Scientific Research Publishing

Open Journal of Regenerative Medicine, 2024, 13, 21-40
https://www.scirp.org/journal/ojrm
ISSN Online: 2169-2521
ISSN Print: 2169-2513

The Use of Biologic Treatments for Osteoarthritis: A Review

William Thornton, Sion Glyn-Jones

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
Email: wje.thornton@outlook.com

How to cite this paper: Thornton, W. and Glyn-Jones, S. (2024) The Use of Biologic Treatments for Osteoarthritis: A Review. *Open Journal of Regenerative Medicine*, **13**, 21-40.
https://doi.org/10.4236/ojrm.2024.132002

Received: March 21, 2024
Accepted: June 25, 2024
Published: June 28, 2024

Abstract

Background: The number of people presenting with osteoarthritis is increasing due, largely, to an ageing population and advances in medical treatments. This is driving the demand for new clinical solutions and treatments for the disease. Biologic therapies have been touted as an adjunct, or even alternative to established treatments for osteoarthritis. The term "biologics" refers to protein-based therapeutics that are derived from the proteins of living organisms. These treatments include, but are not limited to: autologous blood products such as platelet rich plasma (PRP), cell therapies such as autologous chondrocyte implantation (ACI) and mesenchymal stem cells, growth factors and cytokines, gene therapy. **Aim:** This study aims to provide a clear definition of these technologies and describe the evidence supporting their clinical efficacy to treat osteoarthritis. This is to provide clarity to both clinicians and patients on the range of technologies available. **Method:** Literature databases Embase and PubMed were searched for keywords such as "biologic", "osteoarthritis". **Results:** The literature identified 4 primary categories of biologic treatments for osteoarthritis: stem cell therapy, somatic cell therapy, protein therapy and gene therapy. The evidence level varied in its quality from treatment to treatment, as did the conclusions of published studies. **Conclusion:** Autologous chondrocyte therapy had the most convincing evidence to support its use as a treatment for osteoarthritis, however, current methods of use produced variable results. Other treatments such as platelet rich plasma and bone marrow derived stem cells show promise as potential future therapies, with more refinement, but evidence does not support their use currently. Other treatments including autologous stem cells should be avoided until there is a greater quantity and quality of evidence supporting their use.

Keywords

Osteoarthritis, Biologics, Gene Therapy, Stem Cell, Protein Therapy

1. Introduction

10 million people in the UK are affected by osteoarthritis (OA) [1], and this number is set to rise in the future [2]. OA is one of the most common chronic joint pathologies worldwide [3], causing pain and immobility in tens of millions of people, which in turn impacts quality of life and mental health [4]. It is a disease of the whole joint that is characterised by the breakdown of articular cartilage, joint space narrowing, osteophyte growth, synovitis, and muscle weakness [5]. The most affected joints are the hands, knees, hips, and spine [6], but almost any joint can be affected.

Conservative, medical, and surgical treatments are presently available for OA. Conservative management includes physiotherapy and mobility aids, and medical management is predominantly analgesia and anti-inflammatory drugs such as NSAIDs [7]. All joints can be targeted with conservative and medical treatments, and most patients will receive a combination of both types of therapy, with the resultant patient satisfaction varying greatly amongst individuals [7] [8].

Surgical management for OA is predominantly an arthroplasty, total or partial, although this is only routinely performed on hips and knees as other joints are less amenable to replacement. In the UK around 200,000 hips and knees are replaced per annum, but the procedure is time consuming and expensive, with the average hip replacement costing the NHS £10,000. The COVID-19 pandemic put immense time and financial strain on the NHS, creating a backlog of patients awaiting treatments. Currently, it is estimated that it will cost £5.4 billion to clear the current backlog [9], which highlights a growing need for cost-effective and easily deliverable treatments for common diseases, such as OA.

Currently, available conservative and (non-biologic) medical therapies do not prevent disease progression, but only provide symptomatic relief. Additionally, used alone, they do not always lead to high patient satisfaction. Surgical management is often only used as treatment in advanced disease pathology, and not all patients, or all joints are amenable to surgical management. Therefore, there is a gap in the treatment of OA [10] for interventions that can either halt or reverse disease progression and be deployed earlier in its presentation than surgical management as well as being less expensive and time consuming than joint replacement [11]. Patients with early OA would benefit from the ability to slow, halt, or reverse disease progression if promptly diagnosed and treated.

Treatments that have been derived from living organisms, known as biologics, could have the potential to fill this clinical gap. These new treatments aim to slow, halt, or even reverse disease progression and are therefore particularly targeted towards a younger patient demographic, with less advanced disease compared to those that typically receive arthroplasties. Biologic treatments for OA are an exciting prospect because of the number of people who are living with OA, but ineligible for arthroplasty.

The size of the population that suffers from OA, that is potentially treatable with biologics is difficult to quantify due to challenges in the diagnosis of ear-

ly-stage OA [10]. Over half of the patients diagnosed with symptomatic OA are done so before the age of 65 [12], and there is concern that many young people are diagnosed late in their disease progression, leading to individuals living decades with pain and reduced mobility. What is known is that most OA patients are not and will not be eligible for arthroplasty [13]. When one considers the ineffectiveness of current practices at picking up mild OA, combined with the large proportion of the population that has significant risk factors for OA such as their occupation [14], femoral acetabular impingement (FAI) [15] and previous injuries such as labral tears [16], the potential patients that could be treated with biologics is staggering.

Some biologic treatments are aggressively marketed and have little evidence supporting their use [17]. As a result, there is great debate about their efficacy and their value for money.

This review aims to explore the range of treatments that are being promoted, their method of action and efficacy. It will attempt to highlight any safety issues and concerns in practice and look to the place of biologics in the future of OA treatment. In order to review the literature, a search of the databases Embase and PubMed was conducted using MESH terms relevant to the scope of the literature review, such as "biologics" and "osteoarthritis".

2. Biologics

The term biologics refers to "protein-based therapeutics that are produced using living organisms" [18]. They have been used medicinally for decades with the most notable examples including insulin or blood products.

Whilst regenerative medicine has been applied to OA for the past 70 years [19], biologics in the treatment of orthopaedic pathologies has only been a concept for the past 30 years [20], with the initial development of mesenchymal stem cell therapies (MSC). Since then, the range of biologics, from different sources, has increased and encompasses a variety of methods of action.

Biologic treatments for OA are intended to work by slowing disease progression, but it has been claimed that certain therapies can halt degeneration and, in some cases, reverse it in a regenerative manner, which is not currently offered by any other contemporary treatments. As a result, some see the role of biologics as an intervention in early-stage OA.

Many types of biologic treatments have been proposed, with varying availability across both private and public health care sectors. Some of them are administered via a purely surgical route such as autologous chondrocyte therapy, and some are purely delivered to outpatients, via intra-articular injections. Finally, some treatments have the flexibility of being delivered surgically or as an outpatient depending on the scenario and concurrent treatments.

2.1. Stem Cell Therapy

Stem cell therapies are widely publicised in both the professional and public spheres. The cells are defined by their ability to divide into different cell types or

lineages, known as pluripotency. It is because of this ability that stem cells have been targeted as a source of treatment for degenerative diseases such as OA. There are several methods of preparation and application of stem cells to treat osteoarthritis, with a common methodology shown in **Figure 1**. Cells can be harvested from the patient who is undergoing treatment (autologous) or from a donor (allogenic). Tissues that are rich in stem cells that can maintain their ability to differentiate and proliferate rapidly without causing immunological reactions are preferred [21]. Anatomically, the cells that are usually harvested are the mesenchymal cells of bone marrow (BMDSC), adipose derived stem cells (ADSC) and foetal derived stem cells (FDSC). Foetus-derived sources, by definition, are always allogenic, and their use is sometimes controversial for ethical, legislative, and religious reasons [22].

The mechanism of action of this treatment is not fully understood [23], in part because it depends on the lineage into which the cells differentiate [24], but there appears to be anti-inflammatory elements as well as potentially some tissue regeneration. The belief is that the therapeutic effect derives from the expression of proteins that suppress inflammatory responses and are linked to growth such as cytokines and growth factors, as well as the cells themselves differentiating into different cells such as chondrocytes, osteoblasts and adipocytes [25].

