Level V Article

Biological Treatment for Osteoarthritis of the Knee: Moving from Bench to Bedside—Current Practical Concepts

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Abstract: Biological-based therapies for cartilage pathology have gained considerable recognition in the last few decades due to their potential benefits including their minimal invasiveness, capacity for unprecedented healing, and potential for rapid recovery. Consequently, these therapies are likely to have the most noteworthy impact on patients with degenerative joint changes who want to remain active. Currently, the most researched treatments include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and cell-based therapies. Although further basic science research and well-designed randomized clinical trials are needed to elucidate the long-term role of these therapies in the treatment of osteoarthritis, there is compelling evidence for their use for certain indications. This article aims to review the existing literature for biological-based treatment options for osteoarthritis, critically assessing the current evidence-based recommendations and identify potential avenues for development.

Osteoarthritis (OA) is not only a significant cause of morbidity, limitation to physical activity, and health care utilization, it is also a source of increased mortality.[1] A recent systematic review reported that patients with symptomatic hip or knee OA had 55% greater all-cause mortality compared with the general population. Additionally, a history of walking disability was associated with excess all-cause mortality and mortality due to cardiovascular disease, even after adjustment for age and sex.[2] Furthermore, OA also accounts for up to 18% of all health care visits in the United States,[3,4] which translates into an annual cost of more than $460 billion to the economy, secondary to lost wages and treatment costs.[5]

Currently, the most effective therapies for OA are prophylactic/preventative measures to avoid the development or slow the progression of the degenerative process (chondroprotection).[6] In this regard, it is vital to understand the concept of "chondropenia," which represents the early stage of degenerative cartilage disease. Chondropenia is not only the loss of articular cartilage volume, but it is also a rearrangement of biomechanical, ultrastructural, biochemical, and molecular properties typical of healthy cartilage tissue.[7] Hence, most of the therapies described herein will aid in chondrofacilitation—strategies that seek to facilitate intrinsic repair of damaged articular cartilage.[6]

As of now, no curative therapies for OA exist, and thus health care providers should acknowledge that management of OA should be directed toward pain control, function optimization, and, more importantly, therapies that can modify the natural history of the disease (disease-modifying therapies).[8-10] In recent years, there has been an exponential increase in the use of orthobiologics for the treatment of cartilage disease due to their minimal invasiveness, potential disease-modifying properties, and rapid recovery.[8,10,11] These include among others, platelet-rich plasma (PRP),[12-14] bone marrow aspirate concentrate (BMAC),[15-17] and the use of cell based-therapies.[18,19] Table 1 summarizes the source, Food and Drug Administration (FDA) status, and advantages/disadvantages of each of these therapies.

Despite the growing use of these biologic treatments, and the existing excitement and drive by both the medical and lay press, the body of literature lacks substantial evidence in regards to its indications, timing and

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Table 1. Summary of the Source, Food and Drug Administration (FDA) Status, and Advantages/Disadvantages of Platelet-Rich Plasma (PRP), Bone Marrow Aspirate Concentrate (BMAC), and Stem Cells

