy in phase 1 clinical trials, adipose injections are a potential therapeutic orthobiologic for knee OA.[26-28]

While the pathophysiology of the effect of adipose and adipose-derived products on knee OA remains elusive, multiple studies have investigated the clinical outcomes of adipose products in knee OA. A randomized control trial by Hong et al. investigated the clinical and radiographic outcomes in a cohort of 16 patients with bilateral K-L II-III OA who were randomized to receive an intra-articular 4 mL injection of autologous SVF obtained from abdominal liposuction in 1 knee and a 4 mL intra-articular injection of HA into the other knee.[29] SVF is thought to contain adipose-derived stromal cells that could provide anti-inflammatory and immunomodulatory effects. Knees that received SVF had significant improvement in pain and stiffness scores compared to baseline. In addition, the SVF group had better scores on the magnetic resonance observation of cartilage repair tissue (MOCART) score ($P < 0.01$) on follow-up MRI compared to the HA group. Despite a small cohort that may lead to the study being underpowered, this study suggests the potential of SVF treatments for treating knee OA.

Additional randomized clinical trials have investigated clinical outcomes in patients who receive autologous AD-MSC injections. In one such trial, Lu et al. compared intra-articular injection with AD-MSC from abdominal liposuction samples to HA injection.[30] Patients with K-L I-III were included in this study and a total of 53 patients were randomized to the 2 study arms. Patients who underwent the AD-MSC injection had significantly improved VAS scores at 6 ($P = 0.0486$) and 12 months ($P = 0.019$) as well as SF-12 scores at 6 ($P = 0.0161$) and 12 months ($P = 0.0097$) compared to the HA group. In addition, there was a significant increase in the volume change of cartilage based on MRI 3D spoiled gradient-recalled acquisition in the steady state (SPGR) with fat suppression sequence in the AD-MSC injection group compared to the HA group, which had the largest impact on the femoral condyle cartilage at 12 months ($P = 0.0038$). Another randomized clinical trial by Lee et al. performed in South Korea, investigated the differences in clinical outcomes between 24 patients who received either intra-articular AD-MSC injection or saline.[31] AD-MSC injections were created from culture expanded cells from adipose tissue samples, which were collected from abdominal liposuction. Patients in the AD-MSC group received 1×10^8 cells. Patients who received the AD-MSC injection had a 55% improvement in WOMAC score from baseline to 6 months follow-up ($P < 0.001$), while no significant improvement was observed in the control group. Similar findings were observed for decreases in VAS knee pain score in the AD-MSC group at 6 months compared to baseline ($P < 0.001$). In addition, range of motion significantly improved after AD-MSC injection ($P = 0.0299$), however, no significant change in K-L grade was observed at 6-month follow-up.

The effect of the number of AD-MSC injections has also been investigated. Freitag et al. studied 30 patients with K-L II-III OA who were randomized into 3 groups: single injection of AD-MSC (1×10^8 cells), 2 injections of AD-MSC (1×10^8 cells at baseline and 6 months), or a control group which maintained conservative management.[32] They found that patients who underwent either 1 or 2 injections of AD-MSC had significantly improved pain ($P < 0.05$) and WOMAC score ($P < 0.05$) compared to the control group at 12-month follow-up. In addition, they observed that 84.1% and 87.1% of the 1 and 2 injection groups reached the minimal clinically important difference, respectively. However, due to the small sample size this study is likely underpowered. Radiographic analysis was also conducted using the MRI Osteoarthritis Knee Score (MOAKs) grading scheme to investigate the progression of OA. Similar MOAK scores were observed between the 2 injection groups and the control group at 12-month follow-up; however, the 2 injection group had fewer patients with worsening articular cartilage pathology MOAK score at final follow-up (control: 67%, 1 injection: 30%, 2 injection: 11%) ($P = 0.043$).

