Glenohumeral Osteoarthritis: The Role for Orthobiologic Therapies

Platelet-Rich Plasma and Cell Therapies

Luciano A. Rossi, MD

Nicolás S. Piuzzi, MD

Shane A. Shapiro, MD

Investigation performed at the Department of Orthopedic Surgery, Mayo Clinic, Jacksonville, Florida

Abstract

» The glenohumeral (GH) joint ranks third on the list of the large joints that are most commonly affected by osteoarthritis, after the knee and the hip.

» General nonsurgical modalities, including changes in daily activities, physical therapy, pharmacotherapy, and corticosteroid injections, constitute the mainstay of treatment. Most of these options, however, have shown moderate and short-term effectiveness.

» Arthroplasty techniques have proven to be successful for elderly patients. Nevertheless, replacement options are not optimal for younger patients because their functional demands are higher and prostheses have a finite life span.

» This has led to the search for new nonoperative treatment options to target this subgroup of patients. It has been suggested that orthobiologic therapies, including platelet-rich plasma (PRP) and cell therapies, present great promise and opportunity for the treatment of GH osteoarthritis.

» Despite the promising results that have been shown by cell therapies and PRP for treating degenerative joint conditions, additional studies are needed to provide more definitive conclusions.

With an estimated prevalence of 10% in men and 18% in women who are over 60 years of age, osteoarthritis constitutes the most widespread musculoskeletal disease in the world[1]. The glenohumeral (GH) joint ranks third on the list of the most commonly affected large joints after the knee and the hip[2]. Nonetheless, the number of studies addressing the progression of arthritic changes in the shoulder are scarce. Leyland et al. conducted a cohort study that followed the progression of radiographic knee osteoarthritis for 15 years; they found the annual rate of disease progression to be 2.8%[3]. Whether the shoulder follows a similar path or not remains unclear. Unfortunately, to date, no reported interventions that are capable of reversing or slowing the natural progression of early osteoarthritis have been found.

In order to reduce pain, enhance functionality, and potentially minimize disease progression, a nonoperative management approach should be adopted before considering other, invasive alternatives[4,5]. Evidence supporting the use of nonarthroplasty treatments for GH osteoarthritis is scarce compared with the guidelines provided by the

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American Academy of Orthopaedic Surgeons (AAOS) in relation to the use of nonarthroplasty treatments for knee osteoarthritis, which strongly recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs), as well as low-impact rehabilitation, wellness activity, weight loss, and education[6]. On the other hand, for the initial treatment of GH osteoarthritis, the AAOS has failed to either recommend or discourage pharmacotherapy or injectable corticosteroids, and has instead offered a "limited" recommendation in relation to the use of injectable viscosupplementation[7]. Nonetheless, general nonsurgical modalities, including changes in daily activities and sports participation, pharmacotherapy, intra-articular injections, and physical therapy, remain the mainstay of nonoperative management[4,5]. Apart from their potential to improve patient symptoms, these approaches have the advantages of being inexpensive and posing a minimal risk. When disease and symptoms progress, current shoulder arthroplasty techniques have been shown to be reproducibly successful in elderly patients with GH osteoarthritis who have not had success with nonoperative treatment. Replacement options fail to be so auspicious in younger patients who present with osteoarthritis[4,5]. In this sense, prosthetic replacement may be precluded by the superior demands for activity and the higher functional expectations from young patients[8]. Moreover, the possible occurrence of adverse outcomes as well as the limited life span of a prosthesis have led to the search for new nonoperative treatment options to target, especially for this subgroup of patients[8].

Given some early success in the use of autologous orthobiologic therapies for joints such as the knee, we review the role for similar treatments in the GH joint[3,5]. In this context, orthobiologic therapies present great promise and opportunity[9]. For example, different formulations obtained through density separation (centrifugation) of blood (platelet-rich plasma [PRP]) and bone marrow (bone marrow aspirate concentrate [BMAC]) appear as promising alternatives because of their ability to modulate inflammation[10]. Additionally, cells obtained from adipose tissue have been proposed[11]. The multiple cytokines, anti-inflammatory factors, and bioactive molecules present in these preparations constitute vital regulators in a microenvironment with a complex healing process; thus, they may help to treat degenerative joint conditions[12,13]. However, there are multiple challenges and remaining questions regarding the use, safety, and efficacy of orthobiologics.