	PRP	BMAC	Stem Cells
Source	Peripheral blood	Iliac crest (anterior superior iliac spine/posterior superior iliac spine)	Several sources (most common, bone marrow, adipose tissue)
FDA status (human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulation).	Regulated under section 361. Not required to obtain premarket approval/clearance from the FDA: the HCT/P is minimally manipulated and intended for homologous use only. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent; and either (1) the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (2) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function and (a) is for autologous use, (b) is for allogeneic use in a first-degree or second-degree blood relative, or (c) is for reproductive use.		Regulated by the FDA under section 351 of the Public Health Service Act, which requires FDA approval of a Biologics License Application for permission to introduce, or deliver, a biologic product.
Pros	Easy to extract. Does not require sedation. Harvest and processing can be done in clinic. Compelling literature supporting its use for symptomatic treatment of osteoarthritis. Growing evidence of synergistic effects with hyaluronic acid. Can be prepared in multiple forms: activated/inactivated, liquid, and solid matrix. Concentration of platelets can be adjusted depending on the pathology.	No culture expansion. Same day procedure. No risk of allogeneic disease transmission. Low risk of infection. Higher concentration of interleukin-1 receptor antagonist blocked. Can be performed with concomitant procedures.	The underlying premise is that the arthritic knee may be deficient in a stem cell or progenitor cell population and that this deficiency may be mitigated by the harvest and transplantation of cells. Allogenic and autologous cell transplantation can be used. Several tissues types to isolate tissues from. Expanded and differentiated in culture under controlled settings. May be performed with concomitant procedures.
Cons	Potential inflammatory response to high platelet concentrations. No standardized method for intra-articular applications. No optimal preparation method. Potential detrimental effect of red blood cells when used in intra-articular environment. Heterogeneous solution that may indirectly affect other intra-articular tissues (interleukins, reactive oxygen species). Variable growth factor and cytokine quantities depending on several factors such as age, time of extraction, immune status, etc.	Potential pain during harvest with local anesthetic alone. Should be performed under sedation. Variable stem cell quantity and quality. No proven benefit over PRP as of now. Higher concentration of leukocytes and therefore greater inflammatory reaction. Potentially detrimental effect of erythrocytes when used in intra-articular environment.	Cells must be expanded ex vivo and require 4 to 6 weeks. Potential immunologic risk to patients. Risk of allogenic rejection. Safety concerns with proliferation of undesired lineages. Treatment restrictions set by the FDA. Limited understanding of the duration of transplanted cells.

number of applications, processing techniques, and outcomes reporting.[6,20-25] This article aims to review the existing literature for biological-based treatment options for OA, critically assessing the current evidence-based recommendations, and identify potential avenues for development.

PRP

PRP is certainly not a new therapy, with reports that date from 1954,[26] with the first autologous use reported in 1987 following an open-heart surgery, to avoid excessive blood loss.[27] Since then, the application of autologous PRP has been safely used and documented in many fields including orthopedics, sports medicine, dentistry, neurosurgery, ophthalmology, urology, and wound healing, as well as cosmetic, cardiothoracic, and maxillofacial surgery. Although the use of PRP has rapidly expanded over the past few decades, the definition of PRP, type of PRP, processing methods, indications and timing, number of injections, and synergistic actions with other therapies have not been clearly defined in the literature and, therefore, will be the focus of this section.

Definition

Typically, PRP was defined as a volume of plasma that has a platelet count "above baseline" during the early stages of clinical research.[28] However, this definition has more recently been refined to be more quantitative, requiring PRP to contain more than 1 million platelets per milliliter[24] of serum or 5 times the amount of baseline platelets.[29] This elevated platelet count in PRP has been suggested as necessary to stimulate targeted injured cells to proliferate in vitro.[30,31] However, other researchers reported that increased platelet concentration beyond the physiologic level did not improve functional graft healing in anterior cruciate ligament[32] and medial collateral ligament animal models.[33]

Additionally, we know from the hemophilic arthropathy literature that the intra-articular presence of red blood cells (hemosiderin deposits) are thought to be critical in the early phases of hemophilic arthropathy.[34] Thus, it is important to include the number or even an upper limit of red cells present in PRP and deepen our knowledge in this regard as it might produce some chondrotoxicity. Further, the biological mechanism driving the clinical use of PRP involves the action of local growth factors in PRP, which modify the inflammatory response and may affect cell proliferation and differentiation, and therefore PRP anabolic/catabolic main factors and activity should also be taken into account when defining PRP.[8]

Types of PRP

PRP is widely applicable for the treatment of various acute and chronic musculoskeletal conditions that cannot stimulate tissue healing and regeneration on their own. Given that leukocyte-rich PRP (LR-PRP) is composed of high concentrations of both leukocytes (e.g., granulocytes, monocytes, and lymphocytes) and platelets that simultaneously secrete proinflammatory factors that have been found to be beneficial for soft-tissue healing,[35-37] there is still great controversy regarding the optimal quantity of platelets and leukocytes that defines its biological composition for intra-articular applications.[38,39] Leukocytes and platelets can have important anabolic properties but also produce an imbalance within the microenvironment by upregulating catabolic tissue growth factors such as matrix metalloproteinases that can lead to activation of unregulated signaling pathways that cause negative phenotypical changes of the tissue.[40] Thus, to evaluate the optimal leukocyte concentration in PRP, Sundman et al.[41] conducted a systematic review on all randomized control trials (RCTs) that compared the clinical effects of leukocyte-poor (LP) and LR-PRP and hyaluronic acid (HA) for the treatment of knee OA. Three RCTs that used LP-PRP reported positive outcomes compared with HA, while only one RCT using LR-PRP reported positive effects versus HA, suggesting that LP-PRP produces more consistent results intraarticularly.[41]

