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Regenerative methods in osteoarthritis

Nilay Sahin [a], Hilal Yesil [b, *]

[a] Balikesir University, Faculty of Medicine, Physical Medicine and Rehabilitation Department, Balıkesir, Turkey
[b] Afyonkarahisar Health Sciences University, Faculty of Medicine, Physical Medicine and Rehabilitation Department, Afyon, Turkey

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A B S T R A C T

Osteoarthritis (OA) is the most common type of arthritis that can affect all joint structures. The primary goals of osteoarthritis treatment are to alleviate pain, reduce functional limitations, and improve quality of life. Despite its high prevalence, treatment options for osteoarthritis are limited, with most therapeutic approaches focusing on symptom management. Tissue engineering and regenerative strategies based on biomaterials, cells, and other bioactive molecules have emerged as viable options for osteoarthritis cartilage repair. Platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are the most commonly used regenerative therapies today to protect, restore, or increase the function of damaged tissues. Despite promising results, there is conflicting evidence regarding the efficacy of regenerative therapies, and their efficacy remains unknown. The data suggest that more research and standardization are required for the use of these therapies in osteoarthritis. This article provides an overview of the application of MSCs and PRP applications.

* Corresponding author.
E-mail addresses: nilaysahin@gmail.com (N. Sahin), dradanur@yahoo.com (H. Yesil).

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Introduction

Osteoarthritis (OA) is the most common form of arthritis, which is characterized by anatomical and physiological changes such as cartilage degradation, bone remodeling, osteophyte formation, joint inflammation, and loss of joint function [1–4]. With the entire joint being affected, the main affected structure in OA is the articular cartilage [5]. Due to the aneural and avascular nature of the cartilage, it has a low regenerative capacity and therefore limited repair potential of the joint [6]. Pain, limitation of joint movement, and decreased function in OA seriously reduce the quality of life of patients [7]. Because of the high prevalence of OA worldwide, the medical resources and socioeconomic costs associated with its treatment and management are constantly increasing [8,9].

Despite the socioeconomic impact of OA, the treatment options available to OA patients today are quite limited, and therapeutic approaches are mostly in the form of symptom control. For this purpose, various methods are applied to alleviate the patient's symptoms and reduce the progression of the degenerative process [10]. Self-management programs, pharmacologic therapies, thermal therapies, exercises, intra-articular (IA) injection treatments such as steroids and hyaluronic acid (HA), and surgical treatment methods are among the main methods used in treatment [11].

The growing understanding of the pathogenesis of OA, particularly the role of cytokines, growth factors, and signaling molecules, has opened up new perspectives for cartilage repair and treatment [12]. Because conventional management options are ineffective, current research focuses on identifying biological pathways that cause changes in joint homeostasis and accelerate joint healing [13]. Tissue engineering and regenerative strategies based on biomaterials, cells, and other bioactive molecules have emerged as possibilities for osteoarthritis cartilage repair [14]. The most commonly used restorative methods to treat cartilage defects are stem cell and platelet-rich plasma (PRP) injections, chondrocyte transplantation, or surgical procedures such as microfracture and autologous chondrocyte implantation (ACI) [15,16].

Surgically applied approaches such as ACI and microfracture have some limitations. ACI has variable success and is associated with complications such as inadequate fusion, delamination, and graft failure [14,17,18]. The widespread joint involvement and the inflammatory environment in OA also do not make ACI a viable option [19,20]. In the osteoarthritic environment, implanted chondrocytes may undergo undesirable differentiation or apoptosis, affecting treatment efficacy, besides long-term data on ACI are still limited [21,22]. The quality of cartilage repair performed by the microfracture (MF) method, which is often used for cartilage regeneration in OA, is also variable and inconsistent [23–25]. The ‘fibrocartilage’ that occurs after the MF operation has significantly reduced mechanical properties compared to normal articular cartilage [26].

