Injectable Orthobiologic Treatments for Osteoarthritis

PREFACE

In recent years, there has been growing interest in intra-articular (into the joint) injectable 'orthobiologic' treatments for osteoarthritis (OA),[1] aiming to relieve symptoms and/or slow down or prevent disease progression before, and/or without, a joint replacement. High quality research into the potential and outcomes of these type of treatments is valid and important.

The COVID-19 pandemic has caused a significant disruption to the normal provision of treatment for patients with osteoarthritis. Versus Arthritis (a charity which supports patients with arthritis) has had callers to their helpline seeking advice on the use of orthobiologics as a treatment option and consequently approached the British Orthopaedic Association (BOA) for a view. In response to this approach the BOA has written this paper to help people who are thinking about trying orthobiologic treatments.

We want to provide a reliable source of information on this topic to help people make informed decisions about their medical care. We hope it will also be a useful resource for all health professionals involved in the care of this group of patients and who would like to know more about these treatments. There is a wide variety of these treatments and the British Orthopaedic Association wishes to provide authoritative advice as to the present state of knowledge to patients and those who advise them. This advice has been adopted by the Council of the BOA in February 2022 and will be updated if further evidence becomes available.

INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal condition of the joints in adults - over 6.5 million people with it seek treatment from their GP each year.[2] Non-operative measures are recommended in the earlier stages of the disease and joint replacement surgery is the main well proven treatment option for people with severe disease.[3]

We are aware that some people with OA may have seen publicity for 'orthobiologic' treatments in the media or online, and wonder if they may be suitable for them. These might be people with early stages of OA for whom joint replacement is not yet recommended, or people who are due to have a joint replacement but have encountered long waiting times for their procedure and are seeking temporary relief.

WHAT IS AN ORTHOBIOLOGIC TREATMENT?

Orthobiologic treatments can be defined as treatments obtained from a human source used in the treatment of certain musculoskeletal conditions including osteoarthritis. There are three distinct treatments that have to be distinguished:

1. Autologous orthobiologic treatments are prepared from a patient's own blood, bone marrow, or fat. Once prepared, they are most commonly injected into the affected body part such as the hip or knee.
2. Donor orthobiologic treatments are prepared from a different person, a 'donor'.
3. Both are different from the 'biologics' used to treat inflammatory conditions including rheumatoid arthritis and ankylosing spondylitis – although they have a similar name they are very different and NHS information for these can be found here: [https://www.nhs.uk/conditions/biological-and-biosimilar-medicines]

WHERE ARE THESE TREATMENTS AVAILABLE?

Orthobiologic treatments are not widely available on the NHS. Various orthobiologics are now marketed directly to patients who may wish to pay for private treatment.[4]

The National Institute for Health and Clinical Excellence (NICE), having reviewed the available evidence, has determined that there is insufficient evidence of efficacy. (Only one is available on the NHS and only in certain circumstances – it is called Platelet Rich Plasma (PRP) and is discussed further below.)

All UK registered doctors are bound by the GMC's guidance on consent and decision making, including, in this context, to tell the patient whether an option is an innovative treatment designed specifically for their benefit and any conflicts of interest that the doctor or their organisation may have.

TERMINOLOGY

Names used to describe orthobiologic treatments can be varied and confusing. There is huge variation in the contents of the treatments and in the way they act, despite many having similar names**.**

In particular the term 'stem cells' is widely used despite very few, if any, true stem cells being present.[5] The term 'stem cell' refers to special cells that have the ability to develop into all or many different cell types and can also replicate themselves. Using the term stem cells might be seen to imply that the cells injected will turn into new tissue - this has **not** been shown for any preparations currently available.

In our view, the use of the term may be misleading and liable to confuse people into supposing that the treatment has some of the advantages that have been proven in other areas of medicine.

DO THEY WORK?

At present, in our view, we do not have enough research evidence to support the routine use of orthobiologic therapies in the treatment of OA.

Symptoms

Studies to date, of variable scientific quality, have focused on the possibility that current products might alleviate symptoms in the short term. There are a range of symptoms effects reported in these studies some positive and some no change as highlighted below. There may be various reasons why patients may experience a short-term improvement other than the material injected. These can include the other aspects of 'a package of treatment' such as a clear diagnosis, support/education, physiotherapy and possibly the simple placebo effect of injecting any fluid into a painful joint. It has not been determined clearly as yet.

Structural change or new tissue development

There is no medical evidence that they result in any structural improvement or creation of new tissue such as articular cartilage.

