УДК: 616.748.2–007.21./796.071:616-071–059
HTTPS://DOI.ORG/10.37647/2786-7595-2024-121-2-39-44

Biological Treatment of Knee Osteoarthritis. The Role of Mesenchymal Stem Cells and Platelet-Rich Plasma

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Summary. *Osteoarthritis (OA) is the most common joint disease, which is associated with growing population ageing. Beyond conventional medical and surgical interventions, there is an increasing number of «biological» therapies. These therapies may have a limited evidence base and, for this reason, are often only afforded brief reference (or completely excluded) from current OA guidelines. The aim of this review was to analyze current evidence regarding mesenchymal stem cells (MSCs) therapy and platelet-rich plasma (PRP). There is some evidence to suggest symptomatic improvement with MSCs injection in knee OA, with the suggestion of minimal structural improvement demonstrated on MRI, and there are positive signals that PRP may also lead to symptomatic improvement, though variation in preparation makes inter-study comparison difficult. Although controlled studies have been conducted to evaluate effectiveness in OA, they have been often of small size, limited statistical power, uncertain blindness, and using various methodologies. These deficiencies leave open the question of whether they have been validated as effective therapies in OA. The conclusions of this review are that all biological interventions definitely require clinical trials with robust methodology to assess their efficacy and safety in the treatment of OA beyond contextual and placebo effects.*

Keywords: *osteoarthritis; knee; mesenchymal stem cells; platelet-rich plasma.*

Background

Osteoarthritis (OA) is the most common joint disease in the world, diagnosed in more than 500 million patients, and more than half of them have OA of the knee joint [1]. OA is becoming an increasingly serious socioeconomic and public health issue, as the number of patients with disability increased by 64% from 1990 to 2010.

The current dogma is that OA may have differing causes but with a common, multi-tissue morphology including cartilage fibrillation, fissures and loss of intracellular substance, subchondral bone changes, and synovitis. OA is more prevalent in females than males and, although it can affect any joint, the most common anatomical sites include the knee, distal interphalangeal joints, and hip [2]. Clinically, OA is characterized by joint pain, significant stiffness and leads to functional decline and a reduced quality of life for the affected individual.

There are a number of different treatments for OA including non-pharmacological and pharmacological approaches.

However, despite a number of well-written and well-considered guidelines [3–6], there is no direct advice regarding the application of what may be termed ‘alternative’ or biological treatments including autologous/heterologous mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP).

The first study on MSCs was published in 1966 by Fridenshtein et al., who cultured bone-forming cells from guinea-pig bone marrow and spleen cells [7,8]. Subsequent studies have characterized MSCs as clonogenic progenitor cells capable of differentiating into mesoderm-derived cells such as osteoblasts, chondrocytes, and adipocytes [7,9-11]. The term «mesenchymal stem cells» was first used in 1991 to represent cells originating from embryonic mesodermal tissues [11,12]. While MSCs imply mesenchymal «stem» or «stromal» cells at the same time, it is suggested only to refer progenitor cells with self-renewal and differentiation ability as «mesenchymal stem cells». Mesenchymal stromal cells, on the other hand, refer to a bulk population of cells with immunomodulatory and homing properties. Some researchers, however, have recently argued that MSCs should be renamed «medicinal signaling cells» because these cells secrete therapeutic regenerative bioactive factors to stimulate the site- and tissue-specific resident stem cells of patients rather than differentiating into tissue-producing cells [13].

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Introduction of mesenchymal stem cells

MSCs have evolved to be a promising technique for the management of knee osteoarthritis (OA) as they have high plasticity, self-renewal capabilities, and immune-suppressive and anti-inflammatory properties [14]. However, the recent popularity gain of cell therapies is not without its drawbacks as we can observe a considerable overflow of contradicting or unclear information or even misinformation about them.

MSCs can be administered either as injectables or surgically (i.e., transplants). The intra-articular injection is most commonly applied as it is a relatively easy and safe procedure that could also be used in ambulatory care. Nevertheless, this technique could not guarantee the proper administration of the cells in the area of interest. Conversely, MSCs surgical implantation is more invasive but overpasses this limitation and ensures the accurate deposit of the cells in the target territory.

The origin of MSCs can vary, but the two most common types of MSCs used for knee OA are bone marrow derived stem cells (BMSCs) (or bone marrow aspirate concentrate, BMAC) and adipose derived stem cells (ADSCs) (or adipose-derived stromal vascular fraction, AD-SVF). Stromal vascular fraction (SVF) is a heterogeneous product that contains AD-SCs, macrophages, blood cells, pericytes, fibroblasts, endothelial cells, and their progenitors [15].

