Review Article

Biologics in hip preservation

Leandro Ejnisman[1,2], Marc R. Safran[1]

[1]Department of Orthopaedic Surgery, Stanford University, Redwood City, California, USA; [2]Instituto de Ortopedia e Traumatologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Contributions: (I) Conception and design: All authors; (II) Administrative support: MR Safran; (III) Provision of study materials or patients: MR Safran; (IV) Collection and assembly of data: L Ejnisman; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Marc R. Safran. 450 Broadway, Redwood City, CA 94063, USA. Email: msafran@stanford.edu.

Abstract: The identification and understanding of non-arthritic hip conditions has grown rapidly in the last two decades. New pathologies have been described including femoroacetabular impingement, hip microinstability, deep gluteal syndrome and greater trochanteric pain syndrome. Even though the treatment of these disorders has yielded good clinical results, there is always a desire to improve outcomes and the speed in which they are attained. Biologic therapies have emerged as a new or adjunctive modality to improve clinical outcomes of hip pathology, as well as, a potential way to accelerate healing times and return to play. This review focuses on the use of current biologic therapies, specifically platelet-rich plasma, hyaluronic acid and stem cells, in the treatment of various hip pathologies.

Keywords: Hip; regenerative therapy; bone marrow aspirate concentrate (BMAC); platelet-rich plasma (PRP); hyaluronic acid (HA); stem cells

Received: 29 March 2018; Accepted: 25 May 2018; Published: 15 June 2018.

doi: 10.21037/aoj.2018.05.08

View this article at: http://dx.doi.org/10.21037/aoj.2018.05.08

Introduction

Hip preservation surgery has seen tremendous advances in the last two decades. The understanding of hip biomechanics has evolved, and new concepts have been developed. Femoroacetabular impingement (FAI) was described in the English literature in 1999, and is now considered one of the main causes of hip pain in the athletic population, and is a potentially major cause of premature hip osteoarthritis (OA) in the young population (1,2). Labral pathology and chondral damage, which occur mainly as a result of FAI, was initially managed primarily with open techniques, but can now be treated arthroscopically, a less invasive surgical procedure. Hip microinstability has also been described as a cause of intra-articular disease, adding complexity to the treatment of patients with hip complaints (3).

In addition to new understanding of the pathogenesis of intra-articular pathology, extra-articular causes of hip pain have also been studied with renewed interest, identifying previously unrecognized causes and further refining diagnoses and treatments. Patients presenting with lateral hip pain, which was simply labeled as having trochanteric bursitis, now may represent one of a number of diagnoses, and are now grouped under the category of greater trochanteric pain syndrome (4). Likewise, patients presenting with gluteal pain, which used to be called piriformis syndrome, now are understood to have many different potential causes of pain, and have now been grouped under the category of deep gluteal syndrome (5). Understanding these complex concepts is of paramount importance to the physician working with patients and athletes with hip disease.

Treatment of these multitudes of pathologies and syndromes around the hip yields excellent clinical results, both from a conservative and surgical perspective. However, our patients push us to provide better outcomes, less invasive treatments, and quicker recovery, and not just in our athletic populations. There has been a recent explosion of interest in the role of biologics in the treatment of

various musculoskeletal maladies. These biologics provide some hope to improve clinical outcomes in the treatment of hip lesions (with or without surgery), as well as a potential way to accelerate healing times and return to play. Biologics are substances that can be used as a stand-alone treatment or as an augmentation to other treatment modalities, mostly in injectable forms. The most common biologics used in orthopedics are platelet-rich plasma (PRP), hyaluronic acid (HA) and stem cells. The goal of this article is to review these main biologics, and their potential role in the management of hip pain.

PRP

PRP is a volume of autologous plasma that exhibits a platelet concentration above baseline levels and is rich in growth factors (6-8). Two methods have been described to prepare PRP: centrifugation (8) and apheresis (9). Centrifugation produces PRP in a less expensive and more practical manner, however apheresis yields a higher platelet concentration (10). Unfortunately, there is wide variation in the reported protocols for standardization and preparation of PRP, and lack of characterization of tested products in most articles on this topic. First, PRP may differ in the actual platelet count, having concentrations ranging from 2.5 to 9 times the baseline concentration (11). The biological difference among individuals and hematocrit variability can contribute to the observed variation in PRP content and quality, as well as, the cellular responses to autologous blood products (12). Secondly, PRP may or may not be activated. The process of activation leads to: (I) degranulation of platelets to release growth-factors, and (II) fibrinogen cleavage to initiate matrix formation, a clotting process which allows the formation of a platelet gel (13). Each type of activator may produce varying effects and significantly influence growth factor kinetics. Most commonly used activators are thrombin and calcium chloride. Some physicians prefer to inject PRP without activators, relying on the spontaneous platelet activation occurring after exposure to the native collagen present in the connective tissues. And finally, PRP preparations differ on the presence and concentration of leukocytes, which is related to the preparation system used (11). There are two main methods: buffy coat-based systems, which yield PRP with higher concentration of leukocytes, and plasma-based systems, which yield lower concentrations of leukocytes. The former preparation is known as leukocyte-rich PRP, while the latter is known as leukocyte-poor PRP. There is an ongoing debate regarding which concentration of leukocytes is ideal, however there is evidence that the concentration should be matched to the desired result. For example, leukocyte-rich PRP may increase inflammation and catabolic pathways, whereas leukocyte-poor PRP may decrease inflammation and anabolic pathways (13,14).