This narrative review provides a comprehensive analysis of the pathophysiology of GH osteoarthritis and the basic science underlying the potential use of injectable autologous PRP and clinically available cell therapies that are targeted for its treatment. Furthermore, a complete description of the recommended techniques for the application and a summary of the existing clinical evidence supporting the use of orthobiologics in shoulder osteoarthritis are provided.

Etiology of GH Osteoarthritis

GH osteoarthritis can be broadly classified into primary and secondary osteoarthritis. The former represents about 90% of the cases; it usually affects patients who are ≥60 years old and is characterized by damage to the articular cartilage and dense subchondral bone, osteophytes, posterior glenoid erosion, and posterior displacement of the humeral head, without prior injury or surgery[14]. Various risk factors have been associated with the development of shoulder osteoarthritis, including obesity, injuries resulting from shoulder overuse, occupations requiring excessive use of the upper limbs, the practice of overhead sports, and a history of previous trauma or dislocation[14,15].

Patients who are <60 years old usually present with secondary causes of GH osteoarthritis[4,15]. Secondary osteoarthritis may result from GH dislocations and subluxations through osteochondral fractures and subchondral bone injury involving the glenoid and the humeral head[4]. Hovelius and Saeboe conducted a study that followed 223 shoulders for 25 years after primary anterior dislocation[16]. Of the total number of shoulders that did not experience recurrence, 18% had moderate-to-severe arthropathy. In the patients who experienced recurrent dislocations, osteoarthritis developed in 39% of those who had been treated nonoperatively and in 26% of those who had surgically stabilized shoulders[16].

Atraumatic osteonecrosis also can lead to secondary osteoarthritis. It is worth noting that, after the hip, the proximal aspect of the humerus ranks second as the most commonly affected site in the body in terms of osteonecrosis[17]. Multiple risk factors have been associated with proximal humeral osteonecrosis, including the use of systemic corticosteroids, chemotherapy/radiation, alcohol abuse, hematopoietic diseases, human immunodeficiency virus (HIV), and treatment with cytotoxic drugs[18].

Proximal humeral or glenoid malunion also can trigger secondary osteoarthritis due to aberrant joint biomechanics or posttraumatic osteonecrosis[19,20].

During surgical intervention about the shoulder, iatrogenic causes can result in osteoarthritic sequelae, including capsulorrhaphy arthropathy, which consists of the rapid posterior chondral wear that is caused by anterior capsule overtightening and the resultant compressive joint forces and loss of external rotation[21]. Iatrogenic postarthroscopic chondrolysis also has been described and can lead to early GH osteoarthritis in young patients[22]. This condition has been related to the use of intra-articular pain pumps that deliver local anesthetics[22], nonabsorbable prominent suture anchors, and thermal devices[22-24].

Finally, other possible but less common causes of secondary shoulder osteoarthritis include inflammatory arthropathy[25], radiofrequency/thermal capsulorrhaphy[26], and sequelae from a previously infected joint[27].

Physiopathology of Shoulder Osteoarthritis

Osteoarthritis is a complex multifactorial condition. Its pathogenesis is associated with the critical roles played by cartilage, subchondral bone, and synovium[1]. Subchondral bone changes are correlated with articular cartilage degeneration. In this sense, bone volume and trabecular thickness increase as cartilage degeneration progresses[28,29]. With osteoarthritis, the bone becomes stiffer. This may reduce its ability to absorb impact loads, thus causing more cartilage stress[28,29].

Type-II collagen, the main structural protein of cartilage, constitutes a meshwork that is stabilized by other collagen types and noncollagenous proteins, including the cartilage oligomeric matrix protein. In addition, it provides cartilage with tensile strength[30]. Within this framework, proteoglycans bring water to the cartilage, thus providing compressive resistance[30]. Cartilage destruction in osteoarthritis is not only caused by mechanical wear. In fact, it may also be influenced by various proteases, including matrix metalloproteinases (MMPs) such as ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs)-4, ADAMTS-5, and MMP-13[31,32]. ADAMTS-4 and ADAMTS-5, also referred to as aggrecanases, are capable of destroying the aggrecan, which is the most common proteoglycan found in articular cartilage. It is involved in load distribution in the joints during movement and provides hydration and elasticity to cartilage tissue[31,32]. In turn, collagenases, particularly MMP-13, have the ability to degrade the most abundant collagen in cartilage, type-II collagen, which, as mentioned above, is responsible for its tensile strength[33,34]. A crucial factor involved in the development of osteoarthritis is the overexpression of MMPs[31,32].