Due to the limitations of current treatment approaches to address OA, there has been significant interest in cell-based therapies for cartilage regeneration in recent years [27]. Regenerative medicine is a rapidly developing technology that allows the repair, and regeneration of damaged and diseased cells, tissues, and organs of the body [28]. Cell therapy is the insertion of cells into damaged tissue in order to reconstruct cell function, and tissue engineering is the application of cells with a three-dimensional tissue scaffold to create a tissue-like structure for the repair of dysfunctional tissue or organ [29]. In this article, mainly cell-based therapies will be discussed.

Mesenchymal stem cells

Because of their ability to differentiate into cartilage, tendon, and bone cells, mesenchymal stem cells (MSCs) have yielded promising results in these tissues [19,30]. MSCs are defined as cells with elongated morphology, plastic adherent, anti-inflammatory, antiapoptotic, antifibrotic, and immunomodulatory capacities by the International Cell Therapy Society Mesenchymal and Tissue Stem Cell Committee [31]. Human cells, tissue, and cellular and tissue-based products should meet the following criteria, according to the Food and Drug Administration, in 2017; they should be used for homologous use only, they should not be combination products, they should not have a systemic effect, and they should be minimally manipulated so that they are not dependent on the metabolic activity of living cells [32].

MSCs are non-hematopoietic precursor cells that can be obtained from a variety of sources [33]. In recent years, the most studied sources have been bone marrow, subcutaneous fat, and umbilical cord [34]. MSCs interact with the immune system to promote immunoregulation, migrate to the injury site to improve peripheral tissue tolerance, prevent inflammatory factor release, promote tissue repair, increase the activity of injured cells and have a high potential for multidirectional differentiation and reproduction [35–38]. Reduced inflammation in the osteoarthritic joint can result in less neurogenic pain and general pain pathway downregulation. These MSC properties could be advantageous to OA, which contains inflammatory components [19].

MSCs also direct chondrogenesis via paracrine activity, which reduces cell apoptosis and inflammation while activating cell proliferation and mobilization [39–43]. MSCs transmit a number of signaling substances to the body via paracrine, including growth factors, cytokines, and extracellular vesicles. By creating a repair microenvironment through the uptake of local endogenous stem cells, stem cells can suppress synovial activation and heal cartilage damage [44]. Besides, IA MSCs in the rat model decreased the number of apoptotic chondrocytes, demonstrating MSCs' anti-apoptosis effect in the treatment of OA [45].

For optimal differentiation into chondrocytes, MSCs should be cultured in serum-free conditions or with micro-mass, hydrogels, and scaffold materials [46]. In the process of chondrogenic differentiation, MSCs synthesize cartilaginous matrix components [47]. This reconstructed extracellular matrix (ECM) can interact with chondrocytes or MSCs, and it can also regulate cell viability, differentiation, and migration, as well as tissue morphogenesis and remodeling [48,49].

The clinical outcomes and cartilage regeneration efficacy of mesenchymal stem cells in OA remain unknown [50]. Meta-analyses and reviews published in recent years have yielded mixed results. Migliorini et al. [51] found improvements in both the visual analog scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scores at the sixth and twelfth months of a systematic review evaluating stem cell injections for knee OA. They also stated that the average walking distance of the patients increased and that the Lequesne and Knee injury and Osteoarthritis Outcome Score (KOOS) scores improved [51]. According to the available evidence, the authors concluded that bone marrow concentrate (BMC) knee OA could be an option. This resulted in a remarkable improvement in all clinical and functional outcomes. They also reported that patients who were treated at an earlier stage of degeneration had significantly better outcomes [51]. Patients with early to moderately advanced OA are considered potential MSC candidates. Harrel et al.'s [46] study emphasized that the severity of OA can affect the effectiveness of MSCs. Clinical and radiographic improvement of autologous MSCs was observed 2 months after IA injection in mild OA, but beneficial effects were observed only after 6 months in animals with severe OA.