As a result of the variability among PRP preparations, DeLong *et al.* described a classification system, named PAW (pneumonic for Platelets, Activation, and White cells), to standardize reporting of PRP preparations, making comparisons of studies more practical (15). This classification is based on the absolute number of platelets, the method of platelet activation, and the presence/absence of white cells. Another classification was described by Mishra *et al.* (16). According to this classification PRP type 1 presents white blood cells above baseline and no activation, type 2 presents white blood cells above baseline and the PRP is activated, type 3 presents no white blood cells and no activation, and type 4 presents no white blood cells and the PRP is activated. A subtype is also added: subtype A presents an increase of 5 times the blood concentration of platelets, whereas subtype B presents an increase of less than 5 times. PRP has been described for various indications in orthopaedics such as rotator cuff repair (17), knee OA (18), lateral epicondylitis (19), plantar fasciitis (20), in addition to many other musculoskeletal conditions.

PRP injections have been used as an adjunct with conservative treatment of multiple chronic tendinopathies, as well as, acute tendon/muscle lesions about the hip. Typically, injections are performed under ultrasound guidance to ensure precise delivery to the correct location. A recent randomized controlled trial (RCT) investigated the effect of a single PRP injection with a rehabilitation program compared to rehabilitation program alone in 28 patients with acute grade 2 hamstring muscle injury (mean age 21 years) (21). PRP was classified as P4-x-A according to the PAW classification, meaning platelet concentration was above 1,250,000, with no activation, and total white blood cell count was above baseline. The authors described a faster return to play in the PRP group (42.5 *vs.* 26.7 days). Patients in the PRP group also demonstrated lower pain severity scores. Dallaudière *et al.* (22) published a retrospective case series of 408 PRP injections for tendinopathy of multiple tendons throughout the body, including 40 patients with hamstring or adductor longus tendinopathy. PRP contained 900,000 platelets per mm^3, 200 leukocytes per mm^3, and was not activated. WOMAC scores improved from 35.9 to 12.9, and pain scores improved from 5.8 to 2.3 after 6 weeks

of PRP injections. Unfortunately, the results were grouped as lower and upper extremities, so it is impossible to discern the specific outcomes of PRP injections on hamstrings and adductor tendinopathy in this study.

PRP has also been described in the treatment of gluteus medius tendinopathy with promising results (23,24). Mautner *et al.* (24) reported the clinical outcomes of non-activated PRP for chronic tendinopathy at multiple anatomical sites in 180 patients (mean age, 48±13 years) including 16 gluteus medius tendon injections. Based on a retrospective survey at 15±6 months from time of last injection, pain scores improved from 7.0±1.8 to 1.8±2.0 on the visual analog scale (VAS); 83% of patients reported moderate-to-complete resolution of symptoms with a single injection, 82% reported the same after two injections, and 76% reported the same after three or more injections. The authors determined the need for multiple injections depending on the subjective improvement after the first injection. This study also reported grouped results including all anatomical sites, demonstrating the need for future investigation of the specific clinical results of PRP injections for each tendon in the hip region.

Treatment of hip OA with PRP has also been studied (25,26). Sánchez *et al.* (25) reported a series of 40 arthritic hip patients treated with three serial injections of PRP. The PRP demonstrated a moderate enrichment in platelets (1.4-fold in the peripheral blood), no white blood cells and was activated by calcium chloride. Eight mL of PRP was injected under ultrasound guidance into the hip joint. A clinically relevant reduction of pain, measured by the VAS and the Harris Hip Score (HHS), was observed in 57.5% of patients. Sixteen (40%) of these patients were classified as excellent responders and demonstrated an early reduction of pain at 6–7 weeks, which was sustained at 6 months. A recent systematic review explored the treatment results of PRP for hip and knee OA; 29 articles were found (26) examined knee OA, and 3 examined hip OA) (27). Overall, PRP was found beneficial for the treatment of hip and knee OA. However, when analyzing the results of this review, there was a clear lack of uniformity in treatment protocols with respect to the type of PRP preparation, administration, and dosing. The authors emphasized that no correlation was found between outcomes and any specific PRP characteristic and/or administration protocol. In the knee OA studies, a trend toward better results was found in young patients with early arthritic change. In the hip, Battaglia *et al.* (28) reported a case series of 20 patients presenting with unilateral hip OA, who underwent three ultrasound-guided PRP injections. The make-up of the PRP, with regard to white blood cell presence, activation, and concentrations of platelets was not reported. HHS and WOMAC scores improved after 12-month follow-up (from 49±7 and 43±10 to 58±15 and 54±17, respectively). In contrast to knee OA, this study found no correlation between sex, age, BMI, OA grade and clinical outcomes. The same authors published a RCT comparing PRP and HA in the treatment of unilateral hip OA (29). The number of platelets in the PRP preparation increased on average 600% when compared with whole blood and calcium chloride was added to activate the platelets. All patients underwent three consecutive (once every 2 weeks) intra-articular ultrasound guided injections of 5 mL of PRP or HA. Both groups demonstrated improvements in HHS and VAS, with neither demonstrating superiority over the other. The best results were demonstrated between 1 and 3 months of follow-up, followed by a slightly progressive worsening from 6 to 12 follow-up, although the final scores remained better compared with baseline. Results were not influenced by age, gender, body mass index or degree of OA.

Dallari *et al.* (30) in a RCT investigated if the combination of HA and PRP was more effective than PRP or HA alone. A total of 111 patients were randomized to three weekly injections of either PRP, HA, or PRP plus HA. The PRP was activated, but the number of platelets and white blood cells were not reported. The three groups demonstrated improved outcomes as measured by VAS, WOMAC and HHS. At 6-month follow-up, the mean VAS score (0–100 points) was 21 in the PRP group, 35 in the PRP and HA group, and 44 in the HA group. At the latest follow-up (12 months postoperatively), almost all of the patients showed a decrease in clinical outcomes, with the least reduction seen in the PRP group. The authors concluded that intra-articular PRP injections offer a significant clinical improvement in patients with hip OA, and the addition of HA did not lead to a significant improvement in pain symptoms.