This is a view adopted by the Council of the BOA and shared by:

1. The National Institute for Health and Clinical Excellence (NICE) in the UK[6],
2. The Osteoarthritis Research Society International (OARSI)[7] and
3. The American College of Rheumatology (ACR) / Arthritis Foundation.[8]

All of these bodies have scrutinised the literature describing scientific research about the safety and efficacy of these treatments.

Later in this document we discuss some of the individual orthobiologics and go into more detail about the research and evidence for their use.

ARE ORTHOBIOLOGIC TREATMENTS SAFE?

No treatment that involves the injection of any substance into a joint can be described as being without risk. Studies suggest that the occurrence of adverse effects following injection of treatments derived from a patient's own tissue are extremely low, but less is known about potential complications after donor treatments.[9] Serious infections have been reported, albeit rarely, following some orthobiologic injections for OA, with some cases requiring multiple

operations to eradicate the infection.[10] [11] Regulation of these 'point of care products' is being currently reviewed by the MHRA.[1]

HOW ARE ORTHOBIOLOGICS ADVERTISED?

As with other treatments particularly in the private sector these may be advertised or marketed in a variety of ways. Orthobiologics are sometimes described as 'stem cell treatments'. This could be misleading as often there are few or no stem cells involved or any evidence of 'true' stem cell actions.

Such representation may not provide a fair balance of the quality research evidence including risks, benefits, limitations and outcomes as would be expected in peer-reviewed literature.[5] [12]

It has been highlighted that some clinics are using marketing that overstates the benefits of these treatments. A recent study of 896 clinics in the USA, found that 95% of their websites contained at least one statement of misinformation.[12] Poor practice has been seen in the UK too; for example a clinic offering orthobiologics was found to have included misleading wording in an advertisement investigated by the Advertising Standards Authority (ASA). The clinic was criticized for claiming or implying that their treatments permanently relieved pain without having evidence to support this.

The BOA believes that it is very important that patients (and their members who treat them) receive fair and balanced information about these orthobiologics, and are clear about what is in them, and this is part of the reason for writing this document.

WHAT TYPES OF ORTHOBIOLOGIC INJECTABLE TREATMENTS ARE THERE?

There are several different types of treatment that are marketed, and we realise this can be confusing. We have provided a description of some of these products below:

1. AUTOLOGOUS BLOOD PRODUCTS (PRODUCTS PREPARED FROM PATIENTS OWN BLOOD)

PLATELET RICH PLASMA (PRP)

What is it?

Blood is known to contain many factors that can aid healing. In particular, cells known as platelets are rich in molecules that can promote healing and reduce inflammation. Preparations that contain high numbers of platelets – known as **platelet rich plasma** (**or PRP**) - are increasingly common. However, there are a wide range of different PRP preparations, and any individual PRP is distinct. This means that research about safety and efficacy of one product or technique may not apply to others.

[1] https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing].

How does it work?
We do not know exactly how PRP may work to improve symptoms of OA but any effect most likely occurs by reducing inflammation within the joint and therefore pain. PRP formulations are typically classified based on whether they contain low concentrations of white blood cells (**Leukocyte-poor PRP**) or high concentrations of white blood cells (**Leukocyte-rich PRP**). PRP is the one orthobiologic that can be available on the NHS, but only under certain conditions, and if you are considering PRP on the NHS you should refer to the following document from NICE for patients: https://www.nice.org.uk/guidance/IPG637/InformationForPublic

Is it safe and is it effective?
PRP is the most widely studied orthobiologic injectable and there have been over 25 trials comparing PRP with other injections. In 2019, The National Institute for Health and Clinical Excellence (NICE) published a guideline concluding that while PRP was reasonably safe, 'there is not enough evidence to be sure how well it works'. NICE recommended that the procedure only be used with special arrangements for clinical governance, consent and audit or research.[6]

Overall, there is no evidence that PRP can restore cartilage or slow progression of OA[10]. There is some evidence that PRP can give variable relief of symptoms in the short term (1-2 years). Reviewing bodies such as NICE, OARSI and ACR cite conflicting results and heterogeneity that limited support at this stage pending further high quality studies.[6-8]

AUTOLOGOUS ANTI-INFLAMMATORIES (AAIs)

What is it?
With increasing appreciation that many of the anti-inflammatory factors within blood arise from white blood cells rather than platelets, strategies focussing on concentrating white blood cells or the anti-inflammatory factors they release have been developed. These include **Autologous conditioned serum** (ACS) – a cell-free serum that contains anti-inflammatory factors released from white blood cells that have been activated. **Autologous Protein Solution (APS)** is produced by processing PRP that is rich in white blood cells, to simulate the release of anti-inflammatory factors and to concentrate them.