Dai et al. [52] found no significant difference in the VAS, WOMAC pain, function, and stiffness scores for MSCs compared to placebo in a recent meta-analysis of 13 randomized controlled trials. However, they stated that additional tests and combination trials of different types of cells, doses, and MSC injections are required to improve clinical decision-making for people with symptomatic knee OA [52]. In another review comparing MSCs of various origins with placebo or each other in the treatment of knee OA, MSCs were superior to placebo for pain control and improvement of knee function, but no significant differences were found with placebo for enhancing cartilage regeneration [53].

Frequency of administration of the MSCs

Currently, there is no agreement on the frequency of MSC application, which may have an impact on application efficiency [19,54]. It has been noted that the extent of joint damage and inflammation influences MSC-induced cartilage regeneration, and multiple MSC injections should be considered for the treatment of severe OA to increase the total number of MSCs injected. An article also stated that using MSCs on a regular basis can effectively inhibit progression in an OA model [55]. It has also been reported that the effectiveness of MSCs in cartilage production is proportional to the number of cells injected. The results of a magnetic resonance imaging (MRI) study using autologous adipose-derived stem cells (AD-MSC) at three different doses revealed that the size of the cartilage defect was significantly reduced in the high-dose group (100×10^6 cells) [56].

Bone marrow-derived stem cells (BM-MSCs)

The term "BM-MSCs" refers to mesenchymal stem cells isolated from bone marrow aspiration (BMA) or bone marrow concentrate (BMC). The features of BM-MSCs such as easy obtaining, rapid in vitro proliferation, low surface expression of major histocompatibility complex (MHC) antigens, and long-term coexistence in the host provide their therapeutic use [57].

Clinical trials have shown that BM-MSCs show promise in a variety of orthopedic conditions, including spinal OA, knee, and hip OA [56,58–61]. It has been reported that BM-MSC has beneficial effects, particularly in studies with patients suffering from severe OA [62,63]. In their study, Gigante et al. [64] augmented type I collagen tissue scaffolds with BM-MSC, and applied them to knee cartilage lesions by taking biopsy samples from their secondary arthroscopies 1 year later and analyzing them histologically. They concluded that the addition of BM-MSC to the tissue scaffolds provided almost normal arthroscopy findings and satisfactory histological scores.

In a recent study, Lamo-Espinosa et al. [65] evaluated the clinical effects of a dose of 100×10^6 BM-MSCs in combination with PRP as an adjuvant in a phase II trial. Patients were followed up for a year, and they stated that the BM-MSCs are safe, and clinically effective in terms of pain and functionality. However, it is stated that especially the combination treatments of biological products should be recommended carefully, and more data should be collected before routine application [66].

Anz et al. [67] found that both BMC and PRP treatments performed similarly in pain and function scores over 24 months in patients with knee OA. They stated that platelet-rich plasma (PRP) was not superior. As a result, they stated that considering the cost in these patients, multiple PRP injections over time may be a more appropriate treatment modality [67].

Adipose-derived stem cells

Although MSCs have a similar immune phenotype and immunosuppressive properties, they differ in their proliferation capacity and differentiation potential [68]. One of them is adipose-derived mesenchymal stem cells (AD-MSC).

Enzymatic digestion (by collagenase) or mechanical fractionation can be used to obtain adipose-derived stem cells; both techniques are designed to separate mature adipocytes from the stromal vascular fraction (SVF), which contains pre-adipocytes, endothelial cells, smooth muscle cells, pericytes, macrophages, fibroblasts, and AD-MSCs (around 9.5%) [69]. AD-MSCs are found in the capillary and perivascular adventitia of large blood vessels within adipose tissues and are thought to be derived from pericytes [70]. Although AD-MSCs share morphology and phenotype with BM-MSCs, obtaining BM-MSCs is a highly invasive procedure, and because BM-MSCs taken from patients with end-stage OA have also decreased in proliferation and differentiation capacity, AD-MSCs have been investigated as an alternative source [19,71,72]. In addition, the density of MSCs varies greatly between BM-MSCs and AD-MSCs. A 1-mL bone marrow aspirate yields approximately 6×10^6 nucleated cells, with approximately 0.01% of these cells being true BM-MSCs. A gram of adipose tissue yields about 2×10^6 nucleated cells, with about 10% of these being AD-MSCs [73,74]. Considering the low number of MSCs in both BM-MSCs and AD-MSCs, it has been suggested that cell therapy derived from AD-MSCs may be more beneficial [75].