Processing Methods

A recent analysis of the reporting of PRP processing for musculoskeletal conditions (105 studies) showed that only 11.5% of studies reported on all necessary variables of PRP processing required to repeat the protocol.[24] Moreover, there was no consensus on the machines to be used to prepare the PRP (manual or automatic), number of spins, or speed and time of centrifugation. Automated commercial systems and manual processing methods are used to minimally manipulate desired blood fractions to concentrate LR-PRP and LP-PRP but have been found to produce product variations in blood cell and growth factor concentrations.[42-46] In this regard, both systems can produce similar results when performed correctly.[47]

PRP devices can usually be divided into lower (2.5-3 times baseline concentration) and higher (5-9 times baseline concentration) systems. The high-yielding devices include Biomet GPS (Biome, Warsaw, IN) II and III (platelet count 3-8×), Harvest SmartPRep 2 APC+ (Harvest Autologous Hemobiologics, Norwell, MA) (4-6×), and ArterioCyte-Medtronic Magellan (Minneapolis, MN) (3-7×). The lower concentration systems include Arthrex ACP (Naples, FL) (2-3×), Cascade PPR therapy (Edison, New Jersey) (1-1.5×), PRGF by Biotech Institute (Vitoria, Spain) (2-3×), and Regen PRP (Regen Laboratory, Mollens, Switzerland).[46] In a processing review, the most common first-spin combination of parameters was 3,200 rpm for 15 minutes. The median rate for spin 2 was 3,300 rpm (range, 200-

4,500 rpm), and the median time was 10 minutes (range, 2-25 minutes).[24] As noted before, evidence suggests that a double-spin protocol results in a higher concentration of platelets.[48] It should also be considered that variations in platelet concentrations and other platelet-derived constituents are influenced by harvest, patient demographics, and severity of pathology.[49]

Activating platelets within PRP via endogenous or exogenous coagulation triggers degranulation and subsequent secretion of several platelet-derived growth factors (e.g., cytokines and chemokines).[44,50] There is no consensus on whether or not platelets must be previously activated before their application and with which agonist. Calcium chloride is the most common activator used in the majority of clinical studies that activate PRP before the injection. Other investigators suggest that not activating the platelets results in a more sustained effect,[51] although no study to our knowledge has investigated this specific characteristic in OA. The content of fibrin in the gel is the most important factor controlling subsequent release. Platelet concentration, fibrinogen concentration, and the enzymes involved in the procoagulant pathway influence the final fibrin content.[52]

Indications and Timing

It has been reported that PRP stimulates HA production, reduces cartilage catabolism and joint inflammation (nuclear factor kappa B and cyclooxygenase-2), and increases cartilage synthetic activity (through collagen II and prostaglandins).[52] The apoptotic pathway of osteoarthritic chondrocytes is influenced as insulin-like growth factor-1 in PRP may down-regulate the expression of programmed cell death 5.[53] Concerning the timing, 3 separate reports have concluded that better results can be achieved in early versus late OA.[54-56] A recent prospective, randomized, double-blinded clinical trial (vs corticosteroid) on advanced knee OA (Kellgren-Lawrence [K-L] III and IV)[57] reported that statistical differences between groups were not found for the majority of the outcome variables, although the magnitude of improvements tended to be greater in the PRP group. Quality-of-life differences between values at 3 and 6 months versus baseline increased significantly more in the study group ($P = .05$ and .03, respectively) and so did general health perception differences at 6 months ($P = .018$).