Does it work?
There have been a smaller number of trials exploring the use of AAIs. Although these initial studies have demonstrated that AAIs have the potential to improve pain symptoms in the short term, more evidence is required to justify its widespread use. So far it appears to be reasonably safe.

Neither PRP nor AAIs contain true 'stem cells'.

2. CELL BASED THERAPIES

There are a considerable range of cell-based therapies offered as treatment for OA. Sometimes these are presented on the basis that they contain cells that can become cartilage cells and can release molecules that can promote healing. These cells have been given many different names but are most widely referred to as **'mesenchymal stromal cells' or MSCs.**

These cells are present in bone marrow, fat and other tissues and so different products derived from each of these tissues are available. There is no evidence that any of the treatments contain many/if any cells that act in the same way as stem cells and turn into new tissue. These cell based treatments possibly have anti-inflammatory effects and provide some relief of pain symptoms in the short term.

There are two broad groupings of cell therapies:

A. those in which the cells are delivered immediately after being harvested at the 'point of care'
B. those that require a delay for processing and growth of cells in the laboratory ('cultured' preparations).

Although point of care therapies have the advantage that they can be harvested, processed and delivered back to the patient at the same clinic visit, they contain very low concentrations of 'MSCs' (fewer than 0.001-0.005%): It is unknown but probably that these are unlikely to be useful concentrations.

Cultured preparations may contain almost 100% MSCs, but there is little scientific evidence of sustained clinical efficacy.

A. 'POINT OF CARE' CELL BASED THERAPIES

Bone Marrow Aspirate Concentrate (BMAC)

What is it?

Bone Marrow can be obtained easily by needle aspiration in the clinic, most commonly from the pelvis. It can be concentrated to increase the proportion of cells at the clinic and the **bone marrow aspirate concentrate (BMAC)** can be injected immediately. Similar preparations from bone marrow include **Bone Marrow Mononuclear Cells (BM-MNCs)**. [13] BMAC contains a wide range of cells and tissue fragments with fewer than 1 in 1000 cells considered MSCs, and almost none are true stem cells. [14 15] While bone marrow cells can release molecules that reduce inflammation and attract other cells, current evidence suggests they do not act to form new tissue.

Does it work?

There have been very few trials to establish whether concentrated bone marrow treatments work, and these have reported conflicting results. [13 16-18]

Stromal Vascular Fraction (SVF)

What is it?

Stromal vascular fraction (SVF) is derived from fat tissue. The cells are separated from one another using either natural chemical substances or mechanically. Fat cells are then removed and the remaining cells are then injected. [19] As with most orthobiologic treatments, the composition can be extremely variable. [20] The most up to date evidence indicates that that any beneficial effect of this treatment is from the ability of these cells to release molecules to reduce inflammation rather than directly forming new healthy tissue.

Does it work?

There have been a few trials comparing SVF to hyaluronic acid and a placebo injection to treat OA. These studies suggest that SVF may reduce symptoms of pain. [21] However, there is no clear evidence to support the proposition that these treatments slow the progression of OA or to justify routine use other than to provide symptomatic relief amongst those waiting for surgery.

Microfragmented Adipose Tissue (MFAT)

What is it?

Fat also contains MSCs and is an attractive source of cells because fat tissue is easily accessible and relatively expendable. **Microfragmented adipose (fat) tissue (MFAT)** products (such as the product marketed as 'Lipogems') are made from liposuction fat that is further disrupted into smaller fragments and then injected. The final product contains a range of cells types with a small proportion (fewer than 1 in 100 cells being MSCs). [22] These cells may release molecules that reduce inflammation and may attract other cells, but they have not been shown to form new healthy tissue. There is no evidence to substantiate these products provide some 'cushioning and support' within the knee.

Does it work?

There are no high quality trials evaluating the effectiveness of MFAT products to treat OA. There are some lower quality studies reporting symptomatic improvement. [23-28].

B. CULTURE DERIVED 'MESENCHYMAL STROMAL CELLS' (MSCS)

What is it?