Chondrocytes synthesize and break down the matrix that is regulated by cytokines and growth factors. In arthritis, their balance may be compromised[30]. When they are activated, chondrocytes produce various inflammatory response proteins, including cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, as well as matrix-degrading enzymes, such as the MMPs and a disintegrin[30,35]. Both at early and late stages of osteoarthritis, IL-l plays a key role[35]. This multifunctional proinflammatory cytokine produces various effects, which include cartilage breakdown, lymphokine production, interference with growth factor activity, or reduction of the synthesis of the key matrix components such as aggrecan[35]. IL-1β also induces reactive oxygen species (ROS) as well as lipid peroxidation, which have been associated with cartilage matrix degradation[35]. Chondrocytes produce ROS, including hydrogen peroxide, superoxide anions, and hydroxyl radicals in response to IL-1, and are capable of inducing collagen and aggrecan degradation in chondrocytes[36]. In addition, activated macrophages and neutrophils participating in inflammatory responses may generate ROS[36]. IL-1 and TNF-α stimulate nitric oxide production, a potent mediator that is produced by articular chondrocytes during inflammatory reactions by inhibiting proteoglycan synthesis, enhancing MMP production, or increasing oxidant stress to arthritis disease in joints[37]. NF-κB cells (nuclear factor kappa-light-chain-enhancer of activated B cells), one of the key regulatory mechanisms involved in regulating and controlling expression of cytokines, are critical in immune function, namely inflammation[38]. The stimulus of NF-κB is known to lead to the expression of TNF-α and IL-1β[8].

Since it stimulates proteolytic enzyme secretion from chondrocytes and synovial fibroblasts, TNF-α, an effective proinflammatory cytokine, plays a major role in inflammation and matrix degradation[37]. IL-1 and TNF-α both induce production of IL-6, and higher levels of these cytokines might lead to the development of osteoarthritis[37]. Interferon-γ (IFN-γ) is produced as a result of inflammation and worsens the inflammatory process like arthritis[37,39]. Finally, patients with osteoarthritis have been found to exhibit elevated levels of transforming growth factor beta (TGF-β) activity in their synovial fluid. In turn, cells are triggered to form osteophytes when TGF-β is released by tissue damage and inflammation[40].

PRP for Osteoarthritis: Basic Science Background

PRP consists of a sample of autologous blood with platelet concentrations above baseline values, which has been produced through the separation of whole blood by centrifugation[13]. PRP is considered to be minimally manipulated and falls under the scope of section 361 (Public Health Service Act, 21 Code of Federal Regulation 1271) of minimally manipulated therapies. In addition to platelets, and depending on the preparation protocol, PRP contains varying levels of blood components such as leukocytes (namely monocytes and neutrophils) and red blood cells. Hence, platelet, leukocyte, and red blood cell concentrations in each individual PRP preparation may vary depending on the system and the protocol that are utilized. In addition, substantial variations in blood component concentrations have been reported, even in the same patient over a 2-week period[41,42]. The majority of the characteristics shown by platelets are determined by the megakaryocytes from which they arise. The membrane bodies of the alpha granules are made in megakaryocytes[43]. However, some of the granule contents of the platelets actually are taken up from the plasma[43]. Specifically, the alpha granules of platelets contain numerous platelet proteins and growth factors[43]. During megakaryocyte development, the granule body itself is made early, before the demarcation membrane system[44]. Part of the granule contents, including platelet-derived growth factor (PDGF), TGF-β, and platelet factor 4, are synthesized in the megakaryocyte and then transported to the alpha granules[43]. However, there are other proteins, including fibrinogen, albumin, and immunoglobulin G

(IgG), that enter the alpha granules by endocytosis[44].