Number of Injections

A recent randomized prospective study reported that PRP investigated whether one, 2, or 3 PRP injections (2-week intervals) was more effective for moderate knee OA, concluding that a minimum of 2 injections was more successful in treating the symptoms ($P < .001$).[58] Additionally, Gormeli et al.[59] recently reported that for patients with early OA, multiple (3) PRP injections are useful in achieving better clinical results ($P < .001$). For patients with advanced OA, multiple injections do not significantly improve the results of patients in any group ($P > .05$).[59]

Filardo et al.[60] suggested that the median duration of the clinical improvement was 9 months and therefore yearly intervals could be beneficial to maintain the effects in a consistent manner. Gobbi et al.[61] supported this by suggesting that the improvement obtained after 12 months can be further enhanced at 18 months by annual repetition of the treatment. Finally, Hart et al.[62] reported on a receptor loading administration (6 injections with weekly intervals), followed by 3 injections with a 3-month interval. Although they reported clinical improvement, they failed to demonstrate objective cartilage improvement on magnetic resonance imaging.

Synergistic Actions

It has been reported that PRP in combination with HA may have a synergistic action, by enhancing the migratory potential of fibroblasts based on in vitro studies.[63] Andia et al.[64] suggested that combining PRP and HA may produce a benefit from their dissimilar biological mechanisms and help in controlling delivery and presentation of signaling molecules. Chen et al.[65] reported that the combination of HA and PRP could synergistically promote cartilage regeneration and inhibit OA inflammation.

Clinical studies have replicated these findings even with more severe OA grades (K-L III/IV).[66] A randomized control clinical trial comparing PRP alone, HA alone, and both in combination demonstrated that combining HA and PRP resulted in a significant decrease in pain and functional limitation when compared with HA alone at one year post-treatment and significantly increased physical function at one and 3 months when compared with PRP alone ($P < .05$ for all variables).

Adverse Events

Most of the reported complications for PRP use are nonspecific, with the symptoms including pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia. No severe complications were reported, and all the events were self-resolved in days. Of note, more inflammatory effects were seen when LR-PRP was used.

Summary of PRP Utilization and Authors' Preferred Treatment

Based on the current literature, PRP is a reasonable approach after the first line of treatment has failed (activity change, weight loss, physical therapy [strength, agility]). Specifically, we use LP-PRP (Arthrex Angel System, 7%) in patients with symptomatic OA, administered in sets of 3 injections

separated by a week and repeated one year after the first set of injections. As noted above, the addition of HA has been reported to produce synergistic effects with PRP in both in vitro and in vivo studies and therefore we routinely use the combination of PRP and HA to improve our results.

BMAC

The indications for BMAC use are similar to the ones described above for PRP. However, it was theorized that the progenitor cells from the marrow could help improve the regenerative potential of BMAC, and therefore it could allow its use in more severe cases of OA.[67] Thus, BMAC use to treat knee OA has recently grown in popularity as it is one of the few approaches to deliver progenitor cells that are currently approved by the United States FDA and that can be performed in a single-stage procedure.[15] This is because BMAC is considered to be minimally manipulated and for homologous use, which falls under section 361 of minimally manipulated therapies (Public Health Service Act, 21 Code of Federal Regulation 1271) as long as it is not previously activated (more than minimal manipulation).

Bone marrow is harvested and centrifuged to isolate its cellular components in distinct layers concentrating the mononucleated cells (white blood cells, mesenchymal stem cells [MSCs], hematopoietic stem cells, and platelets) in one layer and the red blood cells in another. MSCs are of particular interest because they are capable of self-renewal and differentiation into mature muscle, bone, and cartilage.[68] Despite comprising only 0.001%-0.01% of cells in BMAC, the MSCs that are present may play a role in healing through homing capabilities that recruit more cells to the injury site.[69,70] MSCs' regenerative potential, in conjunction with the ability to signal the surrounding tissue to secrete growth factors that modulate the immune response and encourage regeneration at the injury site, suggests that MSC presence provides BMAC with potentially strong regenerative properties, even for avascular tissues like articular cartilage.

Besides that most of the reports claim the use of MSCs, to our knowledge none have fully characterized these progenitor cells according to the International Society for Cellular Therapy: (1) culture-expanded cells that adhere to tissue culture plastic; (2) cells that retain the capability for trilineage differentiation (bone, cartilage, and adipose); (3) cells expressing CD105, CD73, and CD90 (with 95% prevalence); and (4) cells lacking expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules.[71] If these criteria are not met, the term "MSC" should not be used.