There are anecdotal reports of PRP use in the conservative management of FAI and labral tears. Kraeutler *et al.* (23) describe the use of PRP injections in high-level athletes who presented with acute hip inflammation due to intra-articular pathology such as FAI-induced labral tears or ligamentum teres strains. The authors suggested PRP improves inflammatory symptoms and enables a quick return to play without the possible negative effects of steroids. Afterwards, athletes can proceed to definitive

surgery during the offseason. However, objective measures of outcomes, and the number and types of athletes that were treated were not reported.

PRP has also been described in conjunction with hip arthroscopy (14). At the end of the arthroscopic procedure, a cannula was placed in the peripheral compartment, and the arthroscopic fluid was drained from the joint. PRP was then injected into the osteoplasty site, repaired hip joint capsule and soft tissues deep to the arthroscopic portals. The PRP used with this technique demonstrated a platelet count greater than or equal to 1,000/μL and an overall leukocyte count less than or equal to 1,000/μL. A total of 25–30 mL of PRP was injected, approximately half of the preparation was delivered inactivated, and half was delivered activated by calcium chloride. The authors described their technique in detail, however no clinical results were reported. Redmond *et al.* (31) published a prospective comparative study of PRP versus bupivacaine injection after hip arthroscopy for the treatment of labral tears. PRP was injected in 91 patients (study group), and bupivacaine was injected in 180 patients (control group). The PRP contained 2 to 3 times the platelet level of whole blood, minimal to no white blood cells and was not activated. The two-year modified HHS (mHHS) was slightly lower in the study group (78.6) when compared with the control group (82.6). While this outcome reached statistical significance, it is unclear whether this difference was clinically significant. Other clinical scores demonstrated no difference, and no significant difference was found between groups for conversion to total hip arthroplasty or revision surgery. The authors concluded PRP injection does not appear to improve the clinical results of patients undergoing hip arthroscopy for labral treatment. LaFrance *et al.* (32) also studied the effects of PRP after hip arthroscopy. Concentration of platelets, presence of white blood cells and activation of PRP are not documented. Twenty patients received a 5-mL PRP injection after labral repair and osteoplasty of the femoral neck, and 15 patients in the control group received a saline injection. There was no significant difference in outcome scores between the two groups after one year. The PRP group presented a statistically lower incidence of ecchymosis on the lateral thigh (4/20 *vs.* 10/15).

HA

The concept of viscosupplementation was developed based on the finding that the visco-elastic properties characterizing the healthy joint are altered in OA (33). HA is believed to be chondroprotective, increase proteoglycan and glycosaminoglycan synthesis, and act as an anti-inflammatory (34). These effects are thought to be caused by HA binding to cluster of differentiation 44 (CD44) receptors. There are a large number of commercially available HA products with differences in derivation and molecular weight from manufacturing processes (35). A recent meta-analysis of 68 RCTs concluded that HA products with molecular weight ≥3,000 kDa and those derived from biological fermentation relate to superior efficacy and safety (36). The use of HA in the treatment of OA started in the knee, and numerous studies have demonstrated good clinical results with this approach. A meta-analysis of RCTs comparing HA with saline control injections including 29 studies and 4,866 patients found HA to be safe and efficacious in patients with symptomatic knee OA (37). HA yielded significant treatment effects between 4 and 26 weeks for knee pain and function compared to both pretreatment values and sham injections with saline. Limitations of this meta-analysis was the significant heterogeneity in efficacy outcomes among included studies and smaller treatment effects seen in higher quality trials. The authors also disclosed that financial support for the study was provided by a viscosupplement manufacturer.

Eymard *et al.* (38) investigated the predictors of response to HA in hip OA. The authors found that joint space narrowing (JSN) negatively correlated with response to viscosupplementation, demonstrating HA may be more effective in early cases of OA. Migliore *et al.* (39) in a double-blind RCT compared HA with mepivacaine administered twice for 42 patients with hip OA. Patients in the HA group exhibited a significantly reduced Lequesne algofunctional index score 3 and 6 months after treatment, and significantly reduced VAS pain scores 3 and 6 months after treatment compared with the local anesthetic group.

HA injection has also been used in the treatment of FAI. Abate *et al.* (40) performed a prospective trial with 20 patients with FAI (23 hips). HA was injected at baseline and after 40 days, the same dosing schedule was repeated after 6 months. Improvements in pain scores, Lequesne Index, HHS, and anti-inflammatory medication consumption were observed for 12 months.

Additionally, HA injection has been used as a supplement at the conclusion of knee arthroscopy with the goal of reducing joint stress after the surgical procedure, controlling pain and swelling, and promoting faster functional recovery for patients (41). However, the results

of HA injection after knee arthroscopy were inconclusive. There is evidence that HA injection after anterior cruciate ligament reconstruction yields improved pain control, swelling and active range of motion in the early recovery phase (42,43). It has also been demonstrated to reduce pain in the short-term recovery period after arthroscopic meniscectomy (44). On the other hand, Filardo *et al.* (41) found no significant clinical benefits of HA injection after arthroscopic meniscectomy, and Baker *et al.* (45) also found no benefit of HA injection after knee arthroscopy for meniscal tears and osteochondral defects. Doral *et al.* (46) compared clinical outcomes in microfracture of the talus between patients that underwent HA injection with those without injection after ankle arthroscopy. Clinical scores were better in the injection group after 2 years of follow-up. Hip arthroscopy lacks specific studies regarding the use of HA, albeit authors have reported its use in association with PRP at the end of arthroscopic procedures (14).