The term "platelet-rich plasma" includes a wide spectrum of PRP preparation protocols and formulations[45]. Several authors have attempted to characterize and classify the various techniques available in the market in terms of preparation (centrifugation speed and use of anticoagulant), content (platelets, leukocytes, and growth factors), and applications[45-48]. However, no consensus has been reached thus far among experts in the field. As an example, in the last 6 years, 5 different classifications have been described[45-48]. Comparing the results of different studies poses a challenge since there are multiple PRP classification systems available. Therefore, it is essential to achieve a consensus among experts in the field to define a unique and standardized classification for the reporting of PRP use in future studies.

The rationale underlying the use of PRP is that growth factors are released as soon as platelets are activated, with approximately 70% of them being released within the first 10 minutes following activation[49]. Specifically, platelets possess biologically active growth factors inside alpha granules, which have the potential to reduce joint inflammation, decrease cartilage breakdown, and promote tissue repair[50]. It is believed that such elevated concentrations of growth factors, as well as bioactive proteins, may induce healing. These factors include TGF-β, insulin-like growth factor, PDGF, basic fibroblast growth factor, and vascular endothelial growth factor[51]. Chondrogenesis and stem cell proliferation have been shown to be positively affected by PRP by means of the effects of the various growth factors[51]. Moreover, it has been shown that PRP may increase anti-inflammatory mediators and decrease proinflammatory ones[13]. In turn, the transactivation of NF-κB, the critical regulator of the inflammatory process, has been found to be reduced[52-54]. In addition, the expression of the inflammatory enzymes cyclooxygenase 2 and 4 (COX-2 and COX-4), the disintegrins, and the MMPs are reduced by PRP[52-54]. Of note, most of the claimed mechanisms of action of PRP have been shown in vitro and are still to be determined in vivo.

The efficacy of PRP to treat osteoarthritis may lie in its observed ability to inhibit catabolic processes[55]. The MMP enzymes have the potential to cause multiple extracellular matrix protein degradation and may prevent the development of matrix formation during the healing process[55]. In addition, since PRP has the ability to substantially reduce MMP-3 and MMP-13 activity, matrix formation may be improved and the healing process may be facilitated[56,57]. As a result of these combined effects, PRP constitutes a potential injectable alternative for treating shoulder osteoarthritis. Finally, the combination of PRP and hyaluronic acid has been suggested to have a synergistic action. A study conducted by Chen et al. reported that cartilage regeneration might be promoted and osteoarthritis inflammation might be inhibited by means of a synergistic effect of hyaluronic acid combined with PRP. This, however, has yet to be proven clinically[58].

Finally, there are some limitations related to PRP therapy that have not yet been resolved. Most clinical studies evaluating PRP fail to adequately report scientific details that are critical to the outcome[59,60]. Although expert consensus has been suggested in relation to the minimum requirements to be met when reporting clinical studies evaluating PRP, its use has not yet been universally adopted[60]. Furthermore, since it is challenging to compare the results among studies because of the variety of PRP classification systems, the reporting of blood-derived products in orthopaedics encounters limitations[59,60]. A universally accepted system for describing autologous blood preparations is likely to improve communication among researchers. Lastly, the role of some of the components present in PRP that have been shown to influence clinical outcomes in other joints have not yet been studied in the shoulder. For example, the growth factor and cytokines delivered in the target tissue are strongly influenced by leukocyte concentrations[61]. It has been shown that, in the treatment of knee osteoarthritis, leukocyte-poor PRP (LP-PRP) is more effective than leukocyte-rich PRP (LR-PRP) for intra-articular injection[62]. However, the relation between leukocyte concentrations and functional outcomes has not been specifically studied in shoulder osteoarthritis.

PRP for Shoulder Osteoarthritis: Clinical Outcomes

Clinical studies evaluating the use of PRP injections to treat GH osteoarthritis are scarce. In 2013, Freitag and Barnard described a case report in which 3 intra-articular PRP injections (each 1 week apart) were administered to a 62-year-old woman under ultrasound guidance[63]. The patient experienced a reduction in the VAS (visual analogue scale) from 6 to 1, which lasted for the full follow-up period of 42 weeks. Moreover, an improvement in the DASH (Disabilities of the Arm, Shoulder and Hand) score also was observed, decreasing from 65 at preinjection to a score of 5 at week 42[63]. Lo et al. evaluated the results of using human dermal matrix allograft and PRP to perform hemiarthroplasty and biologic resurfacing of the glenoid in 55 patients[64]. In their study, hemiarthroplasty with biologic resurfacing led to positive midterm outcomes with satisfactory revision rates. Specifically, an average postoperative American Shoulder and Elbow Surgeons (ASES) score of 76 was obtained, while the Western Ontario Osteoarthritis of the Shoulder index score was 76% and the VAS score was 2.4. Five cases (9.1%) were revised to anatomic total shoulder arthroplasty with implantation of a glenoid component. However, the lack of a control group constituted an important limitation of this study. Therefore, isolating PRP's individual effects from those of the acellular human dermal allograft is challenging[64].