The current literature does not adequately suggest that stem cell treatments have the potential to deliver a therapeutic benefit, but suggests that it merits further study, with particular focus on the source of the stem cells as a key determinant in success [17].

In the case of BMDSC, there are many publications with some suggesting therapeutic benefit [26]-[30]. The difference in results is likely due to the high level of inconsistencies between methodology of studies [17] which prompted Delanois *et al.* to undertake independent analysis of level-of-evidence I studies. Of the four studies analysed, none showed negative effects of using BMDSC's and one showed no significant difference in outcome with a placebo control [31]. However, the other three studies analysed demonstrated significant improvements in patient outcomes in a variety of metrics such as patient pain and functionality [29] [30] [32]. Improved patient outcomes can be supported by radiological evidence of tissue regeneration in BMDSC treatments [33] [34]. This is encouraging and suggests that BMDSCs have a future as a treatment and work should be undertaken to improve the methodology of treatment.

ADSC have been suggested as an alternative source of stem cells for treatment of OA and can be harvested in a manner more tolerable than the invasive procedure used to source BMDSCs [35] [36]. Studies that do exist assessing the use of ADSCs are primarily animal studies or preclinical trials examining safety and preclinical efficacy. A contemporary level-of-evidence I study has been published and demonstrated improved patient reported outcomes but no change in radiological imaging [37], something that was achieved in an RCT study by Freitag *et al.* [38]. Similar results have been mirrored in another phase IIb other

clinical trial, which assessed the efficacy of adipose stem cells to treat knee OA with much the same outcome [39], however, with a sample size of 24 (50% being placebo), and a follow up period of only 6 months, trials on a greater scale are necessary. More trials reaching the same conclusion would need to be undertaken to have confidence in the efficacy of ADSCs.

FDSC are controversial on many grounds but could have the potential to be used therapeutically. Studies show some positive benefits of using them as treatment [40] [41]. However, these studies have been criticized for their methodology and lack of control group and so do not provide compelling evidence [17].

There is a huge variety in the quality of studies that are produced assessing efficacy and safety, as well as variety in methodology [17]. The current literature consists mainly of small studies with short follow up periods, inappropriate control cohorts and biases. It is appreciated that studies with hundreds of patients per arm are necessary to give statistical confidence in the conclusions of studies [17]. This makes it difficult to make meaningful comparisons between cell sources and joints treated and probably accounts for the contradictory clinical findings in some studies. However, the evidence that does exist suggests that it would be worthwhile undertaking further studies on stem cell therapies, particularly BMDSC's. If these future studies reflected the current findings in the literature, suggesting that SC therapies are a viable treatment of OA then and give the community greater confidence to use BMDSC therapies.

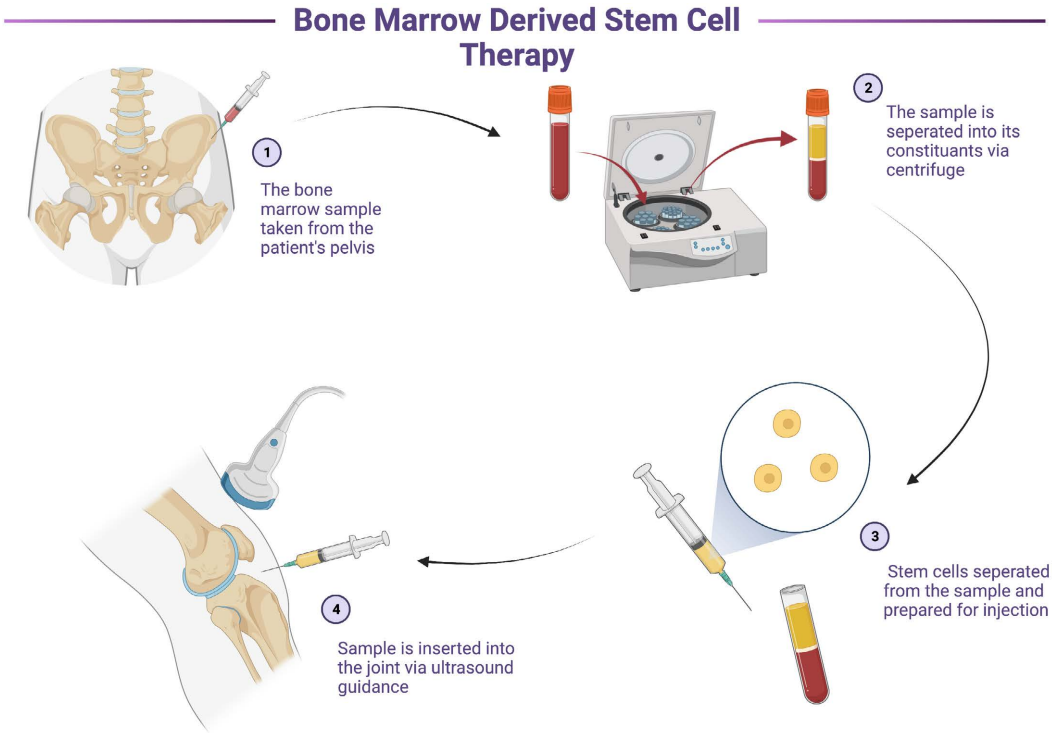

Figure 1. A diagram demonstrating the steps involved in delivering bone marrow derived stem therapy to a patient in order to treat osteoarthritis.

2.2. Somatic Cell Therapy

Autologous chondrocyte therapy (ACT) is one of the oldest and well-established biologic therapies for cartilaginous damage and subsequently has gone through several refinements in methodology and checks on efficacy. Whilst ACT is provided on the NHS it is much less commonly used to treat OA. NICE guidelines only recommend treatment on cases of OA where there is "mild damage" and is delivered via an operation. The procedure aims to replace damaged chondrocytes and stimulates growth of new ones, thus repairing cartilaginous damage. ACT is a procedure aimed at repairing the intraarticular chondrocytes. The process involves taking a biopsy of healthy cartilaginous tissue from an autologous source and culturing the chondrocytes *in vivo*. The chondrocytes are then layered onto a hydrated scaffold, which is operatively applied to the cartilage lesion in the damaged knee (**Figure 2**). ACT underwent its first trial in 1994 [42] and since then, the technique has been refined and characterised into a series of "generations", with procedural differences.

First generation ACTs involves injecting the chondrocytes after the damaged cartilage is blanketed by a periosteal flap. Second generations ACT involves creating a scaffold from tissue such as fibrin or collagen, which is then used to hold and carry the chondrocytes. The newest generation of ACT has evolved beyond using scaffolds (known as MACI) and inserts the cells in a "pellet" form.

The results of ACT when used as a treatment for cartilaginous repair are well documented [43] [44]. 1st generation repair is less common nowadays in clinical practice. 2nd and 3rd generation ACT have been shown to effectively treat damaged cartilage and significantly improve patients' symptoms such as pain and range of motion [45] [46]. Some studies have shown that MACI can improve knee functionality by 200% (Lysholm scoring) following treatment [45].

However, ACT is still not routinely recommended to treat advanced OA, primarily because it is not effective at regenerating larger lesions. Chondrons are units that include a chondrocyte with the pericellular matrix. Chondrons form a more realistic extracellular matrix (ECM) and produce a better biological replica of the original cartilage [47], however, biopsies are necessarily small to preserve cosmesis and/or functionality. Therefore, to perform ACT, biopsies are taken, and the chondrocytes are proliferated in *in-vitro* expansion. However, during this expansion, chondrocytes can undergo de-differentiation [48] and the ECM is lost, meaning the cartilage is less effective. A contemporary study looking to solve this issue is discussed below.

There are no serious safety concerns with ACT [49]. Implantation dosages also do not seem to have any significant effect on adverse outcomes [50]. Because of its accepted safety, most literature centres around refined techniques as opposed to studies on the occurrence of adverse outcomes. However, this may be set to change as new. The failure rate of second or third generation ACT is low (1.5% - 7.7%) [51] with periosteal ACT having the highest rate of failure of all, although ultimately a third of all cases proceed to a re-operation, so ACT is rarely definitive [51].

ACT has the possibility of becoming a regularly recommended treatment for OA with further modifications and refinement. Davies and Kuiper [52] highlight some ways in which ACT development can improve. Firstly, in the refinement of scaffolds, with a wider range of synthetic scaffolds and the properties they can offer being available [52]. ACT also presents the possibilities of combining itself with other biologic treatments such as gene therapy, HA injections or growth factors to accentuate performance and improve outcomes [53].

