Management of osteoarthritis - biological approaches: current concepts

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ABSTRACT

Osteoarthritis is a major cause of disability and decreased quality of life in millions of patients and costs billions of dollars annually to treat. The current treatment options for osteoarthritis include weight loss, activity modification, anti-inflammatory medications, steroid intra-articular injections, lubricating hyaluronic acid injections and arthroplasty for end-stage cases. There has been interest in recent decades in identifying biological treatment modalities to slow the progression of the disease and preserve native joints. Biologics including platelet-rich plasma, bone marrow aspirate concentrate and adipose-derived mesenchymal stem cells are among the most commonly investigated treatments. Existing literature demonstrates anti-inflammatory properties of orthobiologics, butno treatment has clearly demonstrated significant joint preservation properties, including the ability to reverse progression of osteoarthritis. What is more clear is that these injection treatments have been shown in the majority of studies to be safe. Research is ongoing to identify optimal indications, preparations, compositions, safety profiles and clinical outcomes of biological therapies. This article will review the current evidence of biologics for treatment of osteoarthritis and recent statements made by orthopaedic subspecialty groups on this important topic.

Current concepts

- Osteoarthritis is a major cause of chronic pain, disability and decreased quality of life.
- Steroid and hyaluronic acid injections have not been shown to alter the osteoarthritis disease process.
- Orthobiologics have emerged as potential adjunctive or stand-alone therapies to treat mild to moderate osteoarthritis.
- Platelet-rich plasma has been shown to decrease pain, but no significant disease-altering properties have been consistently reported.
- The current data regarding bone marrow aspirate concentrate are heterogeneous in study design, but early clinical outcomes are encouraging for use in patients with symptomatic osteoarthritis.
- Adipose-derived mesenchymal stem cells are novel orthobiologics that are currently being investigated for use in patients with osteoarthritis.

Future perspectives

- Evaluate clinical differences in outcomes between leucocyte-poor and leucocyte-rich platelet-rich plasma.
- Identify the metabolic properties of mesenchymal stem cells based on patient demographic factors such as age and medical comorbidities.
- Clinical evidence for use of adipose-derived mesenchymal stem cells in a patient with osteoarthritis.
- Refining indications for use of orthobiologic treatments.
- Improvement in scaffolds for use in cell-based orthobiologic treatments.

INTRODUCTION

Osteoarthritis (OA) is a serious condition that can lead to chronic pain, disability, decreased quality of life and inability to perform activities of daily living.[1] A recent study reported that patients with symptomatic knee or hip OA had a 55% higher risk for all-cause mortality when compared with the general population.[2] More than one in four people may develop symptomatic OA in his or her lifetime.[3 4] When conventional non-surgical treatment methods such as activity modification, non-steroidal anti-inflammatory medications, weight optimisation, and low-impact exercise and strengthening programs fail, providers are faced with challenging options of injection therapies or operative intervention. Many patients revert to total joint arthroplasty for definitive management of their OA; however, this is not always a viable option, depending on patient age, surgical risk and medical comorbidities. Non-surgical injection therapies have been developed in an attempt to achieve durable symptomatic relief and ideally offer disease-modifying benefits.

CURRENT INJECTION THERAPIES

Injections have been used as treatment options for OA, specifically of the knee, dating back over a century.[5 6] Despite the widespread use of corticosteroid agents for OA, the American Academy of Orthopedic Surgeons (AAOS) Clinical Practice Guidelines approved in 2013[7] graded corticosteroid agents as an 'inconclusive' evidence rating and stated that 'we are unable to recommend for or against the use of intra-articular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee'. The level I–II literature regarding corticosteroid use in these patients is mixed at best.[8–11] Shortly after widespread use of corticosteroids began, hyaluronic acid (HA) was approved by the Food and Drug Administration, but it too has not provided

the disease-altering effects that are desired.[6] The AAOS guidelines for treatment of knee OA offer a 'strong' recommendation that they cannot recommend using HA for symptomatic OA.[7] As the authors of the AAOS guidelines note, while meta-analyses have demonstrated improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function and stiffness subscales, none of the improvements met the minimal clinically important improvement thresholds.[7]