Although MSCs make up a small proportion of cells in tissues such as bone marrow and fat, these cells can be grown in laboratories to increase their numbers (a process known as being 'cultured'). If using a patient's own cells, this process requires a delay of several weeks between taking the sample of tissue, growing the cells and then injecting the final treatment.[27]

[28] As with other cell based preparations, these strategies try to harness the ability for these cells to become cartilage cells, reduce inflammation and release molecules that promote healing. These preparations are pure MSCs, unlike treatments such as BMAC, MFAT and SVF that are not cultured in the laboratory.

Does it work?
Several studies have evaluated the value of culture expanded MSCs produced from bone marrow[31-36] and fat[37 38] for OA. Overall, these relatively small studies report a positive effect on patients' symptoms.

Interestingly there are some limited studies indicating these treatments may improve cartilage quality but most studies only report one-year outcomes, and larger studies with longer follow-up are required. This is not the same as restoring cartilage when absent, as in advanced arthritis.

WHERE CAN I READ MORE?

It can be difficult for healthcare providers and patients to identify reputable sources online. Where possible, clinicians and patients should look at official websites of recognised institutions and societies rather than private clinics. Networks such as EuroStemCell (www.eurostemcell.org) provide independent, expert-reviewed information and educational resources about stem cells and their impact on society. Several academic societies have invested considerably in public engagement and education resources including the International Society for Stem Cell research (ISSCR), who have an online forum for patient education (www.closerlookatstemcells.org). NICE publishes guidance on interventional procedures as evidence emerges. Their most recent guidance on PRP injections for OA is at https://www.nice.org.uk/guidance/ipg637.

The following recent guidelines and recommendations are also free to access.

- the American Academy of Orthopaedic Surgeons (AAOS) - https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf
- OARSI - https://oarsi.org/education/oarsi-guidelines-0
- ACR/Arthritis Foundation - https://www.rheumatology.org/Portals/0/Files/Osteoarthritis-Guideline-Early-View-2019.pdf

Early osteoarthritis and related conditions, where joint replacement is not recommended, are an important area of unmet need. Orthobiologics, together with other repair and regenerative treatments, represent a potential new approach but research is at an early stage. As with the introduction of all new technologies, a clear understanding of how the treatment works should be underpinned by laboratory and clinical trial evidence to support its use. The BOA is committed to clinician and patient education and is partnering with other stakeholders and charities to produce current material in this fast-moving field.

This statement has been issued in February 2022 and will be updated as and when further evidence becomes available.

Table 1: Biologic Grouping

Biologic Grouping	Preparation	Subtype	Examples of commercial products
Autologous Blood Products	**Platelet Rich Plasma (PRP)**	Leukocyte Poor - PRP (LP-PRP)	*ACP®, Arthrex* *A-PRP®, Regenlab* *Cascade®, MTF* *ClearPRP®, Harvest* *PurePRP®, EmCyte* *Endoret® (PGRF®), BTI*
		Leukocyte Rich – PRP (LR-PRP)	*GPS III®, ZimmerBiomet* *Angel®, Arthrex* *GenesisCS®, EmCyte* *Magellan®, Arteriocyte* *SmartPReP®, Harvest*
	Autologous Anti-inflammatories (AAIs)	Autologous Protein Solution (APS)	*nStride®, ZimmerBiomet*
		Autologous conditioned serum (ACS)	*Orthokine®, Orthogen*
Cell Therapies	**Point of Care Cell-based therapies**	Bone Marrow aspirate concentrate (BMAC)	*BMAC®, Harvest* *Angel®, Arthrex* *PureBMC®, EmCyte*
		Stromal Vascular Fraction (SVF)	*Adiprep®, Harvest* *Progenikine®, EmCyte* *ACP® SVF, Arthrex*
		Micro-Fragmented Adipose Tissue (MFAT)	*Lipogems®*
	Cultured 'Mesenchymal Stromal Cells' (MSCs)	Autologous MSCs	*LifePlus Stem Cells*
		Allogeneic MSCs	*LifePlus Stem Cells*