To overcome the dilemma of chondron vs. chondrocyte harvest contemporary trials are assessing the use of spheroids [50]. These are neocartilage units that contain both *in-vitro* proliferated chondrocytes and the pericellular matric necessary to make bio-realistic cartilage. This aims to compromise the clinical benefit of chondron implants vs. the expandability of chondrocytes as well as turn a two-step procedure into a single-step procedure.

The evidence shows that ACT can be recommended as a treatment for OA and may be particularly beneficial for patients with small lesions and early disease. However, it is still far from being gold standard. Consensus needs to be sought over chondron vs. chondrocyte harvesting for example, and the ability to regenerate large lesions should be confirmed before it is routinely provided to patients.

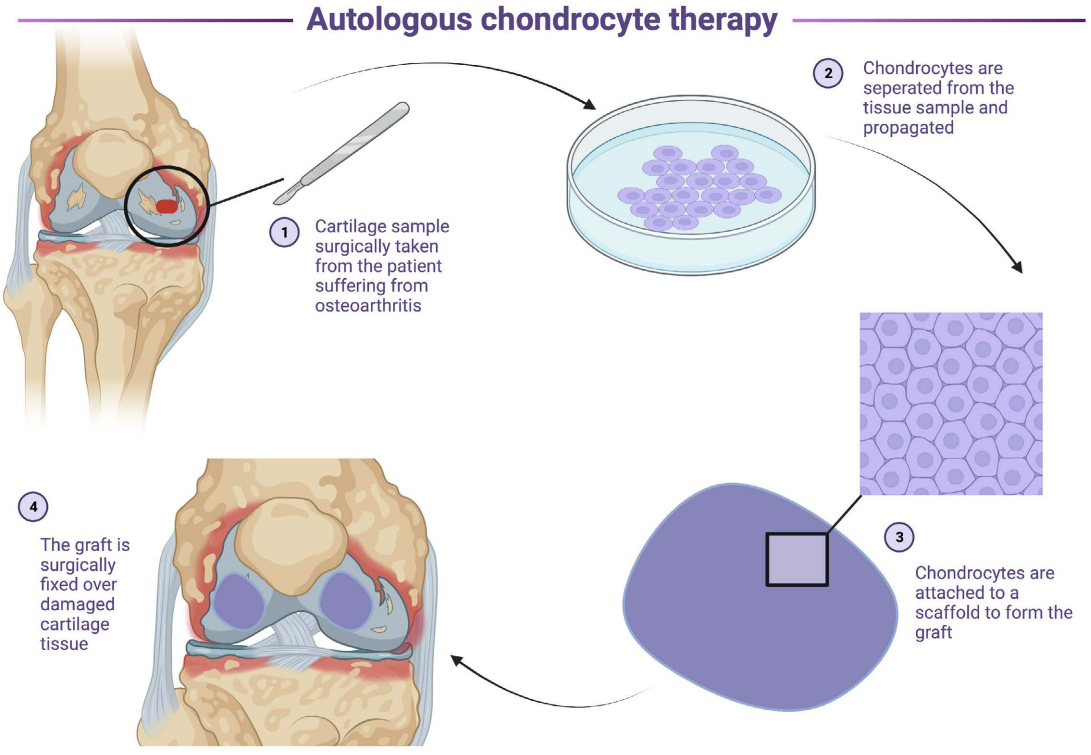

Figure 2. A diagram demonstrating the steps involved in delivering autologous chondrocyte therapy to a patient in order to treat osteoarthritis.

2.3. Gene Therapy

Gene therapy (GT), like protein therapy, aims to increase the anti-inflammatory

molecules and other proteins linked to reducing disease progression and stimulating tissue repair. Examples of the desired protein products are: transcription factors, anti-inflammatory cytokines, miRNA and growth factors [54] However, gene therapy enables a greater quantity of biologic proteins to be delivered and sustains the delivery over a period of time. It does this by introducing complementary DNA (cDNA) strands, which code for the intended protein, into the patient via a vector, and these proteins are then synthesised endogenously (**Figure 3**). Non-viral carriers can be used, however viral are often deemed superior because of the specificity and accuracy of target. There are currently 13 licensed gene therapies worldwide [55], but none for the treatment of OA. South Korea is the only country to have issued a licensed GT for the treatment of OA, with "*Invossa*" in 2017, However, this was retracted in 2019 when irregularities with the cell lineage were identified during a clinical trial being undertaken in USA [55].

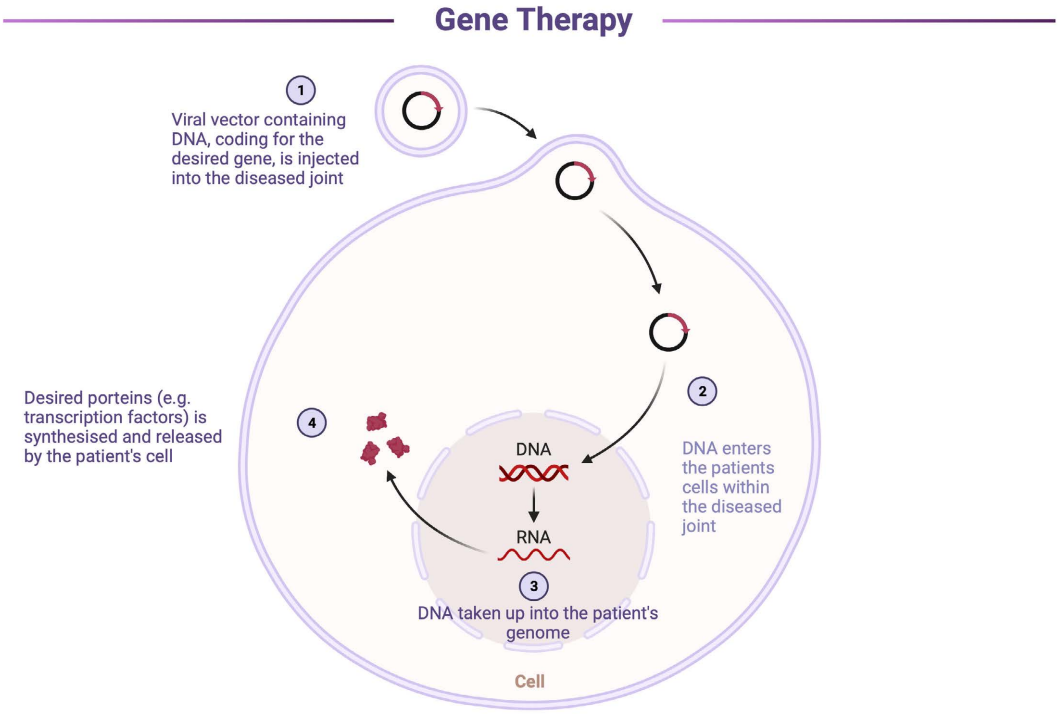

Figure 3. A diagram demonstrating gene therapy in order to treat osteoarthritis.

Translating earlier results into clinical trial success has been challenging [54]. Ex-vivo gene transfer was common amongst early trials. For example, a 1995 trial, which aimed to induce the expression of interleukin-1 receptor antagonist in (IL1Ra) autologous fibroblasts [56], delivered on the trial's aims of a successful translation of the gene and subsequent protein expression, but long-term effects were not assessed. In short, there is scant evidence supporting GT as a clinical option to treat OA currently. GT's safety was reputationally damaged with two high profile cases; the first was the induction of a cytokine storm in an individual who was being treated in a trial for OTC-deficiency [55] and the second was a

cohort of children who developed leukaemia as a result of GT treatment for severe combined immunodeficiency diseases in 2003 [57]. As with any intra-articular therapy, there are inherent risks of inflammation or infection [58], which may be exacerbated by the viral vector [55].

In short, whilst GT is not currently a clinically available treatment for OA, it will possibly have to go further than other biologics to allay the fears of the public due to its history, albeit brief, of adverse events.