Stem cells

The application of undifferentiated cells in orthopaedics has gained attention in the past decade as a biological solution to multiple conditions. Stem cells by definition are undifferentiated cells that have 4 main characteristics: (I) mobilization during angiogenesis; (II) differentiation into specialized cell types; (III) proliferation and regeneration, and (IV) release of immune regulators and growth factors (47,48). Stems cells are divided into embryonic stem cells, induced pluripotent stem cells and mesenchymal stem cells. Mesenchymal stem cells are the most common type used in orthopedics because they are easier to harvest and have less ethical concerns when compared to embryonic stem cells. Different countries have tried to regulate the use of stem cells, and consequently, they each have developed their own regulations, which can vary substantially. For example, bone marrow aspirate concentrate (BMAC) and adipose-derived stem cells, the most common sources of stem cells used in the United States (US), are classified by the US Food and Drug Administration (FDA) as a Human Cell and Tissue Product under the "361 product" (49). Consequently, stem cell treatment must meet each of the following four criteria: (I) minimally manipulated (e.g., centrifugation); (II) intended for homologous use only; (III) not involving a combination of cells or tissues with another article (e.g. drugs); (IV) either "having no systemic effect or metabolic effect" or "being for autologous use, allogenic use in first- or second-degree blood relative, or reproductive use". A "361 product" is not subject to premarket review and approval requirement. In the US, to apply mesenchymal stem cells with culture expansion in humans, the details of the entire procedure for cell preparation has to be approved by the FDA or other governmental regulatory authority for use in clinical trials (50). As such, stem cell expansion is not utilized in the US. Other countries have less strict regulation regarding culture expansion, which facilitates its clinical use.

According to recent research, the beneficial effects of mesenchymal cells are a result of the release of a cocktail of trophic and immunomodulatory factors, rather than actively participating in tissue repair, thus working as "medicinal signaling cells" (51,52). Mesenchymal stem cells can be derived from various sources including bone marrow, periosteum, adipose tissue, and muscle (53-55).

BMAC is one of the potential sources of mesenchymal stem cells. BMAC contains a complex mixture of cellular components, including platelets, white blood cells, red blood cells, hematopoietic precursors, and non-hematopoietic precursors (56). BMAC is technically easy to harvest, needs no culture expansion and may be performed with concomitant procedures (57). However, the number of mesenchymal stem cells in BMAC is thought to be low (only 0.001% to 0.01% of BMAC are stem cells), and the quantity is dependent on the site of extraction (48,58,59). The iliac crest, distal femur, proximal and distal tibia, and the calcaneus have been studied as possible harvest sites (60-63). The phenotype and differentiation potential of the cells harvested from different anatomical sites are similar, however, the iliac crest yields a higher concentration of mesenchymal stem cells. Interestingly, the concentration seems to be higher in aspirates obtained from the posterior iliac crest compared to the anterior portion of the iliac crest (62). The determination of the ideal concentration of stem cells and the ideal site of harvest is a question still not elucidated, and an important area of research.

BMAC is currently used for OA, tendinopathy, articular cartilage injury, meniscal repair, rotator cuff repair, achilles tendon repair and anterior cruciate ligament reconstruction (48). A recent systematic review evaluated the effect of BMAC in the treatment of chondral injuries and OA of the knee (64). The authors identified 11 studies, including three comparative studies; and concluded BMAC is a safe procedure with good outcomes. However, the authors advise about the paucity of high-quality studies on the topic.

Most studies on the use of BMAC in hip pathology focus

on osteonecrosis of the femoral head (ONFH). Mishima *et al.* (65) published a case series of 14 patients with ONFH treated with core decompression where BMAC was added, and low-intensity pulsed ultrasound. Head collapse progressed in 8 of 22 hips, but none required total hip arthroplasty. The authors conclude BMAC associated with low-intensity pulsed ultrasound is safe and efficacious as a joint preserving procedure. However, other comparative studies found no difference between core decompression alone or in combination with BMAC. Hauzeur *et al.* (66) evaluated patients with ONFH stage 3 undergoing core decompression plus saline injection or core decompression plus BMAC. There were 23 hips in each group. No differences were found between the groups for total hip replacement requirements, clinical tests and radiological evolution at final evaluation (24 months). Cruz-Pardos *et al.* (67) retrospectively studied 60 hips with ONFH Ficat 1 and 2 treated with core decompression (19 hips) or core decompression plus BMAC (41 hips). After 24 months, clinical scores and risk of femoral head collapse were similar between both groups. The authors advised that monitoring the number of progenitor cells was not performed in this study and suggested improved outcomes may require cell monitoring.

There is a paucity of literature on BMAC use in the hip for FAI and OA treatment. A case report describes the use of BMAC combined with PRP in a hip capsular injury of a professional soccer player (68). The patient developed heterotopic ossification after a hip arthroscopy, which was removed by a second hip arthroscopy. Although short-term pain relief was achieved, the patient developed recurrent hip pain 3 months after surgery. An MRI demonstrated a tear of the gluteus minimus and a defect in the anterolateral hip capsule. The patient received serial injections of PRP (3 injections) and BMAC (2 injections) under ultrasound injection. A repeat MRI showed improvement in the appearance of the capsule and gluteus minimus, and the patient returned to full activities. Bajwa and Villar (69) presented their experience with mesenchymal stem cells in the treatment of chondral defects of the hip. In a case-control study, 80 patients undergoing hip arthroscopy for FAI with International Cartilage Repair Society (ICRS) grade 2–4 chondral defects were treated with microfracture or microfracture plus mesenchymal stem cells within a biodegradable scaffold. Both groups demonstrated improvement as measured by VAS, mHHS and non-arthritic hip score (NAHS). Surprisingly, 97.5% of patients in the study group (microfracture plus stem cells with scaffold) maintained their clinical improvement at a mean follow-up of 28 months, whereas late deterioration occurred in 17.5% of the control group. Revision hip arthroscopy and conversion to total hip replacement were both higher in the control group (2.5% *vs.* 10% and 2.5% *vs.* 7.5%, respectively). Mardones and Larrain (70) describe a technique for the treatment of chondral lesions in the hip using BMAC and a PRP clot. Hip arthroscopy is performed in the standard fashion and a standard microfracture was performed for full thickness chondral lesions. Bone marrow was then harvested and centrifuged, as well as peripheral blood. Activated PRP, using autologous thrombin, was made to obtain a PRP clot. At the end of the arthroscopic procedure, traction was reapplied, and the fibrin clot was placed over the microfracture using a slotted cannula. Then, a 21-gauge trocar needle was used to insert the stem cells under the PRP clot. They report their preliminary outcomes with this technique in 13 patients. All patients experienced improved symptoms over a follow-up period of 8 months (4–12 months).