While the aforementioned studies suggest a clinical benefit of AD-MSCs injections, these studies have numerous limitations. First, the literature has few randomized control trials on AD-MSC products, and all of the described studies have relatively small sample sizes. In addition, the results of many of these studies is difficult to interpret due to the heterogeneity of the processing and variability of the injection components, as some injections are composed of cultured mesenchymal cells while others are injections of SVF. In addition, the reported randomized control trials were based on 2 separate products, SVF and AD-MSC, and it remains unknown what differences, if any, these preparations may have on clinical outcomes. Furthermore, AD-MSCs are currently not available for use in the United States.

In addition to these early randomized control trials, multiple clinical trials have been proposed to determine the clinical effects of AD-MSCs. An upcoming study at the University of Southern California will investigate the clinical outcomes in patients with K-L II-III knee OA.[33] Fifty-four patients will be randomized to either an intra-articular injection of autologous adipose tissue or HA. Outcome measures will include patient reported outcomes (WOMAC, PROMIS) and synovial fluid assessment (analyzing IL-1β, IL-6, IL-8, TNFα, C-terminal telopeptides of Type I collagen, and C-telopeptide of Type II collagen). One major limitation of this study is the lack of patient blinding. Another proposed study to be performed at Huazhong University in China, involves collection of adipose tissue, expansion of the adipose sample, and cell culturing.[34] Subsequently, flow cytometry will be performed to detect the mesenchymal progenitor cells in the sample. A cohort of 66 patients with K-L II-III knee OA will be randomized to either receive an injection of AD-MSC with low-intensity pulsed ultrasound treatment (LIPUS), AD-MSC with sham LIPUS, or a saline injection with LIPUS treatment. Clinical outcome will be assessed with patient surveys (VAS, WOMAC) and MRI analysis.

Bone Marrow Aspirate Concentrate

BMAC contains mesenchymal progenitor cells as well as growth factors that may provide anti-inflammatory effects in the setting OA. Specifically, analysis of BMAC content showed the presence of interleukin-1 receptor antagonist (IL-1ra), PDGF, IL-8, and vascular endothelial growth factor.[35] In addition, the mesenchymal cells in BMAC may provide paracrine anti-inflammatory and antiapoptotic effects.[36] However, the composition of BMAC has been shown to vary between studies. A systematic review by Piuzzi et al. reported that out of 46 studies evaluating BMAC, only 30% provided qualitative information on BMAC content.[37]

A single-blind randomized control trial on the efficacy of BMAC was performed by Shapiro et al.[38] In this trial a total of 25 patients with bilateral knee OA (K-L I-III) were included in this study and each joint was randomized to a BMAC combined with platelet-poor plasma injection or saline injection. Patient outcomes were obtained with the Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain (ICOAP) and VAS questionnaires at 1-week, 3-, and 6-month follow-up. There were significant improvements in constant pain, intermittent pain, total pain (all of which are ICOAP sub-scores) and VAS pain at each time point for both the BMAC and placebo treated knees. No significant differences were observed between the treatment and placebo group for any pain measurement at any time point. In addition, activity level was measured at each follow-up time point and while activity level significantly improved in both the treatment and placebo knees, there were no differences observed between these groups. While this study showed that the BMAC injections were well tolerated by patients, it failed to show any significant benefit when compared to placebo. This cohort of patients was then followed at 12-month follow-up in an additional study by Shapiro et al.[39] This additional follow-up included ICOAP and VAS questionnaires, algometer-assessed pain scores, and quantitative MRI. Significant improvements in pain from baseline were maintained by both the BMAC and placebo groups, and no significant differences were observed between these groups ($P > 0.23$). Similarly, activity level at 12-month follow-up did not significantly differ between the 2 groups ($P = 0.52$). In addition, 6-month MRI data showed no significant changes in T2 quantitative MRI values compared to baseline for both the BMAC and placebo knees ($P > 0.07$), and no significant differences between these groups were observed ($P > 0.10$). The study authors concluded that BMAC failed to show superiority over saline injection. Additional larger randomized control trials are needed to confirm these early findings.