References

1. Shi WJ, Tjoumakaris FP, Lendner M, et al. Biologic injections for osteoarthritis and articular cartilage damage: can we modify disease? *Phys Sportsmed* 2017;45(3):203-23. doi: 10.1080/00913847.2017.1357421 [published Online First: 2017/07/19]
2. Arthritis Research UK, Osteoarthritis in General Practice. Available via http://www.arthritisresearchuk.org/.
3. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am* 2015;97(17):1386-97. doi: 10.2106/jbjs.n.01141 [published Online First: 2015/09/04]
4. Piuzzi NS, Ng M, Chughtai M, et al. The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. *J Knee Surg* 2018;31(6):551-56. doi: 10.1055/s-0037-1604443 [published Online First: 2017/07/25]
5. Murray IR, Chahla J, Frank RM, et al. Rogue stem cell clinics. *Bone Joint J* 2020;102-b(2):148-54. doi: 10.1302/0301-620x.102b2.bjj-2019-1104.r1 [published Online First: 2020/02/06]
6. National Institute for Health and Care Excellence (2019). Platelet-rich plasma injections for knee osteoarthritis. (NICE Guideline IPG637). Available at https://www.nice.org.uk/guidance/ipg637. [Accessed 30th May 2021].
7. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27(11):1578-89. doi: 10.1016/j.joca.2019.06.011 [published Online First: 2019/07/07]
8. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis & rheumatology (Hoboken, NJ)* 2020;72(2):220-33. doi: 10.1002/art.41142 [published Online First: 2020/01/08]
9. Centeno CJ, Al-Sayegh H, Freeman MD, et al. A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. *Int Orthop* 2016;40(8):1755-65. doi: 10.1007/s00264-016-3162-y [published Online First: 2016/03/31]
10. Eliasberg CD, Nemirov DA, Mandelbaum BR, et al. Complications Following Biologic Therapeutic Injections: A Multicenter Case Series. *Arthroscopy* 2021;37(8):2600-05. doi: 10.1016/j.arthro.2021.03.065 [published Online First: 2021/04/20]
11. Perkins KM, Spoto S, Rankin DA, et al. Notes from the Field: Infections After Receipt of Bacterially Contaminated Umbilical Cord Blood-Derived Stem Cell Products for Other Than Hematopoietic or Immunologic Reconstitution - United States, 2018. *MMWR Morb Mortal Wkly Rep* 2018;67(50):1397-99. doi: 10.15585/mmwr.mm6750a5 [published Online First: 2018/12/21]
12. Kingery MT, Schoof L, Strauss EJ, et al. Online Direct-to-Consumer Advertising of Stem Cell Therapy for Musculoskeletal Injury and Disease: Misinformation and Violation of Ethical and Legal Advertising Parameters. *J Bone Joint Surg Am* 2020;102(1):2-9. doi: 10.2106/jbjs.19.00714 [published Online First: 2019/11/27]
13. Goncars V, Jakobsons E, Blums K, et al. The comparison of knee osteoarthritis treatment with single-dose bone marrow-derived mononuclear cells vs. hyaluronic acid injections. *Medicina (Kaunas, Lithuania)* 2017;53(2):101-08. doi: 10.1016/j.medici.2017.02.002 [published Online First: 2017/04/19]
14. Imam MA, Mahmoud SSS, Holton J, et al. A systematic review of the concept and clinical applications of Bone Marrow Aspirate Concentrate in Orthopaedics. *Sicot j* 2017;3:17. doi: 10.1051/sicotj/2017007 [published Online First: 2017/01/01]
15. Martin DR, Cox NR, Hathcock TL, et al. Isolation and characterization of multipotential mesenchymal stem cells from feline bone marrow. *Exp Hematol* 2002;30(8):879-86. doi: 10.1016/s0301-472x(02)00864-0 [published Online First: 2002/08/06]
16. Anz AW, Hubbard R, Rendos NK, et al. Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 1 Year: A Prospective, Randomized Trial. *Orthopaedic journal of sports medicine* 2020;8(2):2325967119900958. doi: 10.1177/2325967119900958 [published Online First: 2020/03/03]
17. Centeno C, Sheinkop M, Dodson E, et al. A specific protocol of autologous bone marrow concentrate and platelet products versus exercise therapy for symptomatic knee osteoarthritis: a randomized controlled trial with 2 year follow-up. *J Transl Med* 2018;16(1):355. doi: 10.1186/s12967-018-1736-8 [published Online First: 2018/12/14]
18. Shapiro SA, Kazmerchak SE, Heckman MG, et al. A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. *Am J Sports Med* 2017;45(1):82-90. doi: 10.1177/0363546516662455 [published Online First: 2016/08/28]