BMAC has also been reported to contain increased levels of interleukin-1 receptor antagonist and interleukin-1-beta, growth factors that have critical roles in regeneration through immune response modulation (inflammation reduction).[68,72] This could potentially be the explanation for a faster symptomatic improvement than PRP, because the inflammation cascade is targeted through a blockage path. Cassano et al.[43] also reported that BMAC has a high concentration of leukocytes (×12) and therefore could produce more inflammatory symptoms after the injection like LR-PRP when compared with the gold standard LP-PRP for OA.

Harvest of BMAC

Possibly one of the most important questions remains on the methodology of the harvest and how to obtain a larger population of progenitor cells. Bone marrow is typically aspirated from the iliac crest (anteriorly or posteriorly). Hernigou et al.[73] reported that the quality could be improved (300% higher cell progenitor cells concentration) by aspirating at multiple locations with a small syringe (10 mL) as progenitor cells lie in the trabecular bone, which can be accessed by changing the orientation of the trochar. Conversely, a recent study[74] found no significant difference between the cell ratios of single- versus multiple-site groups ($P > .05$ for all groups). Both aspiration techniques were found to provide ample colony-forming units without a marked difference in appearance. Of note, in the single-site group, variations in the position of the trochar were performed by sequential rotation (aspirate-rotate-aspirate method). Additionally, no significant difference was found between groups concerning MSC numbers ($P = .609$). Moreover, pain during and 24 hours after the procedure was significantly greater with the multiple-site method than with the single-insertion method ($P < .046$).

Outcomes of BMAC

Few studies have evaluated the effects of BMAC on OA. Kim et al.[16] evaluated outcomes of BMAC injection with adipose tissue in a case series of 41 patients (75 knees) with knee OA (K-L grades I to IV). At 12-month follow-up, visual analog scale pain score, International Knee Documentation Committee, Short Form-36, Knee Injury and Osteoarthritis Outcome Score, and Lysholm scores increased among the group compared with preoperative scores, although statistical significance was not reported. A significant association was found between higher K-L grade and inferior outcomes at follow-up ($P = .002$). Hauser et al.[17] performed intra-articular injections (mean 4.1 injections per patient) with unfractionated whole bone marrow in combination with hyperosmotic dextrose in a small case series of 7 patients with hip, knee, or ankle OA. At a minimum 6-week follow-up, 5 of 7 patients noted complete relief or strong functional improvement. Based on a visual analog scale from

0 (complete relief) to 10 (maximum limitation), average pain intensity scores improved from 6.2 preoperatively to 0.07 at follow-up ($P = .002$). Likewise, joint stiffness improved from 7.0 to 0.7 ($P = .002$). Centeno et al.[67] compared the efficacy of autologous BMAC with or without an adipose-derived stem cell graft for treatment of knee OA. They defined an adipose-derived stem cell graft as a 5-10 mL lipoaspirate extracted from the subcutaneous tissue on the superior buttocks or lateral thigh that was minimally processed via low-speed centrifugation or by allowing the layers to settle for several hours and then discarding the top layer. The addition of an adipose graft to the BMAC treatment was not reported to improve efficacy. However, both treatment groups received PRP and plasma lysate in addition to BMAC, thereby making it difficult to determine which part of the treatment provided the most benefit.

In a systematic review, which included 3 studies for OA treatment with BMAC (Kim et al.,[16] Hauser and Orlofsky,[17] and Centeno et al.[67]), Chahla et al.[20] reported a lack of high-quality studies (case series, with no control group that uses a multitherapeutic approach), despite the growing interest in the use of BMAC. It was also reported that the use of BMAC was a safe procedure with reported good results; however, there was a varying degree of beneficial results after BMAC application with and without an additional procedure for the treatment of early stages of OA. A recent study that was not contemplated in the review is the only prospective, single-blind, placebo-controlled (saline) pilot study in patients with bilateral OA monitored by FDA. For this study, 25 patients with bilateral knee pain from bilateral OA were randomized to receive BMAC with platelet-poor plasma into one knee and saline placebo into the other. At 6 months, BMAC injections provided the same amount of pain relief and increased activity level as saline injected into the patient's contralateral knee ($P = .09$ for all).[75]

Adverse Events

Reported complications for BMAC were similar to the ones described for PRP above. Centeno et al.[67] reported the frequency of adverse effects after the procedure to be 6% for BMAC and 8.9% for BMAC with adipose graft. Self-limited pain and swelling were the most commonly reported adverse events. Although the Centeno et al. did not define "severity," 0.4% of the adverse effects were considered severe, but it was not possible to establish a causative relationship with the procedure.