An additional cohort study compared patients with knee OA (K-L I-IV) who underwent microfragmented adipose tissue injection (48 knees) versus BMAC (58 knees).[40] At a mean follow-up of 1.80 ± 0.88 and 1.09 ± 0.49 years for the BMAC and adipose groups, respectively, both groups had significantly improved VAS pain scores, KOOS subscores, and pain/discomfort, mobility, and composite Emory quality of life scores. No differences were observed between the 2 treatment groups. The main limitation of this study was its nonrandomized nature and its lack of comparison to a control group. Therefore, while this study suggests positive findings after both adipose and BMAC injections, it is unclear how these treatments compare to a saline, HA, or corticosteroid control group.

There are currently ongoing clinical trials investigating the efficacy of BMAC in knee OA. One such report provided preliminary results for a study that compared injections of PRP and BMAC to HA controls (NCT02958267). Thirty-two patients with K-L I-III knee OA were randomized to injection with both BMAC and PRP or injection with HA as the control group. Although no statistical analysis was provided, preliminary data suggested that injection with both BMAC and PRP improved KOOS subscores at 3, 6, or 12-month postintervention. In addition, the BMAC plus PRP groups had larger decreases in VAS pain at 6 months (BMAC + PRP: -2.45, HA: -1.77) and 12 months (BMAC + PRP: -3.13, HA: -1.56). An additional recently completed clinical trial randomized 180 patients to LR-PRP, BMAC, or an HA control group (NCT03825133). The main outcomes of the study were changes in KOOS, WOMAC, IKDC, SF-36, and VAS pain at 1, 3, 6, 9, and 12 months, however preliminary results have not yet been published.

Bone Marrow and Adipose Derived Culture Expanded Mesenchymal Cell Allogenic Products

In addition to the previously described BMAC and adipose-derived mesenchymal autogenic cell injections, a few early phase 1 and phase 2 trials have been performed on bone marrow and adipose-derived culture expanded mesenchymal cell allogenic injections.

A study by Emadedin et al. randomized 43 patients (K-L II-IV) to either the bone marrow-derived cultured mesenchymal cell (MSC) group (4×10^7 cells) or a saline injection for the treatment of knee OA.[41] At 6-month follow-up, significant improvements were observed in WOMAC total score, WOMAC pain, and physical function subscales ($P = 0.001$ to $P = 0.04$) in the group receiving bone marrow-derived MSCs, compared to the placebo. Another phase 2 control trial on bone marrow-derived MSCs was performed by Gupta et al.[42] Sixty patients were randomized to ascending doses of MSCs or a placebo. Patients in the 25 million cell dose group trended toward having significant improvements on pain and activity outcomes at 1, 3, 6, and 12 months postoperative, however these did not reach significance when compared to placebo. Furthermore, the higher dosage groups (50, 75, and 100 million MSCs) had higher rates of adverse events such as swelling and knee pain.

Kuah et al. performed a pilot phase 2 randomized control trial investigating the safety and efficacy of an adipose-derived culture expanded allogenic MSC product in patients with K-L I-III knee OA.[43] Twenty patients were randomized to 3 groups: 3.9 million MSCs, 6.7 million MSCs, or a cell culture media and cryopreservative placebo. All included patients had an adverse reaction during the 12-month follow-up period, most commonly pain or effusion. There was a significant improvement in VAS scores from baseline at all-time points (1, 3, 6, 9, and 12 months) for both MSC groups (3.9: $P = 0.002$, 6.7: $P = 0.018$). Similar trends were observed for WOMAC pain and WOMAC stiffness and physical function scores. These early clinical studies suggest a benefit from both bone-marrow derived and adipose-derived culture expanded allogenic MSC injections, however understanding an appropriate concentration of MSCs is important to minimize adverse effects of these injections.