2.4. Protein Therapy

Protein based therapies include both plasma rich platelets (PRP) and extracellular vesicle therapy (ECVT), both of which are delivered via an intra-articular injection. Both treatments work by introducing proteins such as cytokines and growth factors that play a role in inflammation and tissue repair [59] [60]. It is these properties that make them useful in treating OA.

Platelet rich plasma (PRP) therapy is an injection of platelets that are obtained from an autologous source. The whole blood product is separated out, either by filtration or in a series of centrifuges to isolate a concentrate of platelets along with other associated proteins and metabolites (**Figure 4**). This is then injected into the affected joint as a treatment. The method of production can vary widely, leading to variations in the constitution of the end-product and its subsequent efficacy. Preparations can be "activated" prior to injection with a range of methods such as the addition of other chemicals, for example, thrombin, freezing [59] or relying on the patient's body to activate the platelets once injected.

Trials on animal models, in vitro, have contributed largely to our understanding of PRP's method of action [61]. Moreover, results in these trials have suggested that PRP could be used to treat OA. For example, in Porcine models that had OA induced with bovine albumin injections PRP injections lead to an increase in a concentration of interleukins and growth factors and reduced the decline of cartilaginous proteins such as Col II and proteoglycan when compared to saline controls. Similar results can be seen in leporine models PRP treated models showed reduced levels of OA compared to controls [62].

A 2020 review on PRP as an OA treatment assessed 5 systematic reviews with meta-analysis and encapsulating a total of 19 different studies found PRP to be an effective treatment for OA [59]. The 19 studies compared the effect of intra-articular injections of PRP (either commercially purchased or a custom preparation) against other available intra-articular injections. These controls included corticosteroids and saline but most commonly, HA was used. The knee was the only joint studied. Treatment results were assessed using internationally recognised systems such as WOMAC or IKDC scoring, which in turn look at measures such as pain or mobility. Imaging was not widely used and so it would be difficult to use the studies included in the meta-analysis to comment on PRP's ability to reverse disease progression. One paper study that was included in 4 of the 5 literature reviews compared PRP injections to saline and noticed an approximate reduction of WOMAC scored of 50% after a 6 month follow up [63].

A second study, also included in 4 of the 5 reviews compared PRP to HA and demonstrated that following treatments, 83% of patients treated with PRP had at least a 30% decrease in their WOMAC score for pain (indicating they were in less pain) compared to 17% of those treated with HA [64].

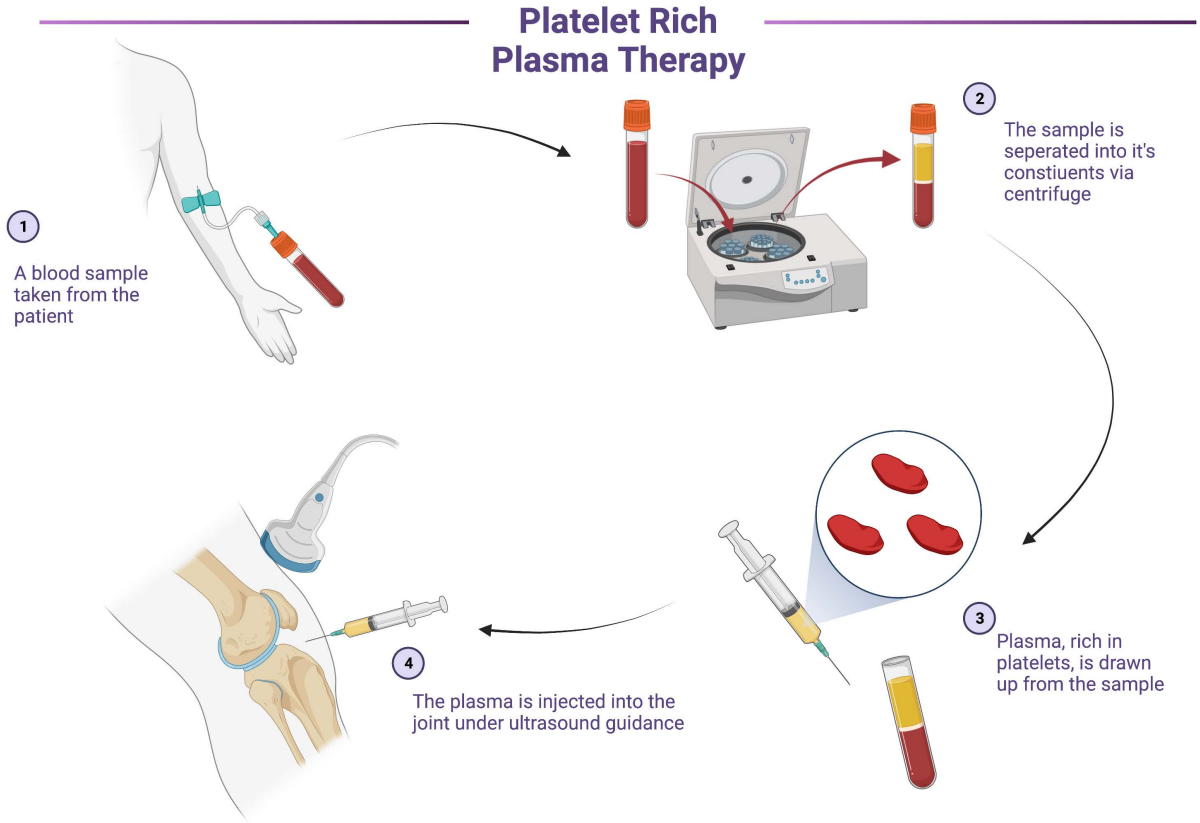

Figure 4. A diagram demonstrating the preparation and administration of platelet rich plasma order to treat osteoarthritis.

However, the lack of standardisation between preparations used in each study and the methodology of assessing success of treatment means it is hard to quantify how effect PRP is as a treatment. Indeed, a more recent study by Bennell *et al.* [65] has provided a robust negative trial of PRP in mild and moderate knee OA with no statistically significant difference between PRP and saline injections. However, the paper itself notes that optimised preparation protocols for PRP have not been developed which may be a cause for the lack of significant difference.

A recent systematic review by Aiyer *et al.* [66] also found that the authors could not recommend PRP's efficacy to over 65's. This could be concluded as a limitation on the potential population pool or be reflective of PRP's ability to work on advanced disease, which manifests itself more frequently in the older population compared to those under 65. However, it is hard to see what conclusions can be made from the study as the paper itself highlighted those inconsistencies amongst the preparations and study designs meant it was GRADE scored as "subjectively moderate".

The main attraction of PRPs over other biologics is their safety. PRP is licensed in the UK and NICE guidelines state that it "raises no major safety concerns" [67] Rare side-effects linked to the injection can include mild effusions, joint stiffness, and pain [68], however, these are like any current intraarticular injectable therapy. Indeed, they are considered safer than other injectable treatments currently licensed for lateral epicondylitis such as corticosteroids [69] but there is little evidence looking at its safety when prescribed for OA. However, it is this level of safety that arguably allows biologics to be less scrutinised than other biologic treatments which could be a leading cause for its lack of standardisation which some have called to address [70]. PRP's present an exciting future in the non-surgical treatment as evidenced by the clinical trials that are currently underway. PRP could be a cost effective and easily deliverable solution to mild arthritis [67]. However, there is still the current literature is too conflicted as to its efficacy as it stands. Possibly the greatest contributing factor to this conflict is the lack of standardisation between trials. This is because of the huge variety in the composition of treatments, which in turn will impact the experience each patient will have [71]. This lack of uniformity, standardisation and uniformity could threaten to bring PRP usage into disrepute.

Vesicles are small membrane bound cellular excretions containing regulatory proteins such as chemokines, cytokines, and lipids. They are vital in intercellular interactions *in vivo* [72] and may have roles in modulating the immune system and tissue regeneration. Once secreted in the extracellular space, they can interact and be internalized by target cells, ultimately influencing, and modifying their phenotype. The belief is that they can provide the estimated benefits of stem cell therapy without injecting the whole cell. Whilst there have been preliminary in vitro studies into its effectiveness [73] [74], it is still necessary to learn more about its intraarticular behaviour.

There are many ways of processing tissue aspirates (commonly abdominal adipose) to form vesicles, but a method commonly used in the private sectors produced by Lipogems®. This product is widely marketed in the private sector, but there is very little evidence to support its efficacy [75]. There are thousands of case studies reporting its safety [76], but few published RCT's with a low risk of bias and high-quality evidence supporting its clinical use.