With minimal patient harm, large amounts of adipose tissue, and thus stem cells of adipose tissue origin, can be obtained [76]. From about 10 cc of adipose tissue, 1 cc of concentrated stem cell liquid portion is obtained. A single injection of approximately 3 cc of concentrated stem cells is usually sufficient for treatment.

Lee et al. [77] in their placebo-controlled study using AD-MSC, showed that WOMAC scores, pain reduction, and functional recovery significantly improved in patients with knee osteoarthritis in the sixth month compared to the control group. However, in the same study, it was discovered that MRI controls did not reflect well-being.

Recent research has demonstrated the efficacy of AD-MSCs in the treatment of OA in animal models [78,79]. Autologous AD-MSCs co-administered with hyaluronic acid (HA) have been shown to be effective in preventing the progression of OA and promoting cartilage regeneration in sheep [78]. Feng et al. [79] also used MRI and micro-computed tomography to assess the efficacy of allogeneic AD-MSC in

combination with HA to slow the progression of OA in sheep. As a result, it has been demonstrated that animals treated with AD-MSC + HA have a cartilage layer that is nearly identical to healthy cartilage.

A pig study comparing AD-MSCs and BM-MSCs seeded on collagen scaffold showed no difference in healing rates and bone formation [80]. According to Kim et al. [60] injections of combined autologous BM-MSCs and AD-MSCs used in the treatment of 41 patients with knee OA significantly reduced pain and improved knee function in all patients, and the beneficial effects obtained were more pronounced, particularly in early to middle-stage OA. They stated that the results obtained here were most likely due to AD-MSC-dependent immunosuppression and BM-MSC-mediated cartilage regeneration.

Umbilical cord mesenchymal stem cells

Umbilical cord mesenchymal stem cells (UC-MSCs) are isolated from the umbilical cord and have more robust gene expression profiles as well as the ability to differentiate into other cells [81]. There have been studies that show the safety and efficacy of using umbilical cord-derived allogeneic MSCs alone or in combination with hyaluronate hydrogel [81,82].

Xing et al. [83] also demonstrated that a single injection at week 6 delayed the progression of cartilage degeneration in rats with OA. Ju et al. [45] investigated whether there was a difference in proliferation ability and chondrogenic potentiality between UC-MSC injection and AD-MSC injection in 43 OA rats over a 12-week period and discovered that OA development decreased with both treatments and that the decrease in ECM synthesis was significantly suppressed. In conclusion, study found that one or two injections of AD-MSC and UC-MSC can significantly slow the progression of osteoarthritis. At the same time, in this study, It has been reported that UC-MSCs have greater proliferative ability than AD-MSCs in vitro, implying that more MSC can be collected in less time [45].

Matas et al. [84] demonstrated the safety and feasibility of the repeated IA UC-MSC dosing strategy in 29 knee OA patients in a phase I/II trial, with no serious side effects observed during the 12-month follow-up period. Patients' pain and knee function improved after the treatment ($p = 0.001$).

Exosomes

Based on the understanding that MSCs exert their effects in a paracrine manner, the use of exosomes or extracellular vesicles rather than the cell itself has emerged [85]. Extracellular vesicles are lipid bilayer confined particles that are naturally released from cells and, unlike cells, cannot replicate [86,87]. Exosomes, due to their smaller size, have the potential to migrate efficiently to target organs [88]. Furthermore, higher concentrations of “active ingredients” can be directly administered to the patient, resulting in a greater healing response than is possible with all MSC treatments.

When only paracrine effects are expected from IA injection without consideration for cell survival or vaccination, injection of isolated extracellular vesicles may be a simpler and safer option. However, there are very few translation studies that have proven the efficacy of extracellular vesicles in the treatment of OA [86,87].