Some of the acknowledged SVF actions can be attributed to the viable MSCs found in the SVF, while others could be associated with the paracrine effect of the cells (i.e., stem cells secrete factors that act on surrounding cells and force them to change their behavior in order to initiate the regeneration process) that are present in SVF [16]. Bone marrow aspirate is usually obtained percutaneously from the iliac crest in a safe and minimally invasive technique. BMAC contains high concentrations of IL1-Ra and other antiinflammatory growth factors [17,18].

Many cell therapies for knee OA are available at point-of-care and are easily delivered due to their autologous nature and minimal manipulation required. Notably, the application of MSCs has consistently been shown to be safe, while they do not preclude additional future therapy in case of treatment failure. These treatments seem to be effective in pain reduction and functional improvement, but little is known about their effect on cartilage regeneration and disease modification in clinical practice.

MSCs have been used in one-step or two-step procedures, where the MSCs can be isolated and expanded before their application. Most clinical protocols recommend that a number of MSCs between 10 to 40 x 106 per intra-articular injection tends to demonstrate superior outcomes [19]. The application of BMAC is an FDA-approved method of obtaining progenitor cells and growth factors for intra-articular use in treating knee OA. BMAC is obtained through density gradient centrifugation to remove blood cells, granulocytes, immature myeloid precursors, and platelets [20].

SVF and AD-MSCs (adipose-derived mesenchymal stem cells) contain up to 500 times more MSCs than bone marrow [19]. Adipose tissue is harvested by a minimally invasive procedure, which is painless, safe, and cosmetic. Advantages of AD-MSCs and SVF include the ease of harvesting procedure under local anesthesia and the greater tolerance to ischemia and hypoxia associated with the cell's survival when implanted into the lesion site [21]. SVF contains a more heterogenous cellular population and secretes several cytokines and growth factors, which can further modulate inflammation and immune responses via paracrine signaling [22].

The current literature shows encouraging results for the intra-articular injections of both BMAC and SVF regarding pain reduction and improvement of functional outcomes and overall quality of life [19,21]. Initially, most of the relevant articles were non-randomized studies or case series. However, a recently published systematic review summarized five level 1 studies and demonstrated superior PROMs (patient-reported outcome measures) at 6 and 12 months for AD-MSCs and SVF compared to placebo and hyaluronic acid injections [19]. It remains unclear whether BMAC is superior to SVF/AD-MSCs injections. Both BMAC and SVF single intra-articular injections in patients with knee OA have been associated with symptomatic improvement. A recent systematic review and meta-analysis showed that SVF injection was more effective than BMAC injection in terms of pain relief at short-term follow-up [21].

The literature is vague concerning cartilage regeneration assessed with MRI following MSCs injection with other studies showing improvement in cartilage signal and morphology, while others found no improvement. In a recent relevant systematic review, only 3 studies yielded improved post-injection cartilage status whereas 2 did not observe any changes in the MRI after intra-articular injections of AD-MSCs or SVF [19]. The ESSKA (European Society of Sports Traumatology, Knee Surgery and Arthroscopy) Orthobiologic initiative performed a systematic review to investigate in pre-clinical studies the disease-modifying effects of AD-MSCs injectable therapies in joints affected by OA. Overall, 94.1% of the included studies reported better results with adipose-derived products than controls [23].

Nowadays, two are the leading sources for MSCs implantation, either autologous AD-MSCs or allogen-

ic from the umbilical cord (hUCB-MSCs). Adipose tissue is harvested with simple liposuction from the patient's abdominal or gluteal regions before implantation. On the other hand, hUCB-MSCs are obtained from the maternal umbilical veins and arteries at the time of delivery or from the placental tissue. The culture expansion of both sources may enforce their effect as more cells are applied. The MSCs are often embedded or mixed with three-dimensional scaffolds substances, including hyaluronic acid, collagen, or fibrin glue.