The limited therapeutic benefits of HA and corticosteroids in the long term have given rise to novel, innovative biological intra-articular injection and cell therapies, specifically platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), adipose-derived mesenchymal stem cells (AD-MSCs), antitumour necrosis factor agents, interleukin (IL)-1 receptor agonists and gene therapies. These orthobiologic agents represent a shifting paradigm as the pathophysiology of OA continues to be better understood to target complex cellular signalling pathways that play a role in disease progression.[12–14] To date, the existing human literature is most robust regarding PRP and BMAC, with few early studies published regarding AD-MSCs. Cultivated stem cells expanded in vitro are another source of potential cartilage restoration but are outside the scope of this review. This article will detail the indications for orthobiologics, namely PRP, BMAC and AD-MSC, and discuss different preparations and summarise current clinical outcomes evidence for treatment of symptomatic OA. This review does not aim to report all articles related to orthobiologics, nor does it aim to deeply discuss each subsect of orthobiologics in their entirety.

INDICATIONS

OA is often thought of as a progressive disease of older adult populations; however, OA can also affect young, active people, leading to diminished quality of life if not addressed. Numerous risk factors apart from age have been described, including genetics, obesity, previous joint injury, recreational activities, occupation, gender and race.[15–17] Patients who lead an active lifestyle and do not have radiographic evidence of Kellgren-Lawrence (KL) stage IV OA or advanced imaging evidence of diffuse, full-thickness articular cartilage loss are potential candidates for orthobiologic treatment of their disease. These are the current indications and are subject to change as data continue to emerge. Trials to date have included patients as young as 18 and as old as patients in their 80s. It is unclear what role, if any, age may play on the activity or 'fitness' of autologous products such as BMAC. Authors have reported a reduction in the absolute number of mesenchymal stem cells (MSCs) within BMAC and decreased proliferative capacity with age.[18 19] Further considerations include concomitant meniscal, ligamentous and malalignment pathologies. It may be challenging to address the underlying OA cascade with orthobiologics when secondary aetiologies such as varus malalignment may be contributing to disease progression.

PLATELET-RICH PLASMA

PRP is a concentration of platelets with plasma containing supraphysiological levels of growth factors and cytokines postulated to aid in tissue healing and anabolism.[12 20] The platelets within PRP contain greater than 1100 proteins and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF), which collectively has a chemotactic effect on MSCs.[21] These growth factors also serve anti-inflammatory properties modifying gene expression and limited production of matrix metalloproteinases and nuclear factor-kappa B.[22 23] Some have specifically defined PRP as plasma that contains a higher concentration of platelets that can reach as high as 9.3 times.[24 25]

Preparations and processing

Over 100 publications exist describing various PRP preparations for treatment of knee OA alone.[12] Dozens of different protocols for autologous PRP retrieval, preparation and injection have been described, but the basic steps remain consistent throughout. First, whole blood is drawn from a patient using standard venipuncture technique. The drawn blood is then placed into a centrifuge and separated into its three layers based on density. The bottommost layer consists of red blood cells, the middle layer or the 'buffy coat' contains white blood cells, and the top, least dense layer is the PRP. Preparations differ by being 'leukocyte-poor' (LP-PRP) or 'leukocyte-rich' (LR-PRP) depending on whether the entire buffy coat is incorporated with the PRP (LR-PRP) as opposed to only the superficial layer of the buffy coat (LP-PRP).[22] To isolate LP-PRP, the superficial buffy coat layer and plasma layers are then centrifuged a second time to remove any white blood cells and red blood cells that may have been incorporated. LP-PRP is thought to be superior for use in OA because leucocytes can stimulate an immune response that may be inflammatory in nature due to the release of IL-1β and tumour necrosis factor-α.[26] By excluding leucocytes from the PRP preparation, the thought is that the inflammatory pathways will not be activated as robustly. The biological effects on the osteoarthritic joint and the clinical relevance of leucocytes in PRP have yet to be clearly demonstrated.