Research groups outside of the US have reported their experience with *ex vivo* expanded autologous bone marrow-derived stem cells. Mardones *et al.* (71) published a case series of ten patients that underwent intra-articular injections of stem cells for hip OA. First, bone marrow was harvested from the posterior iliac crest. Then, a fraction of mononuclear cells was isolated, and expanded by means of cell culture. Patients were injected with 3 infusions, each containing 20×10^6 mesenchymal stem cells, each injection separated 1 week apart. Patients demonstrated significant improvement in their clinical outcomes scores after a follow-up period of 16–40 months. The VAS improved from 4.2 to 1.1, and the mHHS from 61.9 to 85.7. No adverse effects were reported. Nine out of ten patients did not show any radiographic progression of OA, and interestingly one patient showed improvement in Tonnis radiographic OA classification. The same authors reported the use of expanded autologous bone marrow-derived stem cells as an augmentation after hip arthroscopy in 29 patients where cartilage lesions were found (72). Four to 6 weeks after surgery, patients received three injections of stem cells. All clinical scores improved, and no serious adverse effects were reported. However, the lack of a control group did not allow any definitive conclusion regarding the superiority of stem cells injection to standard care.

Amniotic-derived stem cells are another promising source of mesenchymal stem cells, which avoids the ethical concerns associated with using embryonic-derived stem

cells due to its extracorporeal nature (48,50). Amniotic-derived stem cells can be isolated from amniotic fluid, human umbilical cord blood (hUCB), or the placenta. Importantly, stem cells derived from hUCB are known not to require tissue matching for allogeneic transplantation, thus they can be used as an off-the-shelf stem cell product (50,73). Park *et al.* (74) reported seven patients with knee OA who were treated with hUCB stem cells. All patients presented with Kellgren-Lawrence grade 3 knee OA and ICRS grade 4 cartilage defects. A composite of culture-expanded allogeneic hUCB mesenchymal stem cells and HA hydrogel were applied surgically to the lesion site. VAS for pain improved from 49.1 at baseline to 19.3 at 24 weeks, and International Knee Documentation Committee (IKDC) subjective scores improved from 39.1 to 63.2. Patients maintained their improvement, as assessed by these outcomes scores, after 7 years. No serious adverse effects occurred, including osteogenesis and tumorigenesis. Adequate healing was observed at second-look arthroscopy. The authors concluded that allogeneic hUCB mesenchymal stem cells appear to be safe and effective for the regeneration of durable hyaline-like cartilage in OA knees.

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are endoproteases with multiple roles in tissue remodeling and degradation of various protein in the extracellular matrix (75). MMPs promote cell proliferation, migration, and differentiation, and could play a role in cell apoptosis, angiogenesis, tissue repair and immune response. Alterations in MMPs expression have been observed in OA, and therefore MMPs inhibitors have been investigated in its treatment. Even though the literature lacks studies of the use of these drugs for FAI and labral tears, some surgeons have reported their use as an adjunct after hip arthroscopy in attempt to enhance clinical outcomes. Moreover, because FAI is considered a pre-arthritic condition, these medications could, in theory, interrupt, or at least postpone, the evolution to advanced joint degeneration.

Doxycycline is a broad-spectrum antibiotic of the tetracycline class, which is also a nonspecific MMP inhibitor. Early studies reported a slower rate of progression of JSN in obese patients with knee OA (33% less than placebo group after 30 months) who used doxycycline, even though it did not change the mean severity of joint pain (76). However, subsequent studies failed to achieve consistently good outcomes. A recent Cochrane systematic review of Doxycycline concluded that "the symptomatic benefit of Doxycycline is minimal to non-existent, while the small benefit in terms of JSN is of questionable clinical relevance and outweighed by safety problems" (77). Various others MMP-inhibitors are under investigation in the treatment of both hip and knee OA, such as PG-116800, CP-544439, AZD-8955 and WAY-170523; but currently there are no published reports of clinical benefit (78).

It has been speculated that blood pressure regulators, such as losartan, could enhance cartilage health after hip arthroscopy (58). Losartan acts on the renin-angiotensin-aldosterone system (RAS), which regulates fluid and electrolyte balance. Losartan and other blood pressure regulators function by blocking angiotensin receptors. Angiotensin receptor expression has also been described in chondrocytes (79). Even though the function of the RAS system in cartilage and bone is still unclear, it may be implicated in the expression of MMPs and tissue remodeling in cartilage matrix, as has been reported in other tissues, such as the heart. Therefore, losartan could play a role in improving cartilage health and function. However, no clinical studies have investigated the effects of losartan after hip arthroscopy or in the treatment of OA.