Amniotic and Umbilical Cord-Derived Products

Amniotic products such as amniotic fluid, amniotic membrane, and umbilical cord products have been proposed as possible treatments for patients with knee OA. These products are thought to provide immunoregulation through inhibition of cytokines such as IL-1 and IL-6, promotion of IL-10, and antimicrobial effects.[44,45]

Few randomized control trials have been conducted utilizing these compounds. One study by Matas et al. evaluated clinical outcomes in 29 patients with K-L II-III knee OA who were randomized to 3 groups: 1 umbilical cord-derived mesenchymal cells (UC-MCS) intra-articular injection (20×10^6 cells) at baseline, 2 UC-MCS intra-articular injections (1 at baseline and 1 at 6 months) or 2 intra-articular injections of hyaluronic acid (one at baseline and 1 at 6 months).[46] No significant differences in adverse events was observed between groups (eg, pain and effusion). There were no significant differences in patient reported outcome measures at 6 months, but the 2 UC-MCS injection group had significantly improved pain (VAS pain [$P = 0.03$] and WOMAC pain [$P = 0.04$]) compared to the HA group at 1-year follow-up. No MRI differences were observed at 6 months or 1-year. This small study suggests preliminary safety and efficacy of UC-MCS intra-articular injection but suggests that 2 injections may be necessary to observe a clinical effect.

In contrast to UC-MCS, a randomized controlled single-blind trial by Farr et al. investigated the clinical effect of amniotic suspension allograft (ASA) in patients with K-L II-III knee OA.[47] In this multicenter study, 200 patients were randomized to ASA intra-articular injection, HA intra-articular injection, or saline intra-articular injection. Significant improvements were observed at 3 and 6 months for KOOS Pain, activities of daily living (ADL), and symptom subscores and at 6 months for all subscores in the ASA group compared to the HA group. In addition, significant improvements were observed in KOOS symptoms at 3 months and 6 months and in KOOS pain and ADL subscores at 6 months when comparing ASA to saline injection. VAS pain scores significantly decreased with ASA injection at 3 and 6 months. These findings suggest improvement with ASA at short term follow-up.

Future randomized controlled trials that will investigate the efficacy of umbilical cord and amniotic products have been proposed. A phase 2B randomized control trial on the efficacy of micronized dehydrated human amnion chorion membrane injection compared to a saline placebo is currently enrolling subjects (NCT03166865). This study will enroll an estimated 318 patients across the United States at 16 sites. An additional study that is currently enrolling will investigate multiple biologic agents including umbilical cord, SVF, and BMAC with corticosteroid injection as the control (NCT03818737). This study will enroll 480 patients at 5 different institutions. This study could help providers understand unique benefits from each of these biologics.

Use of Biologics for Hip Osteoarthritis

Compared to the knee, there is less data on the use of biologics to treat symptomatic primary hip OA. There are a number of clinical trials that are in progress, including a randomized controlled trial in Nova Scotia investigating the effect of combined BMAC and PRP intra-articular injection compared to control local anesthetic with cortisone injection in patients with primary hip OA (K-L I-II) (NCT03410355). Additionally, a clinical trial in Iran is investigating the efficacy and safety of autologous bone marrow-derived MSCs in patients with end-stage OA who are candidates for total hip arthroplasty (NCT01499056). It has been postulated that biologic injections could serve as a treatment that provides durable pain relief, however currently there is a lack of high-quality data supporting biologic use in primary hip OA.

Platelet-Rich Plasma

Three studies have been reported to assess the use of PRP in patients with symptomatic hip OA. However, it was not

specified if leukocyte-rich or leukocyte-poor PRP was used in these studies. A randomized-controlled trial was performed looking at 100 patients with chronic, unilateral, symptomatic hip OA.[48] Patients were randomly assigned to receive 3 biweekly intra-articular injections of either 5 mL hyaluronic acid or PRP. They were then evaluated at baseline, 1, 3, 6, and 12-month follow-up using the Harris hip score (HHS) and VAS outcome measures. Overall significant clinical improvement in both HHS and VAS were observed at 1 and 3 months, however outcome scores deteriorated between 6 and 12 months. Outcome scores at final follow-up were still significantly higher compared to baseline in both groups ($P < 0.005$). The authors concluded that PRP is efficacious in treating hip OA but its effect is limited to several months.