A 2019 systematic review looked at both in vitro and in-vivo (animal studies) found that initial studies show that extra-cellular vesicle therapy (ECVT) has the potential to not only reduce inflammation but can help stimulate cartilage surface regeneration and subchondral bone regeneration [72]. This suggests that ECVT presents an exciting opportunity to refine stem cell therapies to just the necessary proteins and should be a category for further pre-clinical trials.

In short, whilst PRP are considered a safe treatment, there is much variation between their preparations, from patient to patient. This variation has undoubtedly led to the varying results when trialed clinically and so more and better designed studies need to be undertaken to create an evidence-based consensus. ECVT, another protein therapy has shown initial promise in animal studies and

so further development and testing of the product should be endorsed.

3. Discussion

Biologics can generate a lot of interest when they are considered in the treatment of OA. They potentially offer a minimally invasive treatment of the pathology as well as the symptoms at a fraction of the price of conventional arthroplasty. Moreover, they may be able to reverse disease progression. However, currently, only ACT, with its established clinical history and evidence base can be reliably recommended to patients. Even then, the current methodology for ACT does not suitably treat large lesions and so there would not be many cases where it is suitable. The evidence base for PRP is too conflicted at present, but early, positive trials have sparked a growth in current trials, and a more conclusive picture may emerge soon that can allow clinicians to add PRP to the list of recommendable treatments. BMDSCs show great potential as a treatment compared to the other biologic treatments and stem cell therapies from other sources and work should be undertaken to develop best practice for delivering these to patients. Other treatments should not be prescribed yet for a range of reasons outlined below. Doing so, may at worst endanger the patient, but more likely lead to a clinical outcome that is worse than expected, desired, or advertised.

Stem cell therapies show promise in their ability to treat OA, due to their differentiation ability, as well ability to suppress inflammation (21). However, there is not enough literature of quality to suggest they are ready to be used on their own as effective treatments for OA. There is still limited evidence in human trials that current stimulates tissue regeneration, and lead to halting disease progression or leading to reversal. It should be made abundantly clear to patients that current evidence shows very little support that these treatments lead to tissue regeneration [76]. Moreover, as with most biologic treatment studies, there is a lack of uniformity in methodology, in particular dosages [17] and follow up times, meaning optimum protocols for long term benefits have not been developed.

There are concerns about the safety of some biologic therapies, particularly FDSCs and GTs. The first issue of concern is the consequence of using allogenic sources of cells. Studies suggesting the safety of stem cell therapies mostly use BMSCs which are primarily from an autologous source [30] [77]. There are not many studies looking at adverse reactions in FDSCs, which use allogenic tissue. Any studies that do exist, often lacks trial evidence with large cohorts and sufficient follow-up time. Nevertheless, these studies, find the only adverse effects of using FDSC's are procedural side-effects such as inflammation at the site injection, suggesting that amniotic product injections, as well as BMDSCs are safe [78]. The safety concerns surrounding GT are extensively highlighted above, and so in the case of both GT and FDSCT, a wider range of trials is necessary to reassure both the public and clinicians of their safety.

Currently, GTs are expensive. The most expensive gene therapy in the world, *Zolgensma*, an SMA treatment, is priced at over £1.5 million per dose [79]. This

could account for the stalling progress in biologics development and may be a barrier to regular clinical usage. However, it is hoped that OA treatments are more cost effective as they can be delivered intra-articular as opposed to systemically and therefore smaller doses are needed.

Biologics have a history of being poorly received, dating as far back as the first extractions of porcine insulin [80]. As a result, they will often have to work harder to gain acceptance in the public eye than other, more established, medical treatments. Gene therapy has always struggled for acceptance both the public and scientists, centered around safety fears, but also moral, ethical, and religious fears [81], which will not have been allayed by the issues encountered with the "*Invossa*" treatments.

FDSCT also suffers from an issue with public acceptance due to the controversial nature of the therapeutic usage of foetal tissue [82].

In short, biologics, except for ACT, do not have the weight of sufficient evidence backing them to be routinely prescribed in a responsible manner. ACT is not routinely used to treat OA, and so more work should be done to optimise the methodology of the therapy in the context of this disease before it can become a staple of treatment. PRP treatments and stem cell preparations show enough promise to merit more research on the efficacy of the procedures. These studies should also aim to improve our understanding of how these treatments could stimulate tissue regeneration. Thereafter, studies should look at the optimisation and standardisation of procedures to produce the best outcomes, consistently. Other biologics do not show as much promise as the three listed above, and the quality and quantity of evidence supporting them is lacking.

4. Conclusions

Osteoarthritis presents a growing burden of health to the world population, especially in the Western world. Despite this, the definitive treatment for OA in large joints has not changed in over 50 years, and arthroplasty remains the most prevalent definitive treatment for later-stage OA in large joints in most healthcare setting.

Arthroplasty, however, has its limitations: They require an anaesthetic, the prosthesis has a finite lifespan, they are expensive and impractical or impossible for smaller joints. This has generated a demand for alternative treatments.

Current literature suggests that some biologics may be able to provide treatment for OA either as an adjunct to surgery, delivered by surgery or delivered non-surgically to diseased joints. This means that a greater range of joints can be treated, often without the need for anaesthetic. Non-surgical administration of treatment would inevitably be quicker than arthroplasty and relieve bed space pressure in hospital. Finally, some biologics may demonstrate the potential to halt or even reverse disease progression.

However, the term biologics refers to a broad range of treatments, with varying levels of evidence supporting their efficacy and safety. From the trials that

have been undertaken, biologics, appear to present a low risk to safety. However, in general, clinicians and patients should be wary of claims made by providers of biologics treatments and be aware that most treatments have a poor evidence base supporting their clinical efficacy. ACT has a better level of evidence than other therapies and so can be considered as a treatment when appropriate, but should be refined to improve success rates, particularly with large lesions. Other treatments such as PRP and BMDSC's merit more research into their efficacy based on some promising contemporary literature, whilst also understanding their benefits are debated in conflicting studies. Other treatments such as ASC should be avoided until there is a greater quantity and quality of evidence supporting its use.

There is still a lot of research necessary regarding biologics. Firstly, greater evidence supporting their efficacy for disease treatment needs to be undertaken so that can be prescribed with confidence. Secondly, greater work needs to be done in standardising the treatment, such as dosages and composition of injections. Not only will this increase the reliability of treatment outcomes but will give the public greater confidence in the level of care they are receiving. If these are undertaken, then biologics present a truly exciting change to the management of OA amongst the world's ageing population.

Conflicts of Interest

The authors have no declared conflicts of interest.

References

[1] Cooper, C., Arden, N., *et al.* (2013) Health Economics in the Field of Osteoarthritis: An Expert's Consensus Paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis and Rheumatism*, **43**, 303-313.

[2] Ferguson, R.J., Palmer, A.J., Taylor, A., Porter, M.L., Malchau, H. and Glyn-Jones, S. (2018) Hip Replacement. *The Lancet*, **392**, 1662-1671. https://doi.org/10.1016/S0140-6736(18)31777-X

[3] Cui, A., Li, H., Wang, D., Zhong, J., Chen, Y. and Lu, H. (2020) Global, Regional Prevalence, Incidence and Risk Factors of Knee Osteoarthritis in Population-Based Studies. *eClinicalMedicine*, **29**, Article 100587. https://doi.org/10.1016/j.eclinm.2020.100587

[4] Park, H., Kim, H. and Lee, Y. (2020) Knee Osteoarthritis and Its Association with Mental Health and Health-Related Quality of Life: A Nationwide Cross-Sectional Study. *Geriatrics & Gerontology International*, **20**, 379-383. https://doi.org/10.1111/ggi.13879

[5] Berenbaum, F. (2013) Osteoarthritis as an Inflammatory Disease (Osteoarthritis Is Not Osteoarthrosis!). *Osteoarthritis and Cartilage*, **21**, 16-21. https://doi.org/10.1016/j.joca.2012.11.012

[6] Sinusas, K. (2012) Osteoarthritis: Diagnosis and Treatment. *American Family Physician*, **85**, 49-56.