To our knowledge, no other peer-reviewed studies on PRP for shoulder osteoarthritis are available. However, there are studies documenting excellent results in the knee. In 2019, Han et al. evaluated 14 randomized controlled trials comparing PRP with hyaluronic acid for knee osteoarthritis. A total of 1,314 patients were included[65]. According to that meta-analysis, PRP injections were more effective in reducing pain than hyaluronic acid injections in patients with knee osteoarthritis at 6 and 12 months of follow-up with use of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and the VAS pain score. In addition, the PRP group exhibited better functional improvement, as shown by the WOMAC function score at 3, 6, and 12 months[65].

Interestingly, the combination of PRP and hyaluronic acid has been reported to have a potential synergistic effect in the treatment of knee osteoarthritis[66]. Since PRP and hyaluronic acid have different biologic mechanisms, their combination may help to control the delivery and presentation of signaling molecules[66]. In a recent study, hyaluronic acid combined with PRP significantly reduced pain and functional limitation at 1 year post-treatment ($p < 0.05$) compared with hyaluronic acid alone[67]. This is an interesting finding that could be useful for the management of shoulder osteoarthritis. Finally, the number of injections that should be applied has sparked controversy. A randomized prospective study recently conducted by Kavadar et al. aimed at investigating how many PRP injections (1, 2, or 3) administered at 2-week intervals constituted the most effective approach to treat moderate knee osteoarthritis. The authors concluded that 2 injections were the minimum required for successfully treating the symptoms ($p < 0.001$)[68].

In conclusion, despite the fact that the basic science rationale supports the use of PRP for degenerative joint conditions and that favorable clinical outcomes have been achieved in patients with knee osteoarthritis, the clinical effect of using PRP in patients with shoulder osteoarthritis has yet to be proved. Therefore, the need to determine the effectiveness of PRP injections and whether they should be recommended as a standard of care in treating patients with GH osteoarthritis requires additional research through reliable and sizeable randomized double-blind placebo-controlled trials.

Cell Therapies for Osteoarthritis: Basic Science Background

Current human cell and cell-derived products for orthopaedic use are described in Figure 1. BMAC is becoming increasingly popular as a treatment for osteoarthritis since it is included among the limited number of approaches capable of delivering progenitor cells that are currently in line with the recommendations of the U.S. Food and Drug Administration and it can be used in a single-stage procedure[69]. Similar to PRP, BMAC requires minimal manipulation and falls under the scope of section 361 (Public Health Service Act, 21 Code of Federal Regulation 1271), which addresses minimally manipulated therapies[70]. Similar to PRP manufacturing from whole blood, bone marrow is first harvested and then undergoes centrifugation in order to separate cellular components into different layers. Mononucleated cells, which include white blood cells, connective tissue stem and progenitor cells, hematopoietic stem cells, and platelets, are concentrated in 1 layer, while red blood cells are concentrated in another[71]. Even though stem and progenitor cells account for only 0.001% to 0.01% of the total number of cells in BMAC, they are of particular interest because they can contribute to tissue regeneration directly (by differentiating damaged cell types) and indirectly (by limiting inflammation, stimulating angiogenesis, and recruiting local tissue-specific progenitors)[72]. Unfortunately, the reports of BMAC preparation protocols used in clinical trials related to the treatment of musculoskeletal disease are substantially inconsistent[71]. Piuzzi et al. performed a systematic literature review in order to assess the level of reporting in relation to BMAC preparation protocols and the BMAC composition that was used in the treatment of musculoskeletal diseases in published clinical studies[71]. The authors reported that most of the studies failed to provide enough information to allow the protocol to be reproduced and that quantitative metrics of the BMAC final product composition were only provided in 30% of the studies[71].