MMPs are also involved in the development of tendinopathy. The balance between the activities of MMPs and natural MMPs inhibitors regulates tendon remodeling, whereas an imbalance produces a collagen dysregulation and disturbance in tendons. Aprotinin is a broad-spectrum serine protease inhibitor that inhibits plasmin, trypsin and kallikrein. It may block MMPs either directly or by inhibition of plasminogen and plasmin (80,81). Aprotinin has been used to treat patellar and achilles tendinopathy. Maffulli *et al.* (82) described 44 patients presenting with recalcitrant patellar tendinopathy treated with high-volume injections containing aprotinin. Thirty-five of the 44 patients (80%) rated their condition as good or excellent, and of 32 physically active patients, 23 (72%) had returned to sport at the same level practiced before onset of symptoms. However, the authors advised that aprotinin has been withdrawn from the market because of significant side effects related to the injections. Future research with other injectable MMPs inhibitors should elucidate if this drug class can be used in the treatment of tendinopathy, and if it can be used in the hip region.

Conclusions

Biologic treatments hold promise for the management

of intra-articular and peri-articular sources of hip pain, both as a primary treatment as well as an augmentation to traditional options. Several studies report safe use of PRP, HA, and stem cells, with minimal complications; providing good and excellent clinical results. However, further research is warranted in order to obtain more robust evidence, and better determine the precise indications and limitations.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Olufemi R. Ayeni and Ryan P. Coughlin) for the series "Future Perspectives in Hip Preservation and Arthroscopy" published in *Annals of Joint*. The article has undergone external peer review.

Conflicts of Interest: The series "Future Perspectives in Hip Preservation and Arthroscopy" was commissioned by the editorial office without any funding or sponsorship. MR Safran: American Journal of Sports Medicine: Editorial or governing board; Cool Systems, Inc, Cradle Medical, Inc; Biomimedica; Eleven Blade Solutions: stock or stock Options; Cool Systems, Inc; Cradle Medical, Inc; Ferring Pharmaceuticals; Biomimedica; Eleven Blade Solutions: unpaid consultant; DJ Orthopaedics: IP royalties; Ferring Pharmaceuticals: research support; International Society for Hip Arthroscopy: board or committee member; International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine: board or committee member; JISAKOS: Editorial or governing board; Journal of Hip Preservation Surgery: editorial or governing board; Medacta: paid consultant, paid presenter or speaker; Saunders/Mosby-Elsevier: publishing royalties, financial or material support; Smith & Nephew: IP royalties, paid presenter or speaker, research support; Stryker: IP royalties; Wolters Kluwer Health - Lippincott Williams & Wilkins: publishing royalties, financial or material support. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Ganz R, Parvizi J, Beck M, et al. Femoroacetabular impingement: a cause for osteoarthritis of the hip. Clin Orthop Relat Res 2003:112-20.
2. Griffin DR, Dickenson EJ, O'Donnell J, et al. The Warwick Agreement on femoroacetabular impingement syndrome (FAI syndrome): an international consensus statement. Br J Sports Med 2016;50:1169-76.
3. Kalisvaart MM, Safran MR. Microinstability of the hip-it does exist: etiology, diagnosis and treatment. J Hip Preserv Surg 2015;2:123-35.
4. Redmond JM, Chen AW, Domb BG. Greater Trochanteric Pain Syndrome. J Am Acad Orthop Surg 2016;24:231-40.
5. Martin HD, Reddy M, Gómez-Hoyos J. Deep gluteal syndrome. J Hip Preserv Surg 2015;2:99-107.
6. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg 2004;114:1502-8.
7. Marx RE, Carlson ER, Eichstaedt RM, et al. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.
8. Landesberg R, Roy M, Glickman RS. Quantification of growth factor levels using a simplified method of platelet-rich plasma gel preparation. J Oral Maxillofac Surg 2000;58:297-300; discussion 300-1.
9. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg 1997;55:1294-9.
10. Weibrich G, Kleis WK, Hafner G, et al. Comparison of platelet, leukocyte, and growth factor levels in point-of-care platelet-enriched plasma, prepared using a modified Curasan kit, with preparations received from a local blood bank. Clin Oral Implants Res 2003;14:357-62.
11. Oudelaar BW, Peerbooms JC, Huis In 't Veld R, et al.