A second randomized controlled trial was performed on 111 patients to compare the efficacy of PRP, hyaluronic acid (HA), or PRP and HA in patients with hip OA.[49] Patients received 3 intra-articular injections 1-week apart during outpatient surgery. The types of surgical procedures performed were not specified. Patients were then assessed at 2, 6, and 12 months after treatment. The primary outcome was pain as measured by VAS, and secondary outcomes included HHS, WOMAC, and concentration of growth factors in PRP correlated with clinical outcomes. The PRP-only group demonstrated lower VAS pain scores at all follow-up times and significantly greater WOMAC scores at the 2- and 6-month follow-up periods. The addition of PRP and HA did not lead to a significant improvement in pain outcomes.

Additionally, a prospective case series was performed on 40 patients with unilateral severe hip OA.[50] Each patient was given 1 intra-articular injection of PRP weekly for 3 weeks. Baseline pain was reported as mild (approximately 2/10 on VAS). The primary end point was meaningful pain relief, defined as greater than or equal to 30% reduction of pain intensity from baseline as evaluated by the WOMAC subscale at 6-7 week and 6-month follow-up. The HHS score and VAS were implemented to verify the primary end point. Regarding pain, there was a significant reduction in WOMAC scores over 6-7 week and 6-month follow-up periods compared to baseline. This was corroborated by reduction in VAS and HHS scores. However, there were no significant changes in pain scores between the 6-7 week follow-up and 6-month follow-up period. Physical function was also evaluated using the WOMAC subscale for disability. At both timepoints, disability was significantly reduced. While these early studies on PRP in hip OA suggest clinical benefit, future randomized control trials are needed to further validate these findings.

Bone Marrow Aspirate Concentrate

Three studies have investigated the effects of bone marrow aspirate concentrate (BMAC) injections in hip OA. A retrospective case series was performed to analyze the data of 216 hips that received a single 4 mL injection of BMAC for hip OA.[51] Investigators looked at adverse events, subjective percentage improvement, Oxford hip scores (OHS), and numeric pain scale (NPS) at baseline, 1, 3, 6, and 12-month follow-up. Twelve adverse events were reported; however, all were mild, including pain/swelling and 2 skin events (not specified). The mean reported subjective percent improvement was 30.2% overall and mean OHS score at final follow-up was 6.4 points greater than baseline. NPS scores decreased from 4.5 to 3.3. They found that patients less than 55 years of age were more likely to report improvement of at least 4.9 points on OHS and greater than 50% improvement on the subjective percentage scale compared to patients greater than 55 years. This finding is consistent with literature describing superior outcomes for surgical treatment of chronic hip pathologies in younger patient populations, such as with arthroscopic labral debridement.[52]

A second prospective case series evaluated 15 hips and 10 knees treated with one 12 mL intra-articular bone marrow concentrate injection for early OA.[53] Patients completed the WOMAC scale at baseline, 6, 12, 18, and 24-month postinjection. This study found that WOMAC scores significantly improved from baseline to final follow-up. Satisfaction rate (assessed as a yes or no question regarding satisfaction with procedure outcomes) was 73.3% for all patients. Furthermore, the minimal clinically important difference threshold was calculated to be 9.15, and this was reached by 64% of patients in the study. Unfortunately, while these results show promise for the use of MSC in both hip and knee OA, the were no sub-analyses performed to delineate findings between hip and knee OA patients.

Finally, a case report described 4 patients with hip arthritis who were given 4 BMAC injections over a range of 42-146 days.[54] Each patient was noted to have severe hip OA. Functionality was assessed in each patient using 10 of 20 activities from the Lower Extremity Functional Scale. Additionally, resting and active pain were quantified through a numerical scale, and overall improvement was identified through a percentage scale. Patient 1 was given 4 BMAC injections over the course of 49 days. They reported 60% overall improvement after the final injection, and functionality score increased from 33/40 at baseline to 37/40. Patient 2, having received 4 BMAC injections over 42 days, reported 80% total overall improvement after the first treatment alone, and at final follow-up reported a functionality score of 37 compared to 28 at baseline. Patient 3 was given 4 BMAC injections over 54 days and reported baseline scores of 4/10 (resting pain), 5/10 (active pain), and 33/40 (functionality score). After the final injection, the patient's scores improved to 1/10 (resting pain), 2/10 (active pain), and 37/40 (functionality score). Finally, Patient 4 had baseline scores of 2/10 (resting pain), 5/10 (active pain), and 17/40 (functionality score). This patient was given 4 BMAC injections over 146 days, reporting 70% overall improvement 40 days after the final injection. Furthermore, functionality score improved to 30/40 and both resting and active pain decreased to 1/10, respectively. Overall, all of the patients experienced improved functionality and decreased pain compared with baseline scores. However, short follow-up and small sample size in this study limit broader conclusions regarding the efficacy of BMAC injection for hip OA.