Allogenic mesenchymal stem cells

MSCs, despite expressing MHC class I molecules and being targets of the immune response, can be safely transplanted into an allogeneic recipient [89]. MSCs produce immunosuppressive cytokines and express potent inhibitory molecules that suppress the allogeneic immune response [89]. The ready-to-use capability of allogeneic MSCs (a-MSCs) and their lower cost offers significant advantages in advanced OA patients. An added benefit is for elderly patients whose MSCs are known to have lower proliferation rates compared to MSCs from younger donors [90].

Vangsness et al. [91] conducted a study with 55 patients in which patients were injected with a single dose of a-BM-MSC (50×10^6 or 150×10^6) and patients were followed for efficacy and safety for 2 years. In this study, it was stated that IA administration of a-BM-MSCs resulted in significant pain reduction, improvement in articular cartilage regeneration and physical function, and was also a safe treatment modality for OA [91]. Recently, the effectiveness and reliability of IA injection of extended a-UC wjmscs given twice with a 1-month interval in moderate or severe OA patients ($n = 16$) were

studied [92]. During the study period, they observed no local or systemic long-term adverse events. In terms of efficacy, KOOS showed a significant improvement at 6 months, followed by further improvements in the first and fourth years ($p < 0.0001$), and the improvement continued even after 4 years of follow-up. As a result, the authors speculated that it could point to a functional disease-modifying treatment. In terms of MRI recovery, all measured parameters improved significantly. Abnormal alterations' severity either vanished or diminished (such as subchondral sclerosis) [92].

In a recent study, three KOA patients were given a-AD-MSC injections and then monitored for 6 months for clinical parameters like WOMAC, VAS, and KOOS, as well as MRI and serum inflammatory biomarkers. At the end of the study, no patients experienced any severe side effects, and all clinical parameters improved. But, MRI demonstrated a slight improvement in two patients. Furthermore, lower serum cartilage oligomeric matrix protein and hyaluronic acid levels were detected, indicating a lower risk of cartilage degeneration [93].

Platelet-rich plasma (PRP)

The ability of reparative cells to migrate to the site of injury made possible by the angiogenic potential makes it essential for repairing healthy tissue [75]. Blood derivatives have recently been advocated as a safe, simple, cost-effective, and minimally invasive strategy for supplying bioactive molecules that can affect the joint environment, promoting homeostasis restoration and possibly tissue regeneration [94,95]. PRP is a specific strategy that attempts to compensate for this lack of blood supply.

PRP is an autologous blood component that initiates a repair process in cartilage tissue [96]. PRP is prepared from a small amount of autologous peripheral blood and is administered to the patient via IA injection after centrifugation [97]. It is stated that more studies are needed to investigate the optimal platelet concentration related to clinical outcomes in human clinical studies, as previous studies evaluating the optimal platelet concentration required for clinical practice were frequently performed in vitro [98]. PRP has an anabolic and anticatabolic effect on chondrocytes, leading to increased cell proliferation and ECM production, as well as anti-inflammatory effects [99,100].

By modifying the local microenvironment, the fibroblast growth factor family, TGF-, insulin-like growth factor-1, and platelet-derived growth factors have all demonstrated promising applications of PRP in the treatment of osteoarthritis related to cartilage damage and repair [101–103]. Furthermore, several microRNAs involved in mesenchymal tissue regeneration have been found in platelet micro-vesicles, and it has been proposed that microRNA-23b is definitively involved in the differentiation of MSC into chondrocytes [104,105]. PRP also increases HA secretion, which aids in the creation of a highly favorable and balanced environment for angiogenesis [106,107].

There is still no clear agreement on the frequency of the administered dose or whether multiple injections can prolong the effects. Patients also face an additional financial burden because there is no regulation on production costs [95,108]. According to the recent ACR OA treatment guideline, there is heterogeneity and a lack of standardization in current preparations of secreted PRP, as well as the techniques used, making it difficult to determine precisely what is injected [11]. Its use in the treatment of knee and hip OA is not strongly recommended in this regard. A recent randomized trial also compared PRP with placebo in symptomatic mild to moderate radiographic knee OA failed to show symptom improvement and improvement in joint structure [109].