The mechanisms by which BMAC might regulate inflammatory processes are not yet fully understood. On one hand, BMAC contains higher levels of IL-1 receptor antagonist and IL-1β. These growth factors play key roles in regeneration through immune response modulation (inflammation reduction)[12,13]. On the other hand, the high concentration of leukocytes in BMAC may result in more inflammatory symptoms after the injection[73]. Furthermore, other BMAC cell types may play a therapeutic role. When analyzing the use of stem cells for degenerative conditions, it is critical to understand how age-related changes may affect stem cell function. Cassano et al. evaluated the effects of aging on the therapeutic potential of stem cells and showed that despite their promising short-term effects in degenerative orthopaedic pathologies, stem cell therapies do not seem to be capable of reversing age-related tissue degeneration[73]. Since PRP has been previously demonstrated to have therapeutic effects, BMAC's beneficial effects also may be substantially influenced by PRP-released factors[74,75].

Finally, adipose tissue is another major source of cells, considering that it can be easily accessed and harvested and that few complications have been reported with the procedure[13,76]. Adipose-derived therapies can be divided into 2 types: minimally manipulated (micronized fat) and more than minimally manipulated (adipose-derived stem cells [ADSCs]). Mesenchymal stem

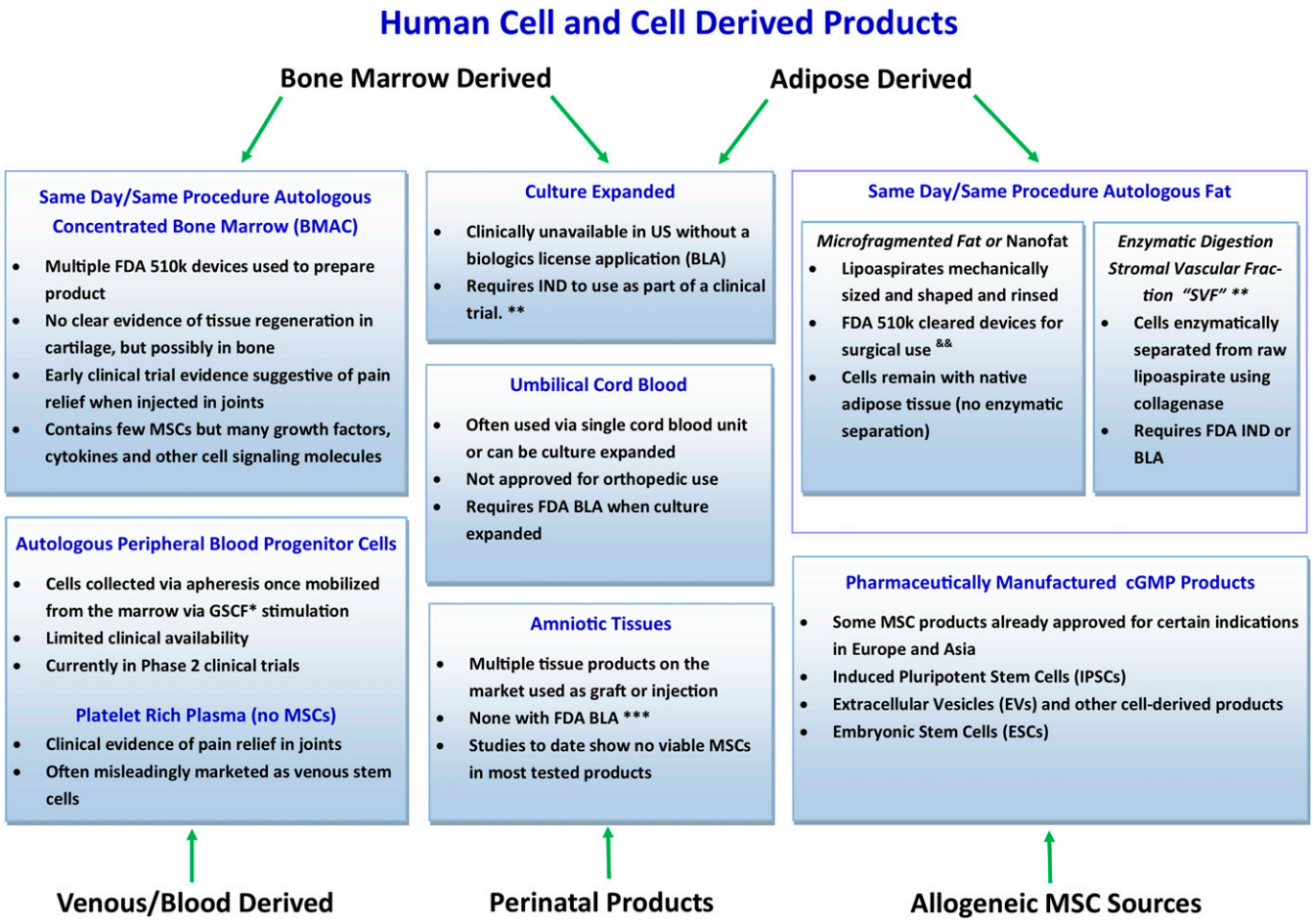

Fig. 1

Conceptual representation of current human cell and cell-derived products for orthopaedic use. *GCFS = granulocyte colony-stimulating factor. **Limited access worldwide, although some options are available in countries with little/no regulation. &&Practice in the United States requires adherence to minimal manipulation, not more than rinsing, sizing, and shaping, as outlined in the U.S. FDA Same Surgical Procedure Exception (SSPE). ***Multiple devices are available that utilize enzymatic digestion of SVF cells from adipocytes. Considered by the FDA to be more than minimal manipulation and thus outside the scope of SSPE; would require FDA IND or BLA to comply with current U.S. regulatory framework. BMAC = bone marrow aspirate concentrate, FDA = U.S. Food and Drug Administration, MSCs = mesenchymal stem cells, IND = Investigational New Drug, and cGMP = current good manufacturing process.