19. Faustini M, Bucco M, Chlapanidas T, et al. Nonexpanded mesenchymal stem cells for regenerative medicine: yield in stromal vascular fraction from adipose tissues. *Tissue Eng Part C Methods* 2010;16(6):1515-21. doi: 10.1089/ten.TEC.2010.0214 [published Online First: 2010/05/22]
20. Aronowitz JA, Lockhart RA, Hakakian CS, et al. Adipose Stromal Vascular Fraction Isolation: A Head-to-Head Comparison of 4 Cell Separation Systems #2. *Ann Plast Surg* 2016;77(3):354-62. doi: 10.1097/sap.0000000000000831 [published Online First: 2016/05/25]
21. Hong Z, Chen J, Zhang S, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. *Int Orthop* 2019;43(5):1123-34. doi: 10.1007/s00264-018-4099-0 [published Online First: 2018/08/16]
22. Carelli S, Messaggio F, Canazza A, et al. Characteristics and Properties of Mesenchymal Stem Cells Derived From Microfragmented Adipose Tissue. *Cell Transplant* 2015;24(7):1233-52. doi: 10.3727/096368914x681603 [published Online First: 2014/05/09]
23. Panchal J, Malanga G, Sheinkop M. Safety and Efficacy of Percutaneous Injection of Lipogems Micro-Fractured Adipose Tissue for Osteoarthritic Knees. *Am J Orthop (Belle Mead NJ)* 2018;47(11) doi: 10.12788/ajo.2018.0098 [published Online First: 2018/12/06]
24. Russo A, Condello V, Madonna V, et al. Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. *J Exp Orthop* 2017;4(1):33. doi: 10.1186/s40634-017-0108-2 [published Online First: 2017/10/05]
25. Cattaneo G, De Caro A, Napoli F, et al. Micro-fragmented adipose tissue injection associated with arthroscopic procedures in patients with symptomatic knee osteoarthritis. *BMC Musculoskelet Disord* 2018;19(1):176. doi: 10.1186/s12891-018-2105-8 [published Online First: 2018/06/01]
26. Hudetz D, Borić I, Rod E, et al. The Effect of Intra-articular Injection of Autologous Microfragmented Fat Tissue on Proteoglycan Synthesis in Patients with Knee Osteoarthritis. *Genes (Basel)* 2017;8(10) doi: 10.3390/genes8100270 [published Online First: 2017/10/14]
27. Gobbi A, Dallo I, Rogers C, et al. Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: a multi-centric, international study. *Int Orthop* 2021;45(5):1179-88. doi: 10.1007/s00264-021-04947-0 [published Online First: 2021/03/03]
28. Heidari N, Noorani A, Slevin M, et al. Patient-Centered Outcomes of Microfragmented Adipose Tissue Treatments of Knee Osteoarthritis: An Observational, Intention-to-Treat Study at Twelve Months. *Stem Cells Int* 2020;2020:8881405. doi: 10.1155/2020/8881405 [published Online First: 2020/08/25]
29. Ma T. Mesenchymal stem cells: From bench to bedside. *World J Stem Cells* 2010;2:13-7.
30. Viswanathan S, Shi Y, Galipeau J, et al. Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy* 2019;21(10):1019-24. doi: 10.1016/j.jcyt.2019.08.002 [published Online First: 2019/09/19]
31. Lamo-Espinosa JM, Blanco JF, Sánchez M, et al. Phase II multicenter randomized controlled clinical trial on the efficacy of intra-articular injection of autologous bone marrow mesenchymal stem cells with platelet rich plasma for the treatment of knee osteoarthritis. *J Transl Med* 2020;18(1):356. doi: 10.1186/s12967-020-02530-6 [published Online First: 2020/09/20]
32. Bastos R, Mathias M, Andrade R, et al. Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial. *Knee Surg Sports Traumatol Arthrosc* 2020;28(6):1989-99. doi: 10.1007/s00167-019-05732-8 [published Online First: 2019/10/07]
33. Lamo-Espinosa JM, Mora G, Blanco JF, et al. 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). *J Transl Med* 2016;14(1):246. doi: 10.1186/s12967-016-0998-2 [published Online First: 2016/08/28]
34. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II). *J Transl Med* 2018;16(1):213. doi: 10.1186/s12967-018-1591-7 [published Online First: 2018/08/02]

35. Gupta PK, Chullikana A, Rengasamy M, et al. 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 Res Ther* 2016;18(1):301. doi: 10.1186/s13075-016-1195-7 [published Online First: 2016/12/21]
36. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation* 2015;99(8):1681-90. doi: 10.1097/tp.0000000000000678 [published Online First: 2015/03/31]
37. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regenerative medicine* 2019;14(3):213-30. doi: 10.2217/rme-2018-0161 [published Online First: 2019/02/15]
38. Lee WS, Kim HJ, Kim KI, et al. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. *Stem Cells Transl Med* 2019;8(6):504-11. doi: 10.1002/sctm.18-0122 [published Online First: 2019/03/06]