Castillo *et al*[27] compared PRP preparations from five healthy donors using three commercially available PRP concentration systems (MTF Cascade, Arteriocyte Magellan and Biomet GPS III). Specifically, the authors compared PRP platelet, red blood cell, white blood cell, fibrinogen, active TGF-β, and several different PDGF and VEGF concentrations between the different commercial systems and found significant differences.[27] While some have reported that higher concentrations of platelets release higher concentrations of growth factors, others have stated that platelet concentrations above 1x10^9/L do not afford additional benefit.[22] This is just one example of the heterogeneity in how PRP is prepared and what is actually injected into patients, making it challenging to evaluate the literature on PRP.

Clinical outcomes

Riboh *et al*[28] performed a meta-analysis of randomised controlled trials (RCT; level I) and prospective comparative studies (PCS; level II) to compare the clinical outcomes between HA, LP-PRP and LR-PRP for treatment of knee OA. Nine studies (six RCT and three PCS) totaling 1055 patients were included. The authors reported significantly better WOMAC scores in LP-PRP as compared with HA or placebo, but no difference when compared with LR-PRP. There were no differences in adverse events between LP-PRP and LR-PRP. However, both PRP preparations did have higher incidences of adverse events than HA.[28] Others have reported superiority of LP-PRP to normal saline controls in a series of 3 weekly injections for patients aged 30–80 with KL grades II–III OA.[29] Specifically, in a randomised, double-blind trial of 30 patients, Smith[29] showed that WOMAC scores significantly improved by 78% from their baseline score at 1-year follow-up compared with just 7% improvement in the saline control group. More recently, a randomised, double-blind trial comparing intra-articular injections of LP-PRP, HA and normal saline was performed in 87 patients with symptomatic

OA stages I–III, aged 20–80 years.[30] The authors randomised patients to one of the three groups receiving 3 weekly injections and had 12-month follow-up. All three groups showed significant improvements in WOMAC and International Knee Documentation Committee (IKDC) subjective scores at 1 month after final injection, but only the LP-PRP group sustained the improvement in scores out to 12 months and met the minimal clinically importance difference (MCID) in the WOMAC score at all postinjection follow-up visits.[30]

To date, there have been over 10 published level I studies of PRP intra-articular injections for treatment of knee OA alone. Several systematic reviews and meta-analyses have been published using level I or II evidence. Dai *et al*[31] analysed 10 RCTs including 1069 patients evaluating PRP versus control injections for symptomatic knee OA. The authors reported similar pain and functional scores on WOMAC and IKDC subscales at 6 months, but significantly better WOMAC pain scores (mean difference −2.83), WOMAC function score (mean difference −12.53), WOMAC total score, IKDC score and Lequesne score when compared with HA at 12 months. It bears mentioning that 8 of the 10 included studies were judged using standardised metrics to have a high risk of bias. In a more recent systematic review, Delanois *et al*[12] identified 11 level I studies and concluded that PRP may reduce pain and lead to modest improvements in function, as was reported in the majority, but not all, of the studies. However, no study has demonstrated the ability of PRP to slow or reverse the OA process.[12] The majority of PRP RCTs suffer from small sample sizes, short follow-up intervals and varying preparation protocols. Currently, PRP may best be used as an adjunct or as non-surgical treatment to achieve short-term pain relief and possible improvement in function without altering disease progression. Johal and colleagues[32] summated the PRP literature within orthopaedic surgery in a systematic review and meta-analysis. The authors identified 78 RCTs including 5308 patients. Interestingly, 44% of studies used PRP as an adjunct during surgical treatment. The data pertaining to OA demonstrated moderate-quality evidence to support a reduction in pain at 1 year regardless of the type of PRP preparation.[32] Taken in sum, these data not only show an exponential increase in research into the utility of PRP for treatment of OA, but that a significant amount of work needs to be done to better elucidate optimal preparation and processing techniques, injection schedules, and patient indications.