cells (MSCs) that are derived from adipose tissue are known as adipose-ADSCs. ADSCs have gained popularity during the last decade because they are abundant and easy to access and because they have a comparable regenerative capability compared with bone marrow-derived mesenchymal stem cells (BMSCs)[11]. The major source of ADSCs is the abdominal fat pad, which can be harvested via liposuction in lipoaspirate form[11,77]. In order to digest the extracellular matrix, collagenase is added once the fat particles have been isolated. Following chemical disruption, the adipose sample is centrifuged for purification[11,77]. After centrifugation, cells are resuspended in culture media, plated in flasks, and incubated for 24 to 48 hours[77]. The multiple molecules that are secreted by ADSCs have proved to be key factors in tissue regeneration and anti-inflammatory effects[13,78,79]. ADSCs require a 2-step procedure before administration, including adipose harvest. In addition, they are generally considered pharmaceutical products that currently require strict clinical trials and regulatory approval[72]. Burrow et al. demonstrated that adipose cells possess an enhanced proliferative capacity and are capable of retaining multipotency longer than donor-matched marrow MSCs during expansion[76]. Along with the anti-inflammatory effects, ADSCs secrete various critical molecules involved in tissue regeneration, including collagens and collagen maturation enzymes, matricellular proteins, MMPs, and macrophage-colony stimulating factor, which may affect the metabolism of the extracellular matrix in osteoarthritic cartilage. This may constitute an advantage for osteoarthritic cartilage since homeostasis is restored between MMPs and the tissue inhibitors of metalloproteinases (TIMPs)[78,79].

Cell Therapies for Shoulder Osteoarthritis: Clinical Outcomes

Clinical evidence regarding the use of the BMAC injection to treat GH osteoarthritis is scarce. Centeno et al. published

the longest series of patients who underwent treatment with autologous bone marrow concentrate in order to treat shoulder rotator cuff tears and osteoarthritis. From a total of 115 patients, 34 (29.6%) were diagnosed with osteoarthritis alone[80]. In order to guide the placement of the intra-articular needle for the BMAC injection, ultrasound or fluoroscopy was used. The assessment of the clinical outcomes was performed serially over time, using the numeric pain scale (NPS)[81], the DASH score, and a subjective improvement rating scale. Specifically in the patients belonging to the osteoarthritis subgroup, a significant improvement was observed in the 3 outcome scores ($p < 0.05$)[81].