[7] Sharma, L. (2021) Osteoarthritis of the Knee. *The New England Journal of Medi-*

cine, **384**, 51-59. https://doi.org/10.1056/NEJMcp1903768

[8] Grässel, S. and Muschter, D. (2020) Recent Advances in the Treatment of Osteoarthritis. *F*1000*Research*, **9**, Article 325. https://doi.org/10.12688/f1000research.22115.1

[9] Ryan-Ndegwa, S., Zamani, R. and Akrami, M. (2021) Assessing Demographic Access to Hip Replacement Surgery in the United Kingdom: A Systematic Review. *International Journal for Equity in Health*, **20**, Article No. 224. https://doi.org/10.1186/s12939-021-01561-9

[10] Mahmoudian, A., Lohmander, L.S., Mobasheri, A., Englund, M. and Luyten, F.P. (2021) Early-Stage Symptomatic Osteoarthritis of the Knee—Time for Action. *Nature Reviews Rheumatology*, **17**, 621-632. https://doi.org/10.1038/s41584-021-00673-4

[11] Food and Drug Administration, US Department of Health and Human Services, *et al*. (2018) Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment. Guidance for Industry.

[12] Driban, J.B., Harkey, M.S., Liu, S., Salzler, M. and McAlindon, T.E. (2020) Osteoarthritis and Aging: Young Adults with Osteoarthritis. *Current Epidemiology Reports*, **7**, 9-15. https://doi.org/10.1007/s40471-020-00224-7

[13] Cross, M., Ngueyon, Sime, W., March, L. and Guillemin, F. (2020) The Burden of Osteoarthritis: Self-Reported Severity in the KHOALA Population-Based Cohort. *Rheumatology*, **59**, 2368-2373. https://doi.org/10.1093/rheumatology/kez619

[14] Cameron, K.L., Hsiao, M.S., Owens, B.D., Burks, R. and Svoboda, S.J. (2011) Incidence of Physician-Diagnosed Osteoarthritis among Active Duty United States Military Service Members. *Arthritis & Rheumatism*, **63**, 2974-2982. https://doi.org/10.1002/art.30498

[15] Hoch, A., Schenk, P., Jentzsch, T., Rahm, S. and Zingg, P.O. (2021) FAI Morphology Increases the Risk for Osteoarthritis in Young People with a Minimum Follow-up of 25 Years. *Archives of Orthopaedic and Trauma Surgery*, **141**, 1175-1181. https://doi.org/10.1007/s00402-020-03522-3

[16] van Buuren, M.M.A., Heerey, J.J., Smith, A., Crossley, K.M., Kemp, J.L., Scholes, M.J., *et al*. (2022) The Association between Statistical Shape Modeling-Defined Hip Morphology and Features of Early Hip Osteoarthritis in Young Adult Football Players: Data from the Femoroacetabular Impingement and Hip Osteoarthritis Cohort (FORCe) Study. *Osteoarthritis and Cartilage Open*, **4**, Article 100275. https://doi.org/10.1016/j.ocarto.2022.100275

[17] Delanois, R.E., Etcheson, J.I., Sodhi, N., Henn III, R.F., Gwam, C.U., George, N.E., *et al*. (2019) Biologic Therapies for the Treatment of Knee Osteoarthritis. *The Journal of Arthroplasty*, **34**, 801-813.https://doi.org/10.1016/j.arth.2018.12.001

[18] Revers, L. and Furczon, E. (2010) An Introduction to Biologics and Biosimilars. Part I: Biologics: What Are They and Where Do They Come From? *Canadian Pharmacists Journal*, **143**, 134-139. https://doi.org/10.3821/1913-701X-143.3.134

[19] Vaish, A., Murrell, W. and Vaishya, R. (2020) History of Regenerative Medicine in the Field of Orthopedics. *Journal of Arthroscopic Surgery and Sports Medicine*, **1**, 154-158. https://doi.org/10.25259/JASSM_12_2020

[20] Bianco, P., Robey, P.G. and Simmons, P.J. (2008) Mesenchymal Stem Cells: Revisiting History, Concepts and Assays. *Cell Stem Cell*, **2**, 313-319. https://doi.org/10.1016/j.stem.2008.03.002

[21] Harrell, C.R., Markovic, B.S., Fellabaum, C., Arsenijevic, A. and Volarevic, V.

(2019) Mesenchymal Stem Cell-Based Therapy of Osteoarthritis: Current Knowledge and Future Perspectives. *Biomedicine & Pharmacotherapy*, **109**, 2318-2326. https://doi.org/10.1016/j.biopha.2018.11.099

[22] Charitos, I.A., Ballini, A., Cantore, S., Boccellino, M., Di Domenico, M., Borsani, E., *et al.* (2021) Stem Cells: A Historical Review about Biological, Religious and Ethical Issues. *Stem Cells International*, **2021**, Article ID: 9978837. https://doi.org/10.1155/2021/9978837

[23] van den Bosch, M.H.J. (2021) Osteoarthritis Year in Review 2020: Biology. *Osteoarthritis and Cartilage*, **29**, 143-150. https://doi.org/10.1016/j.joca.2020.10.006

[24] Kunze, K.N., Burnett, R.A., Wright-Chisem, J., Frank, R.M. and Chahla, J. (2020) Adipose-Derived Mesenchymal Stem Cell Treatments and Available Formulations. *Current Reviews in Musculoskeletal Medicine*, **13**, 264-280. https://doi.org/10.1007/s12178-020-09624-0

[25] Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F.C., Krause, D.S., *et al.* (2006) Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. The International Society for Cellular Therapy Position Statement. *Cytotherapy*, **8**, 315-317. https://doi.org/10.1080/14653240600855905

[26] Shin, Y., Yoon, J., Kim, H. and Lee, S. (2018) Intra-Articular Injection of Bone Marrow-Derived Mesenchymal Stem Cells Leading to Better Clinical Outcomes without Difference in MRI Outcomes from Baseline in Patients with Knee Osteoarthritis. *Knee Surgery & Related Research*, **30**, 206-214. https://doi.org/10.5792/ksrr.17.201

[27] Filardo, G., Madry, H., Jelic, M., Roffi, A., Cucchiarini, M. and Kon, E. (2013) Mesenchymal Stem Cells for the Treatment of Cartilage Lesions: From Preclinical Findings to Clinical Application in Orthopaedics. *Knee Surgery, Sports Traumatology, Arthroscopy*, **21**, 1717-1729. https://doi.org/10.1007/s00167-012-2329-3

[28] Kubosch, E.J., Heidt, E., Niemeyer, P., Bernstein, A., Südkamp, N.P. and Schmal, H. (2017) *In-vitro* Chondrogenic Potential of Synovial Stem Cells and Chondrocytes Allocated for Autologous Chondrocyte Implantation—A Comparison. *International Orthopaedics*, **41**, 991-998. https://doi.org/10.1007/s00264-017-3400-y

[29] Lamo-Espinosa, J.M., Mora, G., Blanco, J.F., Granero-Moltó, F., Nuñez-Córdoba, J.M., Sánchez-Echenique, C., *et al.* (2016) Intra-Articular Injection of Two Different Doses of Autologous Bone Marrow Mesenchymal Stem Cells versus Hyaluronic Acid in the Treatment of Knee Osteoarthritis: Multicenter Randomized Controlled Clinical Trial (Phase I/II). *Journal of Translational Medicine*, **14**, Article No. 246. https://doi.org/10.1186/s12967-016-0998-2

[30] Gupta, P.K., Chullikana, A., Rengasamy, M., Shetty, N., Pandey, V., Agarwal, V., *et al.* (2016) Efficacy and Safety of Adult Human Bone Marrow-Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells (Stempeucel®): Preclinical and Clinical Trial in Osteoarthritis of the Knee Joint. *Arthritis Research & Therapy*, **18**, Article No. 301. https://doi.org/10.1186/s13075-016-1195-7

[31] Shapiro, S.A., Kazmerchak, S.E., Heckman, M.G., Zubair, A.C. and O'Connor, M.I. (2017) A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. *The American Journal of Sports Medicine*, **45**, 82-90. https://doi.org/10.1177/0363546516662455

[32] Vega, A., Martín-Ferrero, M.A., Del Canto, F., Alberca, M., García, V., Munar, A., *et al.* (2015) Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation*, **99**, 1681-1690. https://doi.org/10.1097/TP.0000000000000678