Concentrations of Blood Components in Commercial Platelet-Rich Plasma Separation Systems: A Review of the Literature. Am J Sports Med 2018. [Epub ahead of print].
12. Cheng M, Johnson VM, Murray MM. Effects of age and platelet-rich plasma on ACL cell viability and collagen gene expression. J Orthop Res 2012;30:79-85.
13. Cavallo C, Roffi A, Grigolo B, et al. Platelet-Rich Plasma: The Choice of Activation Method Affects the Release of Bioactive Molecules. Biomed Res Int 2016;2016:6591717.
14. Mannava S, Chahla J, Geeslin AG, et al. Platelet-Rich Plasma Augmentation for Hip Arthroscopy. Arthrosc Tech 2017;6:e763-8.
15. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthroscopy 2012;28:998-1009.
16. Mishra A, Harmon K, Woodall J, et al. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol 2012;13:1185-95.
17. Malavolta EA, Gracitelli ME, Ferreira Neto AA, et al. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. Am J Sports Med 2014;42:2446-54.
18. Meheux CJ, McCulloch PC, Lintner DM, et al. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy 2016;32:495-505.
19. Arirachakaran A, Sukthuayat A, Sisayanarane T, et al. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. J Orthop Traumatol 2016;17:101-12.
20. Franceschi F, Papalia R, Franceschetti E, et al. Platelet-rich plasma injections for chronic plantar fasciopathy: a systematic review. Br Med Bull 2014;112:83-95.
21. A Hamid MS, Mohamed Ali MR, Yusof A, et al. Platelet-rich plasma injections for the treatment of hamstring injuries: a randomized controlled trial. Am J Sports Med 2014;42:2410-8.
22. Dallaudière B, Pesquer L, Meyer P, et al. Intratendinous injection of platelet-rich plasma under US guidance to treat tendinopathy: a long-term pilot study. J Vasc Interv Radiol 2014;25:717-23.
23. Kraeutler MJ, Garabekyan T, Mei-Dan O. The use of platelet-rich plasma to augment conservative and surgical treatment of hip and pelvic disorders. Muscles Ligaments Tendons J 2016;6:410-9.
24. Mautner K, Colberg RE, Malanga G, et al. Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. PM R 2013;5:169-75.
25. Sánchez M, Guadilla J, Fiz N, et al. Ultrasound-guided platelet-rich plasma injections for the treatment of osteoarthritis of the hip. Rheumatology (Oxford) 2012;51:144-50.
26. Fiz N, Pérez JC, Guadilla J, et al. Intraosseous Infiltration of Platelet-Rich Plasma for Severe Hip Osteoarthritis. Arthrosc Tech 2017;6:e821-5.
27. Laver L, Marom N, Dnyanesh L, et al. PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. Cartilage 2017;8:341-64.
28. Battaglia M, Guaraldi F, Vannini F, et al. Platelet-rich plasma (PRP) intra-articular ultrasound-guided injections as a possible treatment for hip osteoarthritis: a pilot study. Clin Exp Rheumatol 2011;29:754.
29. Battaglia M, Guaraldi F, Vannini F, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics 2013;36:e1501-8.
30. Dallari D, Stagni C, Rani N, et al. Ultrasound-Guided Injection of Platelet-Rich Plasma and Hyaluronic Acid, Separately and in Combination, for Hip Osteoarthritis: A Randomized Controlled Study. Am J Sports Med 2016;44:664-71.
31. Redmond JM, Gupta A, Stake CE, et al. Clinical results of hip arthroscopy for labral tears: a comparison between intraoperative platelet-rich plasma and bupivacaine injection. Arthroscopy 2015;31:445-53.
32. LaFrance R, Kenney R, Giordano B, et al. The effect of platelet enriched plasma on clinical outcomes in patients with femoroacetabular impingement following arthroscopic labral repair and femoral neck osteoplasty. J Hip Preserv Surg 2015;2:158-63.
33. Henrotin Y, Raman R, Richette P, et al. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. Semin Arthritis Rheum 2015;45:140-9.
34. Altman RD, Manjoo A, Fierlinger A, et al. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskelet Disord 2015;16:321.
35. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2006;14:154-62.
36. Altman RD, Bedi A, Karlsson J, et al. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of

the Knee. Am J Sports Med 2016;44:2158-65.
37. Strand V, McIntyre LF, Beach WR, et al. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. J Pain Res 2015;8:217-28.
38. Eymard F, Maillet B, Lellouche H, et al. Predictors of response to viscosupplementation in patients with hip osteoarthritis: results of a prospective, observational, multicentre, open-label, pilot study. BMC Musculoskelet Disord 2017;18:3.
39. Migliore A, Massafra U, Bizzi E, et al. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther 2009;11:R183.
40. Abate M, Scuccimarra T, Vanni D, et al. Femoroacetabular impingement: is hyaluronic acid effective? Knee Surg Sports Traumatol Arthrosc 2014;22:889-92.
41. Filardo G, Di Matteo B, Tentoni F, et al. No Effects of Early Viscosupplementation After Arthroscopic Partial Meniscectomy: A Randomized Controlled Trial. Am J Sports Med 2016;44:3119-25.
42. Chau JY, Chan WL, Woo SB, et al. Hyaluronic acid instillation following arthroscopic anterior cruciate ligament reconstruction: a double-blinded, randomised controlled study. J Orthop Surg (Hong Kong) 2012;20:162-5.
43. Di Martino A, Tentoni F, Di Matteo B, et al. Early Viscosupplementation After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. Am J Sports Med 2016;44:2572-8.
44. Thein R, Haviv B, Kidron A, et al. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics 2010;33:724.
45. Baker JF, Solayar GN, Byrne DP, et al. Analgesic control and functional outcome after knee arthroscopy: results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine. Clin J Sport Med 2012;22:109-15.
46. Doral MN, Bilge O, Batmaz G, et al. Treatment of osteochondral lesions of the talus with microfracture technique and postoperative hyaluronan injection. Knee Surg Sports Traumatol Arthrosc 2012;20:1398-403.
47. Caplan AI, Correa D. PDGF in bone formation and regeneration: new insights into a novel mechanism involving MSCs. J Orthop Res 2011;29:1795-803.
48. Saltzman BM, Kuhns BD, Weber AE, et al. Stem Cells in Orthopedics: A Comprehensive Guide for the General Orthopedist. Am J Orthop (Belle Mead NJ) 2016;45:280-326.
49. Piuzzi NS, Khlopas A, Newman JM, et al. Bone Marrow Cellular Therapies: Novel Therapy for Knee Osteoarthritis. J Knee Surg 2018;31:22-6.
50. Park YB, Ha CW, Rhim JH, et al. Stem Cell Therapy for Articular Cartilage Repair: Review of the Entity of Cell Populations Used and the Result of the Clinical Application of Each Entity. Am J Sports Med 2017. [Epub ahead of print].
51. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell 2011;9:11-5.
52. Scotti C, Gobbi A, Karnatzikos G, et al. Cartilage Repair in the Inflamed Joint: Considerations for Biological Augmentation Toward Tissue Regeneration. Tissue Eng Part B Rev 2016;22:149-59.
53. Hung SC, Chen NJ, Hsieh SL, et al. Isolation and characterization of size-sieved stem cells from human bone marrow. Stem Cells 2002;20:249-58.
54. Collier MB, Eickmann TH, Anbari KK, et al. Lateral tibiofemoral compartment narrowing after medial unicondylar arthroplasty. Clin Orthop Relat Res 2007;464:43-52.
55. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell 2002;13:4279-95.
56. Cotter EJ, Wang KC, Yanke AB, et al. Bone Marrow Aspirate Concentrate for Cartilage Defects of the Knee: From Bench to Bedside Evidence. Cartilage 2018;9:161-70.
57. Chahla J, Mannava S, Cinque ME, et al. Bone Marrow Aspirate Concentrate Harvesting and Processing Technique. Arthrosc Tech 2017;6:e441-5.
58. Chahla J, LaPrade RF, Mardones R, et al. Biological Therapies for Cartilage Lesions in the Hip: A New Horizon. Orthopedics 2016;39:e715-23.
59. Martin DR, Cox NR, Hathcock TL, et al. Isolation and characterization of multipotential mesenchymal stem cells from feline bone marrow. Exp Hematol 2002;30:879-86.
60. Narbona-Carceles J, Vaquero J, Suárez-Sancho S, et al. Bone marrow mesenchymal stem cell aspirates from alternative sources: is the knee as good as the iliac crest? Injury 2014;45 Suppl 4:S42-7.
61. Hyer CF, Berlet GC, Bussewitz BW, et al. Quantitative assessment of the yield of osteoblastic connective tissue progenitors in bone marrow aspirate from the iliac crest, tibia, and calcaneus. J Bone Joint Surg Am 2013;95:1312-6.