BONE MARROW ASPIRATE CONCENTRATE

Bone marrow aspirate contains a mixture of cellular components including platelets, white blood cells, red blood cells, haematopoietic precursors, adipose cells and non-haematopoietic precursors.[33] From bone marrow aspirate, the platelets, growth factors and multipotent MSCs can be isolated through centrifugation to form what is known as BMAC. Bone marrow aspirate-derived mesenchymal stem cells (BM-MSCs) have been shown to be able to differentiate into osteocytes and chondrocytes.[33–37] However, studies have demonstrated that BM-MSCs comprise merely 0.001%–0.01% of mononuclear cells within bone marrow aspirate after density gradient centrifugation to remove granulocytes, red blood cells and immature myeloid precursors.[38 39] Numerous growth factors, including many of the same factors found in PRP, have been identified in BMAC but in higher quantities.[40 41] TGF-β superfamily of factors which have been linked to chondrocyte proliferation, and PDGF thought to promote wound healing, collagen synthesis and suppression of inflammatory mediators, such as IL-1β, insulin growth factor-1, fibroblast growth factor-18, bone morphogenetic protein-2 (BMP2) and BMP-7, among others, are present in higher quantities in BMAC than in PRP.[33 42–45]

Preparations

There are several sites in the body from which bone marrow aspirate harvest has been described. Commonly used sites include the iliac crest, distal femur, proximal tibia, proximal humerus and the calcaneus. Authors have reported that bone marrow aspirate taken from the posterior iliac crest has the highest concentration of BM-MSCs.[46–49] There are at least eight commercially available systems that can be used to harvest bone marrow aspirate, all of which require 30 mL at a minimum, but preferably 60 mL.[22] The aspirate then undergoes centrifugation. The centrifugation parameters of commercially available systems differ widely, including centrifugation time from 7.5 to 20 min, speed from 2400 to 4000 revolutions per minute (rpm), and possibly requiring more than one spin cycle.[50] The output volumes of BMAC range from 3 mL to 40 mL. Gaul *et al*[50] performed a review of commercially available point-of-care devices for BMAC and ultimately concluded that the systems differ widely and that no standardised reporting method is currently in place to describe biological potency. As Chahla and Mandelbaum[51] described, there are two main ways of implanting BM-MSCs, namely as an injection with a fluid or delivery of cells through a scaffold that can be implanted. The wide variation in system protocols and lack of standardisation methods make comparisons challenging as the true biological potential of each product from patients is not known.

Clinical outcomes

Kim and colleagues[52] conducted a study in 41 patients (75 knees) diagnosed with KL grades I–IV OA assessing the clinical outcomes following BMAC injection into the knee joint. The majority of the included patients (76%) were radiographically diagnosed with KL grades II or III OA and the mean age was 60.7 years. The authors reported a decrease in Visual Analogue Scale (VAS) pain scores from 7.0 preoperatively to 4.1, 3.5 and 3.3 at 3, 6 and 12 months postinjection. There were also notable improvements in IKDC scores from a mean of 37.7 preoperatively to 69.3 at 12 months. Lysholm Knee Questionnaire increased from a mean of 37.3 preoperatively to 71.0 at 12 months, and Short-Form-36 increased from 31.5 to 47.7 at 12 months. Interestingly, the improvement in VAS pain scores was inferior in patients with grade IV OA, suggesting BMAC is more effective in mild to moderate OA.[52] Shapiro *et al*[53] conducted a single-blind RCT in 25 patients with bilateral symptomatic knee OA excluding KL grade IV. Patients were randomised to receive BMAC in one knee and a saline injection in the contralateral knee. Per their protocol, 52 mL of bone marrow (26 mL from each superior iliac crest) was harvested which resulted in, on average, 6 mL of BMAC, of which 5 mL was injected and 1 mL used for composition analysis. Composition analysis demonstrated a median of 34 400 MSCs with 97% cellular viability. Their results showed a significant decrease in VAS pain scores and improvements in Osteoarthritis Research Society International (OARSI) Intermittent and Constant Osteoarthritis Pain scores in both knees from baseline at 1 week, and at 3 months and 6 months. No differences were seen between BMAC and placebo injections.[53] The same group of authors followed these patients out to 12 months, at which point they obtained MRI T2 quantitative mapping to evaluate cartilage appearance. No significant differences were identified on T2 quantitative MRI