[33] Chahal, J., Gómez-Aristizábal, A., Shestopaloff, K., Bhatt, S., Chaboureau, A., Fazio, A., *et al.* (2019) Bone Marrow Mesenchymal Stromal Cell Treatment in Patients with Osteoarthritis Results in Overall Improvement in Pain and Symptoms and Reduces Synovial Inflammation. *Stem Cells Translational Medicine*, **8**, 746-757. https://doi.org/10.1002/sctm.18-0183

[34] Jevotovsky, D.S., Alfonso, A.R., Einhorn, T.A. and Chiu, E.S. (2018) Osteoarthritis and Stem Cell Therapy in Humans: A Systematic Review. *Osteoarthritis and Cartilage*, **26**, 711-729. https://doi.org/10.1016/j.joca.2018.02.906

[35] Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., *et al.* (1999) Multilineage Potential of Adult Human Mesenchymal Stem Cells. *Science*, **284**, 143-147. https://doi.org/10.1126/science.284.5411.143

[36] Dragoo, J.L., Samimi, B., Zhu, M., Hame, S.L., Thomas, B.J., Lieberman, J.R., *et al.* (2003) Tissue-Engineered Cartilage and Bone Using Stem Cells from Human Infrapatellar Fat Pads. *The Journal of Bone & Joint Surgery British Volume*, **85**, 740-747. https://doi.org/10.1302/0301-620X.85B5.13587

[37] Kuah, D., Sivell, S., Longworth, T., James, K., Guermazi, A., Cicuttini, F., *et al.* (2018) Safety, Tolerability and Efficacy of Intra-Articular Progenza in Knee Osteoarthritis: A Randomized Double-Blind Placebocontrolled Single Ascending Dose Study. *Journal of Translational Medicine*, **16**, Article No. 49. https://doi.org/10.1186/s12967-018-1420-z

[38] Freitag, J., Bates, D., Wickham, J., Shah, K., Huguenin, L., Tenen, A., *et al.* (2019) Adipose-Derived Mesenchymal Stem Cell Therapy in the Treatment of Knee Osteoarthritis: A Randomized Controlled Trial. *Regenerative Medicine*, **14**, 213-230. https://doi.org/10.2217/rme-2018-0161

[39] Lee, W., Kim, H.J., Kim, K., Kim, G.B. and Jin, W. (2019) Intra-Articular Injection of Autologous Adipose Tissuederived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. *Stem Cells Translational Medicine*, **8**, 504-511. https://doi.org/10.1002/sctm.18-0122

[40] Vines, J.B., Aliprantis, A.O., Gomoll, A.H. and Farr, J. (2016) Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. *The Journal of Knee Surgery*, **29**, 443-450. https://doi.org/10.1055/s-0035-1569481

[41] Park, Y., Ha, C., Lee, C., Yoon, Y.C. and Park, Y. (2017) Cartilage Regeneration in Osteoarthritic Patients by a Composite of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells and Hyaluronate Hydrogel: Results from a Clinical Trial for Safety and Proof-of-Concept with 7 Years of Extended Follow-Up. *Stem Cells Translational Medicine*, **6**, 613-621. https://doi.org/10.5966/sctm.2016-0157

[42] Brittberg, M., Lindahl, A., Nilsson, A., Ohlsson, C., Isaksson, O. and Peterson, L. (1994) Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation. *The New England Journal of Medicine*, **331**, 889-895. https://doi.org/10.1056/NEJM199410063311401

[43] Knutsen, G., Drogset, J.O., Engebretsen, L., Grøntvedt, T., Isaksen, V., Ludvigsen, T.C., *et al.* (2007) A Randomized Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Findings at Five Years. *The Journal of Bone & Joint Surgery*, **89**, 2105-2112. https://doi.org/10.2106/00004623-200710000-00002

[44] Ogura, T., Mosier, B.A., Bryant, T. and Minas, T. (2017) A 20-Year Follow-Up after First-Generation Autologous Chondrocyte Implantation. *The American Journal of Sports Medicine*, **45**, 2751-2761. https://doi.org/10.1177/0363546517716631

[45] Basad, E., Wissing, F.R., Fehrenbach, P., Rickert, M., Steinmeyer, J. and Ishaque, B.

(2015) Matrix-Induced Autologous Chondrocyte Implantation (MACI) in the Knee: Clinical Outcomes and Challenges. *Knee Surgery, Sports Traumatology, Arthroscopy*, **23**, 3729-3735. https://doi.org/10.1007/s00167-014-3295-8

[46] Niemeyer, P., Porichis, S., Steinwachs, M., Erggelet, C., Kreuz, P.C., Schmal, H., *et al.* (2014) Long-Term Outcomes after First-Generation Autologous Chondrocyte Implantation for Cartilage Defects of the Knee. *The American Journal of Sports Medicine*, **42**, 150-157. https://doi.org/10.1177/0363546513506593

[47] Vonk, L.A., De Windt, T.S., Kragten, A., Beekhuizen, M., Mastbergen, S.C., Dhert, W., *et al.* (2014) Enhanced Cellinduced Articular Cartilage Regeneration by Chondrons; The Influence of Joint Damage and Harvest Site. *Osteoarthritis and Cartilage*, **22**, 1910-1917. https://doi.org/10.1016/j.joca.2014.08.005

[48] Duan, L., Ma, B., Liang, Y., Chen, J., Zhu, W., Li, M., *et al.* (2015) Cytokine Networking of Chondrocyte Dedifferentiation *in Vitro* and Its Implications for Cell-Based Cartilage Therapy. *American Journal of Translational Research*, **7**, 194-208.

[49] Biazzo, A., D'Ambrosi, R., Masia, F., Izzo, V. and Verde, F. (2020) Autologous Adipose Stem Cell Therapy for Knee Osteoarthritis: Where Are We Now? *The Physician and Sportsmedicine*, **48**, 392-399. https://doi.org/10.1080/00913847.2020.1758001

[50] Becher, C., Laute, V., Fickert, S., Zinser, W., Niemeyer, P., John, T., *et al.* (2017) Safety of Three Different Product Doses in Autologous Chondrocyte Implantation: Results of a Prospective, Randomised, Controlled Trial. *Journal of Orthopaedic Surgery and Research*, **12**, Article No. 71. https://doi.org/10.1186/s13018-017-0570-7

[51] Harris, J.D., Siston, R.A., Brophy, R.H., Lattermann, C., Carey, J.L. and Flanigan, D.C. (2011) Failures, Re-Operations and Complications after Autologous Chondrocyte Implantation-A Systematic Review. *Osteoarthritis and Cartilage*, **19**, 779-791. https://doi.org/10.1016/j.joca.2011.02.010

[52] Davies, R.L. and Kuiper, N.J. (2019) Regenerative Medicine: A Review of the Evolution of Autologous Chondrocyte Implantation (ACI) Therapy. *Bioengineering*, **6**, Article 22. https://doi.org/10.3390/bioengineering6010022

[53] Seidl, C.I., Fulga, T.A. and Murphy, C.L. (2019) CRISPR-Cas9 Targeting of MMP13 in Human Chondrocytes Leads to Significantly Reduced Levels of the Metalloproteinase and Enhanced Type II Collagen Accumulation. *Osteoarthritis and Cartilage*, **27**, 140-147. https://doi.org/10.1016/j.joca.2018.09.001

[54] Bellavia, D., Veronesi, F., Carina, V., Costa, V., Raimondi, L., De Luca, A., *et al.* (2018) Gene Therapy for Chondral and Osteochondral Regeneration: Is the Future Now? *Cellular and Molecular Life Sciences*, **75**, 649-667. https://doi.org/10.1007/s00018-017-2637-3

[55] Evans, C.H. (2019) The Vicissitudes of Gene Therapy. *Bone & Joint Research*, **8**, 469-471. https://doi.org/10.1302/2046-3758.810.BJR-2019-0265

[56] Evans, C.H., Ghivizzani, S.C. and Robbins, P.D. (2021) Orthopaedic Gene Therapy: Twenty-Five Years on. *The Journal of Bone & Joint Surgery Reviews*, **9**, e20.00220. https://doi.org/10.2106/JBJS.RVW.20.00220