Summary of BMAC and Authors' Preferred Treatment

Early basic science and clinical studies have elucidated the benefits of BMAC for the treatment of knee pathologies in both animal and human models with a relatively safe profile. The ideal harvest technique, carrier for BMAC, number of BMAC treatments, and the timing of injections for BMAC have not been well characterized. Although improved outcomes following BMAC injections have been reported in patients with OA, these studies used a variable number of treatments, had limited follow-up intervals, and could not demonstrate a better result when compared with placebo.[16,17,67,75] Thus far, there is no evidence that BMAC is superior to PRP for the symptomatic treatment of OA, and therefore we do not use it routinely in our practice (due to the more invasive nature of the harvest and the lack of literature supporting its benefits over PRP). In this regard, there are 2 studies registered in clinicaltrials.gov that can help elucidate this question (Conventional Platelet-Rich Plasma Versus Concentrated Bone Marrow Stem Cell Injections for Osteoarthritis of the Knee [Shapiro et al.] and Bone Marrow Aspirate Compared to Platelet Rich Plasma for Treating Knee Osteoarthritis [Hackel et al.]).

Cellular-Based Therapies

Progenitor cells that proliferate and differentiate depending on their surrounding biochemical environment act as a highly attractive tool for cartilage restoration. However, there is still limited evidence of the outcomes and safety profile of this treatment, and outcome-reporting characteristics are heterogeneous. As such, it has been proposed that a standardized nomenclature is essential to clarify communication of processing and results of this therapy.[20,21,23,76-78] Connective tissue progenitors are defined as proliferative cells capable of differentiating into various connective tissue phenotypes.[79] Thus, the term "connective tissue progenitors" encompasses not only pluripotent stem cells but also progenitors derived from stem cells, which may be at various stages of cellular differentiation (a heterogeneous sample).

Definition

Stem cells are defined as undifferentiated cells that are capable of proliferation, regeneration, self-maintenance, and replication.[80] Human embryonic stem cells, induced pluripotent stem cells, and MSCs have all been used for treatment of OA.[81] Due to their accessibility, MSCs are the most popular stem cell option for articular cartilage repair.[82] Furthermore, it is more difficult to assure homogeneity in cell division with induced pluripotent stem cell or human embryonic stem cells than with MSCs.[83] Additionally, MSCs are present in a range of tissue types, have anti-inflammatory effects, can be harvested in large quantities, and are shown to produce proteins conducive to cartilage regeneration.[10] In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International

Society for Cellular Therapy defined the minimal criteria for a human cell to be classified as an MSC as stated in the BMAC section.

Source Type

Chang et al.[82] suggested that MSCs also have anti-inflammatory elements, as preclinical trials in small mammals observed an anti-inflammatory response. Due to their easy accessibility and minimal morbidity caused during harvest, adipose-derived stem cells (ASCs) result in a high yield of stem cells and have gained recent attraction for this reason.[84] Furthermore, the growth properties of ASCs are superior to bone marrow-derived MSCs (BMSCs).[84] ASCs may be obtained either through liposuction aspirates or from the infrapatellar fat pad.[8] When cultured with appropriate growth factors (TGF-β, BMP-2, BMP-6, BMP-7), ASCs may differentiate into chondrocytes in vitro or in vivo.[85]

BMSCs are popular due to ease of collection (the procedure is minimally invasive) and the extensive laboratory characterization of these cells.[8,86] Stem cells from adipose, peripheral blood, and synovium can also be used. However, following bone marrow aspiration the cell yield is low, and therefore these stem cells must be isolated and expanded in cell culture prior to clinical use. Common extraction sites are the iliac crest, the tibia, and the femur.[82] MSCs may differ between anatomic regions of the same tissue type regarding yield and characteristics.[87] In the case of BMSCs, bone marrow is aspirated 3 weeks before the transplantation is set to occur. The aspirated cells are then cultured in a monolayer for expansion. Several factors can be used to induce these cells to differentiate into host mesenchymal tissue including cartilage and bone. The cells can then be cultured in scaffolds to transplant into the affected joint. Synovial-derived MSCs have the most promising chondrogenic ability, but little literature exists exploring this topic.[82]