In a study comparing PRP with HA and ozone treatments, PRP was found to be more effective than HA and ozone injections in the treatment of mild to moderate knee OA, as it provided at least 12 months of pain-free activities of daily living with a single application [110]. But, a recent meta-analysis of 43 randomized controlled trials found no difference in pain and functional improvement between PRP and HA [111]. Given these contradictory findings, the evidence for PRP's superiority as a therapeutic agent is inconclusive [112]. Inadequate reporting on bioformulations in clinical practice, as well as a lack of consensus on the standardization of PRP preparation protocols, contribute to inconsistency in reported PRP results [113]. Platelet and leukocyte count in PRP may differ between preparations from the same individual [99]. While it has been suggested that the immune regulatory function of leukocytes in leukocyte-rich PRP may improve wound healing activity, it has also been suggested that the release of inflammatory molecules and catabolic cytokines such as MMP, IL-1b, and TNF-a may have an antagonist effect [114,115].

Limitations, contraindications, and side effects

Mesenchymal stem cells (MSCs) have received increased attention in cell-based therapies in recent years due to their self-renewal abilities, multipotent differentiation potentials, and paracrine effects. However, MSCs have several limitations to their use, including the formation of fibrocartilage rather than hyaline cartilage, and insufficient cell migration [116,117] (Table 1). Furthermore, evidence for a link between cell count and clinical benefit is currently inconclusive [118]. It should be mentioned that MSCs have homing characteristics that allow them to spread to non-cartilaginous tissues, which can significantly impair the treatment efficacy [119]. To address this issue, MSCs can be delivered using injectable tools that modulate the target finding and vaccination of the transplanted MSC [120]. It has been noted that HA improves the attachment and integration of MSCs into damaged articular cartilage the most effectively [121].

Depending on the method of administration and the surrounding environment, the majority of intraarticularly injected stem cells experience fast cell death, with a median survival time of 3 days to several weeks. However, stem cells have been shown to survive longer when implanted focally rather than injected [122]. In these regards, it is critical to determine the appropriate technique in order to develop the most cost-effective MSCs-based OA therapy.

Other limitations related to the MSCs are the ethical concerns, and a decrease in synthetic and proliferative capacity with age [123,124]. Also, there is concern about malignant transformation in stem cell applications (Table 1). The current state of knowledge regarding MSC involvement in tumor

Table 1
Benefits, limitations, and contraindications of therapeutic modalities.

	Benefits	Limitations	Contraindications
Mesenchymal stem cells	- Self regenerate capacity - Differentiation into various cell types - Low immunogenicity - Immunomodulatory and anti-inflammatory effects - Promoting tissue repair	- Ethical concerns, possibility of tumor development -A decrease in proliferative capacity with age -It is unclear how the knee microenvironment and the presence of synoviocytes affect the osteogenic potential -Advanced structural disorders reduce treatment effectiveness -The majority of intraarticularly injected stem cells experience fast cell death insufficient cell migration -The formation of fibrocartilage rather than hyaline cartilage -Evidence for a link between cell count and clinical benefit is inconclusive -MSCs have homing characteristics that allow them to spread to non-cartilaginous tissues, which can significantly impair the treatment efficacy -Insufficiency of clinical trials -Harvesting and preparing process is complex	• Active infection • Neoplasia • Immunodeficiency • Bleeding disorder and antiaggregant use • Acute phase of inflammatory diseases • Severe cardiovascular disease
Platelet-rich plasma (PRP)	-Safe, simple, cost-effective, and minimally invasive -Promoting homeostasis restoration and possibly tissue regeneration -Anabolic and anticatabolic effect on chondrocytes -Anti-inflammatory effects -Increases hyaluronic acid secretion	-Lack of consensus on standardization of PRP preparation protocols -No clear agreement on the frequency of the dose -Age may be important for the efficacy -The degree of osteoarthritis may affect the results -It is unclear whether the timing of implementation should be determined	• Low basal platelet count (<150.000/mm3) • Having a hematological disease • Presence of coagulopathy • Using *anti*-aggregant or steroid therapy • Having a history of malignancy (especially hematologic ones)