62. Pierini M, Di Bella C, Dozza B, et al. The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. J Bone Joint Surg Am 2013;95:1101-7.
63. Davies BM, Snelling SJB, Quek L, et al. Identifying the optimum source of mesenchymal stem cells for use in knee surgery. J Orthop Res 2017;35:1868-75.
64. Chahla J, Dean CS, Moatshe G, et al. Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee: A Systematic Review of Outcomes. Orthop J Sports Med 2016;4:2325967115625481.
65. Mishima H, Sugaya H, Yoshioka T, et al. The safety and efficacy of combined autologous concentrated bone marrow grafting and low-intensity pulsed ultrasound in the treatment of osteonecrosis of the femoral head. Eur J Orthop Surg Traumatol 2016;26:293-8.
66. Hauzeur JP, De Maertelaer V, Baudoux E, et al. Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial. Int Orthop 2017. [Epub ahead of print].
67. Cruz-Pardos A, Garcia-Rey E, Ortega-Chamarro JA, et al. Mid-term comparative outcomes of autologous bone-marrow concentration to treat osteonecrosis of the femoral head in standard practice. Hip Int 2016;26:432-7.
68. Campbell KJ, Boykin RE, Wijdicks CA, et al. Treatment of a hip capsular injury in a professional soccer player with platelet-rich plasma and bone marrow aspirate concentrate therapy. Knee Surg Sports Traumatol Arthrosc 2013;21:1684-8.
69. Bajwa AS, Villar RN. Mesenchymal Stem Cells (MSC) Use In Hip Arthroscopy: Medium Term Results In Case-Control Study Of Patients With ICRS Grade 2-4 Defects? J Hip Preserv Surg 2016;3:hnw030.043.
70. Mardones R, Larrain C. Cartilage restoration technique of the hip. J Hip Preserv Surg 2016;3:30-6.
71. Mardones R, Jofré CM, Tobar L, et al. Mesenchymal stem cell therapy in the treatment of hip osteoarthritis. J Hip Preserv Surg 2017;4:159-63.
72. Mardones R, Via AG, Jofré C, et al. Cell therapy for cartilage defects of the hip. Muscles Ligaments Tendons J 2016;6:361-6.
73. Weiss ML, Anderson C, Medicetty S, et al. Immune properties of human umbilical cord Wharton's jelly-derived cells. Stem Cells 2008;26:2865-74.
74. Park YB, Ha CW, Lee CH, et al. Cartilage Regeneration in Osteoarthritic Patients by a Composite of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells and Hyaluronate Hydrogel: Results from a Clinical Trial for Safety and Proof-of-Concept with 7 Years of Extended Follow-Up. Stem Cells Transl Med 2017;6:613-21.
75. Cui N, Hu M, Khalil RA. Biochemical and Biological Attributes of Matrix Metalloproteinases. Prog Mol Biol Transl Sci 2017;147:1-73.
76. Brandt KD, Mazzuca SA, Katz BP, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52:2015-25.
77. da Costa BR, Nüesch E, Reichenbach S, et al. Doxycycline for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2012;11:CD007323.
78. Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage 2016;24:2013-21.
79. Kawakami Y, Matsuo K, Murata M, et al. Expression of Angiotensin II Receptor-1 in Human Articular Chondrocytes. Arthritis 2012;2012:648537.
80. Castagna A, Cesari E, Gigante A, et al. Metalloproteases and their inhibitors are altered in both torn and intact rotator cuff tendons. Musculoskelet Surg 2013;97 Suppl 1:39-47.
81. Magra M, Maffulli N. Matrix metalloproteases: a role in overuse tendinopathies. Br J Sports Med 2005;39:789-91.
82. Maffulli N, Del Buono A, Oliva F, et al. High-Volume Image-Guided Injection for Recalcitrant Patellar Tendinopathy in Athletes. Clin J Sport Med 2016;26:12-6.

doi: 10.21037/aoj.2018.05.08
Cite this article as: Ejnisman L, Safran MR. Biologics in hip preservation. Ann Joint 2018;3:50.