Cell-Based Therapies Clinical Outcomes

In a recent systematic review, Chahla et al.[76] examined the literature of studies with a level of evidence of III and higher that examined cell therapy delivered by intra-articular injection in the knee. Only 6 studies were included, and the studies varied widely concerning cell sourcing, cell characterization, adjuvant therapies, and assessment of outcomes. All studies reported improved results with intra-articular cell therapy or OA and focal chondral defects and no significant adverse events. However, the investigators concluded that only modest improvement was found and that a placebo effect could not be ruled out. The investigators suggested that a focus to improve study methodology is needed, including blinding, quantitative characterization of methods for cell harvest, processing and delivery, and standardized reporting of clinical and structural outcomes.

Similarly, McIntyre et al.[88] reported on 14 MSCs studies (originating from bone marrow, adipose tissue, synovial tissue, or peripheral blood) for the treatment of OA. From this only 5 OA studies had a control group. Post-treatment imaging was not always positive, and there was an occasional lack of congruity between imaging and clinical results, suggesting that other factors may have accounted for the clinical improvement. Moreover, follow-up procedures, including second-look arthroscopy and imaging, were often conducted on only a small subset of the subjects, increasing the potential influence of bias and limiting the validity of published results. The investigators concluded that autologous intra-articular MSC therapy is safe, with generally positive clinical outcomes; however, further research is needed to elucidate its long-term effects.

Adverse Events

The safety of using MSCs remains not well understood. There is a concern that these cells can further develop into an unwanted lineage as oncologic cells.[89] The risks of short-term processing are primarily the risks of compromised sterile technique or cell toxicity during processing. Culture expansion methods add additional risk of inadvertent selection of clones with undesirable epigenetic or genetic changes.[90] Although no major adverse reactions have been reported for the treatment of OA with MSCs, Goodrich et al.[91] reported ectopic bone formation within the repair tissue of focal chondral defects in 30% of the cases in a horse model (using BMSCs in combination with autologous platelet-enriched fibrin). Among the OA studies reported in a systematic review,[76] 24 minor events were reported, 23 by Vega et al.[19] comprising transient pain, effusion, or inflammation controlled with NSAIDs. Lee et al.[92] reported no complications in their focal chondral lesion study. Saw et al.[93] reported 85 minor events comprising most commonly warmth and swelling, followed by difficulty in knee motion. There was no trend for greater adverse events between treatment and control groups.

Summary of Cellular-Based Therapies and Author's Preferred Treatment

The common denominator of the literature reporting on progenitor cells for the treatment of knee OA has been positive clinical outcomes and no major adverse events. Up to now, the differences that have been reported between the study and control groups are modest, and randomized but unblinded methodologies do not control for patient- or clinician-related bias. Therefore, culture-expanded cell treatments are not a part of our current armamentarium (only used for research purposes in FDA-approved clinical trials). We believe that as our understanding of cell signaling as well as the intra-articular environment evolves, cell-based therapies will become the standard of care for many pathologies.

Conclusions

Despite the increasing and widespread use of biologic treatment agents in knee OA, there are still several areas of controversy and a lack of documentation. No consensus exists on the algorithm for treatment, indications, optimal protocol of processing, and delivery and outcome reporting. Although essential advancements have been made in the field of biologics, these therapies are still in their beginnings. In order to advance the knowledge, it is important to first define a minimal standard for each of these treatments and set a clear nomenclature system for reporting. Nonetheless, there is compelling evidence (several Level I studies) that support the use of biological approaches (namely, PRP) with better results for the symptomatic treatment of knee OA when compared with other several therapies (such as steroids, ozone, and HA). Further, synergistic actions are increasingly being reported for PRP and HA when administered in conjunction, and therefore this constitutes our current recommendation. Although cell-based treatments have shown promising results, further understanding of the joint cytokine milieu at the time of administration and cell epigenetic and genetic signaling will drive a significant improvement that could generalize its use.

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