progression and metastasis, as well as the underlying mechanisms, is in its early stages. It is also unclear how the knee microenvironment and the presence of synoviocytes affect the environment's osteogenic potential [75]. Compared to normal cartilage, a vicious cycle of chronic articular cartilage degradation is triggered by the environment of trauma or OA-related cartilage diseases. Such adverse environments can disrupt regenerative processes by interfering with the quantity and quality of MSCs [125]. In particular, advanced structural disorders, such as misalignment in the knee joint, and acetabular insufficiency in the hip joint, reduce treatment effectiveness.

An analysis of the data from 2372 orthopedic patients who received stem cell injections revealed 325 adverse events. Pain post-procedure (n = 93, 3.9% of the study population) and pain from progressive degenerative joint disease (n = 90, 3.8% of the study population) were the most common. Seven cases had neoplasms, which was a lower rate than in the general population. Patients who received BMC alone had the lowest rate of adverse events [126]. From a safety standpoint, it is also important to pay attention to the conditions associated with bone marrow aspiration in BMAC-induced treatments, including anemia, postoperative pain, neuralgia, and minor complications [127].

Among the main contraindications of stem cell applications are active infection, neoplasia, immunodeficiency, complete ligament or tendon rupture, bleeding disorder and antiaggregant use, acute phase of inflammatory diseases, and severe cardiovascular disease.

There are some considerations that should also be considered for PRP; low basal platelet count (<150,000/mm3), having a hematological disease, presence of coagulopathy, using *anti*-aggregant or steroid therapy, which may impair PRP's biological efficacy, and having a history of malignancy, especially hematologic ones [66] (Table 1).

Conclusion

There is a significant effort to develop therapeutic strategies to alter the natural history of OA. Regenerative therapies are one of the treatments that have been used for this purpose in recent years and are currently being researched.

It is still too soon to draw any conclusions about the final success of IA cell therapy in relation to AC regeneration based on the existing data despite the strong conclusions that the management of osteoarthritis with regenerative therapies is safe and effective. For regenerative medicine to replace traditional OA treatment options, structural repair is required; the symptomatic alleviation offered by these expensive procedures is insufficient. There is a need for studies looking at the effects of long-term use as well as for the standardization of these treatments. The ACR and EULAR communities have not yet recommended the use of stem cell and PRP therapies for the treatment of OA.

Prospective radiological and histological data from larger numbers of patients are needed to prove the cost-effectiveness of these treatments. In addition, precise recommendations are required for which patient groups, at which doses, with which application technique, and at what time the treatments are to be applied. Expanding research in this area will produce more evidence to guide this in the future.

Practice points

- There is a significant effort to develop therapeutic strategies to alter the natural history of osteoarthritis (OA). Regenerative therapies are one of the treatments that have been used for this purpose in recent years and are currently being researched.
- For regenerative medicine to replace traditional OA treatment options, structural repair is required; the symptomatic alleviation offered by these expensive procedures is insufficient.
- The selection of patients suitable for regenerative therapies in OA is critical, and not yet fully defined.
- Although the side effects of regenerative therapies are relatively low, long-term safety and efficacy data are still lacking.

Research agenda

- Because the costs of administering mesenchymal stem cells (MSCs), which do not have a clearly proven disease-modifying effect, are high, evidence should be obtained to determine the amount of dose to be administered and the number of dose repetitions, as well as which mesenchymal stem cell source may be more effective.
- In terms of clinical usefulness, it is critical to determine which MSC application technique, such as intra-articular injection or implantation, in combination with surgery, or in combination with hyaluronic acid or platelet-rich plasma (PRP), will be used.
- In order to maximize the clinical results of PRP administration, it should be tried to obtain clear evidence about the ideal number of injections, content, preparation protocol, and timing of administration.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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