[57] Hacein-Bey-Abina, S., Von, Kalle, C., Schmidt, M., McCormack, M.P., Wulffraat, N., Leboulch, P.A., *et al.* (2003) LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1. *Science*, **302**, 415-419. https://doi.org/10.1126/science.1088547

[58] Kaiser, J. (2007) Death Prompts a Review of Gene Therapy Vector. *Science*, **317**,

580. https://doi.org/10.1126/science.317.5838.580

[59] Gato-Calvo, L., Magalhaes, J., Ruiz-Romero, C., Blanco, F.J. and Burguera, E.F. (2019) Platelet-Rich Plasma in Osteoarthritis Treatment: Review of Current Evidence. *Therapeutic Advances in Chronic Disease*, **10**. 1-18. https://doi.org/10.1177/2040622319825567

[60] Zhang, P., Yeo, J.C. and Lim, C.T. (2019) Advances in Technologies for Purification and Enrichment of Extracellular Vesicles. *Slas Technology*: *Translating Life Sciences Innovation*, **24**, 477-488. https://doi.org/10.1177/2472630319846877

[61] Xie, X., Zhang, C. and Tuan, R.S. (2014) Biology of Platelet-Rich Plasma and Its Clinical Application in Cartilage Repair. *Arthritis Research* & *Therapy*, **16**, Article No. 204. https://doi.org/10.1186/ar4493

[62] Saito, M., Takahashi, K.A., Arai, E., Inoue, A., Sakao, K., Tonomura, H., *et al.* (2009) Intra-Articular Administration of Platelet-Rich Plasma with Biodegradable Gelatin Hydrogel Microspheres Prevents Osteoarthritis Progression in the Rabbit Knee. *Clinical* & *Experimental Rheumatology*, **27**, Article No. 201.

[63] Patel, S., Dhillon, M.S., Aggarwal, S., Marwaha, N. and Jain, A. (2013) Treatment with Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis: A Prospective, Double-Blind, Randomized Trial. *The American Journal of Sports Medicine*, **41**, 356-364. https://doi.org/10.1177/0363546512471299

[64] Vaquerizo, V., Plasencia, MÁ., Arribas, I., Seijas, R., Padilla, S., Orive, G., *et al.* (2013) Comparison of Intraarticular Injections of Plasma Rich in Growth Factors (PRGF-Endoret) versus Durolane Hyaluronic Acid in the Treatment of Patients with Symptomatic Osteoarthritis: A Randomized Controlled Trial. *Arthroscopy*: *The Journal of Arthroscopic* & *Related Surgery*, **29**, 1635-1643. https://doi.org/10.1016/j.arthro.2013.07.264

[65] Bennell, K.L., Paterson, K.L., Metcalf, B.R., Duong, V., Eyles, J., Kasza, J., *et al.* (2021) Effect of Intra-Articular Platelet-Rich Plasma vs. Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients with Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. *Journal of the American Medical Association*, **326**, 2021-2030. https://doi.org/10.1001/jama.2021.19415

[66] Aiyer, R., Noori, S., Schirripa, F., Schirripa, M., Aboud, T., Jain, S., *et al.* (2021) Treatment of Knee Osteoarthritic Pain with Platelet-Rich Plasma: A Systematic Review of Clinical Studies. *Pain Management*, **11**, 419-431. https://doi.org/10.2217/pmt-2020-0052

[67] Glynn, L.G., Mustafa, A., Casey, M., Krawczyk, J., Blom, J., Galvin, R., *et al.* (2018) Platelet-Rich Plasma (PRP) Therapy for Knee Arthritis: A Feasibility Study in Primary Care. *Pilot and Feasibility Studies*, **4**, Article No. 93. https://doi.org/10.1186/s40814-018-0288-2

[68] Bastos, R., Mathias, M., Andrade, R., Bastos, R., Balduino, A., Schott, V., *et al.* (2018) Intra-Articular Injections of Expanded Mesenchymal Stem Cells with and Without Addition of Platelet-Rich Plasma Are Safe and Effective for Knee Osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, **26**, 3342-3350. https://doi.org/10.1007/s00167-018-4883-9

[69] Xu, Q., Chen, J. and Cheng, L. (2019) Comparison of Platelet Rich Plasma and Corticosteroids in the Management of Lateral Epicondylitis: A Meta-Analysis of Randomized Controlled Trials. *International Journal of Surgery*, **67**, 37-46. https://doi.org/10.1016/j.ijsu.2019.05.003

[70] Filardo, G., Di Matteo, B., Di Martino, A., Merli, M.L., Cenacchi, A., Fornasari, P., *et al.* (2015) Platelet-Rich Plasma Intra-Articular Knee Injections Show No Supe-

riority versus Viscosupplementation: A Randomized Controlled Trial. *The American Journal of Sports Medicine*, **43**, 1575-1582. https://doi.org/10.1177/0363546515582027

[71] Southworth, T.M., Naveen, N.B., Tauro, T.M., Leong, N.L. and Cole, B.J. (2019) The Use of Platelet-Rich Plasma in Symptomatic Knee Osteoarthritis. *The Journal of Knee Surgery*, **32**, 37-45. https://doi.org/10.1055/s-0038-1675170

[72] D'Arrigo, D., Roffi, A., Cucchiarini, M., Moretti, M., Candrian, C. and Filardo, G. (2019) Secretome and Extracellular Vesicles as New Biological Therapies for Knee Osteoarthritis: A Systematic Review. *Journal of Clinical Medicine*, **8**, Article 1867. https://doi.org/10.3390/jcm8111867

[73] Wu, J., Kuang, L., Chen, C., Yang, J., Zeng, W., Li, T., *et al.* (2019) MiR-100-5p-Abundant Exosomes Derived from Infrapatellar Fat Pad MSCs Protect Articular Cartilage and Ameliorate Gait Abnormalities via Inhibition of mTOR in Osteoarthritis. *Biomaterials*, **206**, 87-100. https://doi.org/10.1016/j.biomaterials.2019.03.022

[74] Tofiño-Vian, M., Guillén, M.I., del Caz, M.D.P., Silvestre, A. and Alcaraz, M.J. (2018) Microvesicles from Human Adipose Tissue-Derived Mesenchymal Stem Cells as a New Protective Strategy in Osteoarthritic Chondrocytes. *Cellular Physiology and Biochemistry*, **47**, 11-25. https://doi.org/10.1159/000489739

[75] Haq, I., Marudanayagam, A. and Lee, P.Y. (2019) Lipogems in Osteoarthritis: Fact or Fiction?

[76] Murray, I.R., Safran, M.R. and LaPrade, R.F. (2018) Biologics in Orthopaedics: Concepts and Controversies. *Bone & Joint* 360, **7**, 2-8. https://doi.org/10.1302/2048-0105.76.360648

[77] Vega, A., Martín-Ferrero, M.A., Del Canto, F., Alberca, M., García, V., Munar, A., *et al.* (2015) Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation*, **99**, 1681-1690. https://doi.org/10.1097/TP.0000000000000678

[78] McIntyre, J.A., Jones, I.A., Danilkovich, A., Vangsness, Jr. (2018) The Placenta: Applications in Orthopaedic Sports Medicine. *The American Journal of Sports Medicine*, **46**, 234-247. https://doi.org/10.1177/0363546517697682

[79] Nuijten, M. (2022) Pricing Zolgensma—The World's Most Expensive Drug. *Journal of Market Access & Health Policy*, **10**, Article 2022353. https://doi.org/10.1080/20016689.2021.2022353

[80] Ho, E.Y. and James, J. (2006) Cultural Barriers to Initiating Insulin Therapy in Chinese People with Type 2 Diabetes Living in Canada. *Canadian Journal of Diabetes*, **30**, 390-396. https://doi.org/10.1016/S1499-2671(06)04004-4

[81] Delhove, J., Osenk, I., Prichard, I. and Donnelley, M. (2020) Public Acceptability of Gene Therapy and Gene Editing for Human Use: A Systematic Review. *Human Gene Therapy*, **31**, 20-46. https://doi.org/10.1089/hum.2019.197

[82] Al-Agelea, R.A.A., Jabbarb, A.I. and Ibrahimc, R.S. (2020) Do Embryonic Stem Cells Give a New Direction for Therapeutic Purposes? *Journal of Natural Remedies*, **21**, 43-149.