Striano et al. conducted a study to evaluate 18 patients with osteoarthritis and refractory shoulder pain who were treated with microfragmented adipose tissue[82]. Significant improvement was observed at the 1-year follow-up in the NPS and the ASES scores: the average improvement that was registered in the NPS went from 7.5 to 3.6 ($p < 0.001$), and the average improvement in the ASES score went from 33.7 to 69.2 at 1 year ($p < 0.001$). There were no reports indicating any postprocedural complications or serious adverse events. A limitation of this study was that 75% of the patients had a concomitant partial or full-thickness rotator cuff tear. Therefore, it is impossible to know if the original cause of the pain was the osteoarthritis or the tendon tear.

It is important to highlight that although acromioclavicular (AC) joint osteoarthritis is a common cause of shoulder pain that is associated with GH osteoarthritis, it is still an underdiagnosed condition. Freitag et al. conducted the first case report evaluating the use of MSC therapy to treat AC joint arthritis[83]. An autologous ADSC preparation was used as part of MSC therapy to treat a 43-year-old patient with painful AC joint osteoarthritis. Both pain and functional improvements were reported by the patient as assessed by the DASH score and the NPS. As shown in the images taken at 12 months, structural improvement was observed, with a reduction in subchondral edema, subchondral cysts, and synovitis[83].

The number of studies on the use of cell-based therapies, especially autologous BMAC therapy, to treat symptomatic knee osteoarthritis recently has grown[69,84-86]. The currently available studies comparing BMAC injections with hyaluronic acid injections or placebo controls for knee osteoarthritis have shown promising results[69,83,85,86]. Rather than direct modification of the cartilage, immunomodulation and production of anti-inflammatory mediators constitute the claimed mechanism of action. Thus, much like a corticosteroid injection, symptomatic relief after BMAC injection may be consistent, but only temporary and without evidence of cartilage regeneration[85]. It should be noted that, although a potential benefit has been observed for knee osteoarthritis, this finding may not be reproducible in other joints.

Despite the promising results shown by BMAC in the treatment of degenerative joint conditions and obtaining early benefits in the treatment of GH joint osteoarthritis, it will not be possible to draw definitive conclusions until additional studies are conducted.

Finally, intra-articular injection of ADSCs also has shown favorable outcomes in the treatment of knee osteoarthritis. Spasovski et al. treated 9 patients with knee osteoarthritis with only 1 ADSC intra-articular injection at a concentration of 0.5 to 1.0×10^7 cells[87]. At 18 months of follow-up, the results revealed a substantial improvement as assessed by the Tegner and Lysholm score, the Knee Society score, and the VAS. In turn, Freitag et al. randomized 30 patients with symptomatic knee osteoarthritis in order to divide them into 3 groups. Intra-articular ADSC therapy was given to 2 treatment groups that received either 1 injection (100×10^6 ADSCs) or 2 injections (100×10^6 ADSCs at baseline and 6 months), while the third group served as a control. At the end of the 12-month follow-up period, clinically substantial pain and functional improvements were observed in the 2 treatment groups that received ADSCs[88].

Meticulous Level-I studies with properly conducted power analyses that directly compare BMAC and ADSC techniques with placebo or other therapies are necessary to further evaluate their effectiveness and safety in the care of osteoarthritis.

Overview

Evidence supporting the use of nonsurgical therapies to treat GH osteoarthritis is scarce. In addition, most of the available options have shown only partial and short-term relief of symptoms. The capacity of PRP and cell therapies to regulate the healing environment that has been demonstrated in basic science studies and the favorable clinical outcomes that have been achieved in patients with knee osteoarthritis make orthobiologic therapies a promising alternative. Although the few clinical studies that have been developed thus far showed favorable outcomes and minimal complications, there is a need for more robust prospective randomized trials to compare PRP and cell therapies with placebo or other treatments to further evaluate their effectiveness and safety in the care of GH osteoarthritis.

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Luciano A. Rossi, MD[1], Nicolás S. Piuzzi, MD[1,2], Shane A. Shapiro, MD[3,4]

[1]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[2]Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, Ohio

[3]Department of Orthopedic Surgery, Mayo Clinic, Jacksonville, Florida

[4]Mayo Clinic Center for Regenerative Medicine, Rochester, Minnesota

Email address for L.A. Rossi: luciano.rossi@hospitalitaliano.org.ar

ORCID iD for L.A. Rossi:
0000-0002-1397-2402
ORCID iD for N.S. Piuzzi:
0000-0003-3007-7538
ORCID iD for S.A. Shapiro:
0000-0001-5753-0625

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