Recent studies demonstrated promising results using PROMs, radiological evaluation, or second-look arthroscopy. Kim et al. evaluated the midterm clinical results and survival rate in a large case series of 467 patients treated with AD-MSCs implantation on a fibrin glue scaffold for knee OA with a minimum 5-year follow-up. The study showed encouraging functional outcomes with an acceptable duration of symptom relief and a survival rate of 99.8% and 74.5% at 5 and 9 years, respectively, in terms of conversion to high tibial osteotomy or knee arthroplasty [24]. In another study, Song et al. [25] published a large case series, including 128 patients with Kellgren-Lawrence (KL) grade 1 to 3 knee osteoarthritis who underwent hUCB-MSCs implantation combined with a hyaluronic acid (HA) hydrogel, evaluated with a follow-up lasting at least two years. The authors concluded that implantation of UCB-MSC-HA significantly improves pain and function, with no adverse effects or post-operative complications to be noted. Radiological evaluation was also performed using the modified MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score at 3-6 months and one year after surgery, demonstrating increased values (30.58 for the first MRI and 55.44 for the second). It should be noted that a crucial point in managing an osteoarthritic knee is prioritizing the treatment. The approach should start by assessing the limb alignment, afterward, joint stability, and next considering any meniscal and cartilage procedures. In this regard, MSCs administration is often combined with a high tibial osteotomy (HTO) when a substantial varus is present. Indeed, a recent study performed by Yang et al. [26] demonstrated the effectiveness of this combined surgery. Namely, 176 patients who underwent HTO combined with BMAC or hUCB-MSC procedure for medial compartment osteoarthritis were followed for a minimum of 2 years. Clinical outcomes were evaluated using different PROMs (IKDC, KOOS, SF-36, Tegner) and revealed a significant improvement in both groups with no differences between the two groups. However, a second-look arthroscopy showed better cartilage healing in the hUCB-MSC group [27,28].

Platelet-rich plasma for the treatment of knee OA

Platelets play an important role in coagulation but also inflammation, and PRP is a therapy which has been used extensively in equine tendinopathy [29] and has been investigated in the treatment of OA, particularly of the knee [30]. Platelet-rich plasma is a fluid which is rich in growth factors that stimulate cell proliferation, cellular migration, angiogenesis and synthesis of the extracellular matrix, including platelet-derived growth factor (PDGF), tumor-like growth factor-β (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1). It is derived through centrifugation of a patient's blood, with the aim of separating a plasma component which is rich in platelets (>95% platelets) from whole blood which is poor in platelets (4% platelets). The PRP is then extracted and injected into the affected joint. The intricacies of preparation techniques vary and result in significantly different erythrocyte and leucocyte proportions, platelet concentrations, and injection volumes [31]. Indeed, there is a global schism in practice with Europeans preferring to use leukocyte-poor and Americans using leukocyte-rich PRP. PRP has been investigated in randomized controlled trials (RCTs) [32,33], but the broad variation in preparation methods makes inter-trial comparison difficult and robust conclusions harder to ascertain. To emphasize this point we have synthesized and summarized some of the seminal studies below.

The issues surrounding the preparation of PRP are covered in a review of the techniques utilised in a number of RCTs and systematic reviews [34]. There is substantial variation in techniques, including the subject studied (severity of knee OA), PRP preparations, the inclusion of leukocytes, platelet count, number of injections delivered, interval/frequency of administration, volume of injection, whether fresh or freeze-thawed PRP were used, the use of anticoagulants and activating agents, separation techniques, and any co-administered injections. With this in mind, a technical analysis was performed in 2017 to evaluate the similarities and differences between differing PRP formulations, in an attempt to determine the best preparation for the treatment of knee OA.

Filardo et al. [35, 36] performed a blinded trial in which they recruited participants with radiographic knee OA up to a Kellgren and Lawrence score of ≤ III, with 96 randomised to PRP and 96 to hyaluronic acid for comparison. The PRP was centrifuged twice; PRP participants received 3 injections, once a week for three weeks. All participants were followed up for 12 months initially, but the term was extended up to 5

years [37]. The key finding was that both treatments were equally effective in reducing knee OA symptoms and improving function over time, but leucocyte-rich PRP was no more effective than hyaluronic acid.

To summarize the available evidence regarding PRP, a number of systematic reviews have been performed [38–40]. PRP provided significant improvements in knee OA patient outcomes at 12 months, and larger improvements were observed in those with milder radiographic disease (Kellgren and Lawrence ≤ II) [38].

Significant improvements in «patient recorded outcomes» were also observed with PRP as opposed to hyaluronic acid at 3–6 months (WOMAC, Western Ontario and McMaster University Osteoarthritis Index, 28.5 vs. 43.4 respectively, p = 0.0008) and 6–12 months (WOMAC 22.8 vs. 38.1, p = 0.0062) [39].

A further systematic review published in 2018 (including 7 randomized placebo-controlled trials and 908 patients) sought to investigate the superiority of PRP over hyaluronic acid, which was not demonstrated. Regarding PRP, the «minimal clinically important difference» (MCID) was observed in 5 of the 7 papers and suggested that differences in clinical outcomes could be due to variation in the preparation of PRP in terms of centrifugation (speed, frequency, time-length, activating agents), administration (frequency, volume of injection), and post-administration rehabilitation protocols [42]. From a safety point of view, no local or systemic serious adverse events were noted in the reviewed articles.