mapping between the saline control and BMAC knees.[54] Others have reported case series on BMAC for OA, specifically a series of 681 patients (840 knees) by Centeno *et al*.[55] Centeno and colleagues'[55] study reported improved Lower Extremity Functional Scale scores and lower mean Numeric Pain Scale scores in BMAC with and without adipose grafts. There was no difference between the two groups. Taken collectively, these data, although heterogeneous in study design and methodology, demonstrate promising early clinical outcomes for use of BMAC in the treatment of symptomatic OA. Clearly more work is needed in larger, prospective studies to better elucidate the mechanism of action, optimal preparations and indications of BMAC.

ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

MSCs may be obtained through sources other than bone marrow, including adipose tissue which is more easily accessible. AD-MSCs are obtained through liposuction or lipoaspirate. The sample obtained then needs to be purified and processed using a commercially available point-of-care system such as Lipogems (Lipogems International, Norcross, Georgia). With this system, adipose tissue is typically harvested from the abdomen or flank after a minimum of 180 mL of anaesthetic fluid, Klein solution, is placed into the site of harvest. A vacuum syringe is then used to obtain the aspirate sample. The injection is typically less than 25% of the quantity obtained. The aspirated tissue is washed with at least 1 L of normal saline through a filter device to arrive at the final injectable.[56] There are additional systems to obtain AD-MSCS, and Lipogems is currently the most studied system.

Few human studies have been performed evaluating the use of AD-MSCs for treatment of OA. Jo *et al*[57] conducted a proof-of-concept clinical trial to assess the safety and efficacy of AD-MSCs for treatment of symptomatic knee OA. In phase I of their trial, three patients in groups received injections of low dose (1.0×10^7 cells), mid-dose (5.0×10^7 cells) and high dose (1.0×10^8 cells), and phase II included nine patients receiving high dose. The primary outcomes were WOMAC scores at 6 months. There were no adverse events during the trial. The authors reported improvements in WOMAC score from a mean of 54.2 to 32.8 in the high-dose group only, while the mid-dose and low-dose groups did not see improvements. There was no improvement seen radiographically from preinjection to 6-month postinjection in any group. However, it was found that the size of cartilage defects measured on MRI significantly decreased in the medial femoral and tibial condyles in the high-dose group.[57] A research group in Italy reported a case series of 52 patients with grades 0–II KL OA who underwent arthroscopic debridement followed by percutaneous injection of AD-MSCs into the knee. The outcomes of interest were the International Knee Society (IKS) knee and function scores and VAS pain scale. The mean follow-up was 15.3 months, with the authors noting a significant improvement in IKS knee scores from a mean of 37.4 preoperatively to 62.6 postoperatively at the time of final follow-up. The mean IKS function score also improved from 57.2 to 83.0, and the mean VAS pain score decreased from 8.5 to 5.1.[58] Without a control group of surgery alone, it is challenging to determine if the clinical improvement is attributable to the AD-MSC injection to some extent or simply the arthroscopic procedure. This is a new technique and more work needs to be done to evaluate the safety and efficacy in vivo of this procedure.

CONCLUSIONS

Orthobiologics are an intriguing and potentially beneficial category of alternative treatment modalities for OA. To date, there remains a paucity of high-quality, prospective clinical evidence to suggest PRP, BMAC or AD-MSCs alter in a meaningful way the disease process of OA. These treatments currently may serve as short-term palliative options for patients with mild to moderate OA either as stand-alone injection therapies or as an adjunct to surgical options such as debridement or microfracture. Larger scale, multicentre, randomised trials are needed to better elucidate optimal indications, scaffolds for cell therapy implantation, compositions, preparations and processing, and clinical outcomes of orthobiologics.

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