Mesenchymal Cell Products

Only 2 studies have investigated the use of MSCs in alleviating symptomatic hip OA. In a prospective case series, 10 patients with unilateral or bilateral hip OA were given intra-articular injections with autologous bone-marrow derived autologous MSCs in 3 weekly doses (60×10^6 cells).[50] They subsequently looked at radiographic Tonnis score, VAS, WOMAC, HHS, and Vail sport test clinical outcome scores at baseline and final follow-up (range 16-40 months after final injection). There was significant improvement in postinjection VAS and HHS scores. WOMAC and Vail sport test scores trended towards improvement, however, they were not significantly different from baseline. Radiographic Tonnis scores after cell injection remained stable for 9 or 10 patients.

In a case series of 18 patients with hip, knee, or ankle OA, patients were evaluated after 1 intra-articular injection of approximately 5×10^5 cells/kg body weight of autologous bone marrow-derived MSCs.[52] Patients were followed at 2, 6, 12, and 30-month postinjection and completed VAS and WOMAC outcome scores at all follow-up timepoints. An MRI was obtained for all patients at 6- and 12-month postinjection. No adverse events were reported at final follow-up. Walking distance, VAS, and WOMAC scores all improved from baseline to final follow-up. In 3 of 5 hip OA patients, articular cartilage repair was qualitatively evaluated and visualized with MRI. Limitations of this study include a small sample size and lack of randomization with a control group.

Conclusion

Over the last decade, there has been a significant increase in research on orthobiologics as a potential treatment for OA. Many randomized control trials have been performed evaluating PRP, BMAC, adipose, and mesenchymal stromal cell products for knee OA. While heterogeneous in nature, these studies suggest a possible clinical benefit for orthobiologic injections compared to HA, corticosteroid, or placebo for treatment of knee OA. Though clinical data is still evolving, the orthobiologic with the strongest evidence for the treatment of knee OA is LP-PRP. Much less research has been conducted in patients with hip OA and thus conclusions cannot yet be drawn on the efficacy of orthobiologics in this setting. Future studies are needed for both knee and hip OA to clarify how best to provide these biologic treatments and which patients will clinically benefit.

Conflict of interest

Hailey P. Huddleston BS, Bhargavi Maheshwer BS, Stephanie E. Wong MD—None to report.

Jorge Chahla MD PhD:

American Orthopaedic Society for Sports Medicine: Board or committee member

Arthrex, Inc: Paid consultant

Arthroscopy Association of North America: Board or committee member

CONMED Linvatec: Paid consultant

International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine: Board or committee member

Ossur: Paid consultant

Smith & Nephew: Paid consultant.

Brian J. Cole MD MBA:

Aesculap/B.Braun: Research support

American Journal of Orthopedics: Editorial or governing board

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Arthroscopy Association of North America: Board or committee member

Athletico: Other financial or material support

Bandgrip Inc: Stock or stock Options

Cartilage: Editorial or governing board

Elsevier Publishing: IP royalties

International Cartilage Repair Society: Board or committee member

Journal of Shoulder and Elbow Surgery: Editor only: Editorial or governing board

Journal of the American Academy of Orthopaedic Surgeons: Editor only: Editorial or governing board

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Adam B. Yanke MD PhD:

Arthrex, Inc: Research support

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Olympus: Paid consultant

Organogenesis: Research support

Patient IQ: Paid consultant

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