Milants C et al. [41] used a previous definition of «minimal clinically important improvement» in pain (MCII) to determine whether an observed difference had any 'meaningful' effect in clinical practice. This was set at 15 out of 100 for absolute improvement and 20% for relative improvement for knee OA, as defined by Tubach et al. [40]. The Milants technical analysis included 19 RCTs, and studies were classified into two groups depending on outcomes: (1) a 'bad responder group', defined as a response less than the minimal clinically important improvement (MCII) (n = 4 studies), and (2) a 'very good responder group', defined as a response greater than twice the MCII (n = 7 studies) [41].

The reviewers contacted authors of the trials to obtain information regarding the preparation which was missing from the manuscript, and PRP preparation was classified according to the Mishra (a classification in which PRP is divided into 4 types depending on 3 variables: (1) white blood cells, increased or minimal; (2) activation, yes or no; (3) platelet content, > 5 times patient baseline or ≤ 5 times patient baseline) and PAW (Platelet concentration, Activation prior to injection, White blood cell content).

In almost all studies with a very good responder group, PRPs were leukocyte-poor, activated prior to injection and platelets < 5 times baseline or between baseline and 750,000 platelets/μL, administered according to a lower number of injections (1 or 2 rather than 3), with a longer interval between injections (2 to 3 weeks per injection rather than once weekly) and a single (as opposed to double) spinning technique. The use of leukocyte-rich PRP was only found in the bad responder group. The use of calcium chloride and citrate was common in the very good responder group [42].

Conclusions

MSCs are increasingly used for the treatment of knee OA, either as an intra-articular injection (most common) or surgical implantation into the lesion along with a scaffold. They are efficient in short-term pain, improvement of function and quality of life. Limited data exist about MSCs' effect on cartilage status, which shows controversial findings for injectable treatments and short-term improvement of cartilage volume and quality following MSCs implantation. Proper indications are unclear, with available studies reporting on patients suffering from mild to severe (KL grade 1 to 4) knee OA.

Further high-level studies are necessary to evaluate the efficacy of MSCs, especially in terms of disease modification effects and cost-effectiveness compared to other less expensive orthobiologics. Future perspectives should focus on establishing a wide-accepted protocol for MSCs administration, including all parameters that are still controversial such as dosage of cells, preparation and injection protocol, and post-injection instructions and rehabilitation.

Although PRP may have repeated mild symptomatic benefits, there is yet to be experimentally robust demonstration of symptomatic and structural effects in the current literature. Research is required to better understand the mechanism of action, including investigation of the survival and location of platelet-derived factors within the joint after injection. In order for PRP to be considered within the dogma of recommended treatment for OA, at least one large, randomized, placebo-controlled trial and further investigation regarding preparation and dosage efficacy is required.

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Біологічне лікування остеоартрозу колінного суглоба. Роль мезенхімальних стовбурових клітин і збагаченої тромбоцитами плазми

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Резюме. *Остеоартроз (ОА) є найпоширенішим захворюванням суглобів, іще пов'язано зі зростаючим старінням населення. Крім звичайних медичних та хірургічних втручань, існує все більша кількість «біологічних» методів лікування. Ці методи лікування можуть мати обмежену доказову базу, і з цієї причини їм часто надається лише коротке посилання (або повне виключенння) з поточних рекомендацій щодо лікування ОА. Метою цього огляду був аналіз сучасних доказів щодо терапії мезенхімальними стовбуровими клітинами (MSC) та збагаченої тромбоцитами плазми (PRP). Існують деякі докази, що свідчать про симптоматичне покращення при ін'єкції MSC при ОА колінного суглоба, з припущенням про мінімальне структурне покращення, продемонстроване на МРТ, і є позитивні сигнали про те, що PRP також може призвести до симптоматичного покращення, хоча варіації в підготовці ускладнюють порівняння між дослідженнями. Незважаючи на те, що для оцінки ефективності при ОА проводилися контрольовані дослідження, вони часто мали невеликий розмір, обмежену статистичну потужність, невизначену чіткість рандомізації та використовували різні методології. Ці недоліки залишають відкритим питання про те, чи були вони підтверджені як ефективні методи лікування при ОА. Висновки цього огляду полягають у тому, що всі біологічні втручання, безумовно, потребують клінічних випробувань з надійною методологією, щоб оцінити їх ефективність та безпеку при лікуванні ОА поза контекстуальними ефектами та ефектами плацебо.*

Ключові слова: *остеоартроз, коліний суглоб, мезенхімальні стовбурові клітини, збагачена тромбоцитами плазма.*