Research Article ISSN 2639-9512

Stem Cell & Regenerative Medicine

Stem Cell Therapy as a Treatment Method for Rheumatoid Arthritis

Emily Jordan and Dr. Vincent S. Gallicchio

Department of Biological Sciences, Clemson University.

*Correspondence:
Dr. Vincent S. Gallicchio, Department of Biological Sciences, College of Science, Clemson University, Clemson, SC 29634.

Received: 30 March 2020; Accepted: 21 April 2020

Citation: Emily Jordan, Vincent S. Gallicchio. Stem Cell Therapy as a Treatment Method for Rheumatoid Arthritis. Stem Cells Regen Med. 2020; 4(1): 1-10.

ABSTRACT

Rheumatoid Arthritis (RA) is a progressive, autoimmune disorder that causes joint deterioration in the body. RA begins with swelling and inflammation in the joints, and eventually progresses to cause cartilage and bone deterioration at the site of the joint. Early stages of RA typically affect smaller joints, and the impact spreads to larger joints as the disease continues to advance within an individual. There are various treatment methods that are currently used by RA patients, which aim to mitigate RA symptoms and induce periods of remission. However, stem cell therapies using BM-MSCs, hASCs, UC-MSCs, and hUCB-MSCs are currently being studied as potential treatment methods for RA. Many scientists and researchers believe that the characteristics of stem cells will allow stem cell therapy to be an extremely beneficial treatment method. Pre-clinical trials and clinical trials using various stem cell types have been completed, but further testing is necessary to determine the most safe and effective method to treat RA in humans.

Keywords

Rheumatoid Arthritis, Treatment, Stem cells, Mesenchymal stem cells.

Abbreviations and Symbols

RA: Rheumatoid Arthritis; NSAIDs: Non-Steroidal Anti-inflammatory Agents; DMARDSs: Disease Modifying Anti-Rheumatic Drugs (DMARDSs); ASCs: Adult Stem Cells; ESCs: Embryonic Stem Cells; iPSCs: Induced Pluripotent Stem Cells; MSCs: Mesenchymal Stem Cells; CIA: Collagen-Induced Arthritis; AIA: Adjuvant-Induced Arthritis; CFA: Complete Freund's Adjuvant; CII: Type II Collagen; BM-MSCs: Bone Marrow Mesenchymal Stem Cells; hASCs: Human Adipose-derived Mesenchymal Stem Cells; UC-MSCs: Umbilical Cord Tissue-Derived Mesenchymal Stem Cells; DAS28: 28-Joint Disease Activating Score; hUCB-MSCs: Umbilical Cord Blood-derived Mesenchymal Stem Cells; VAS: Visual Analog Scale; HAQ: Health Assessment Questionnaire; TKR:Total Knee Replacement.

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory condition in which the immune system begins to attack the synovium, lining the joints in the body. RA is considered an autoimmune disorder, which is a condition in which the immune system mistakes healthy tissues in the body for harmful substances, and begins to attack those tissues. When the immune system attacks the healthy tissue lining the joints, it causes pain, inflammation of the joints, and other symptoms, and may eventually lead to destruction of the joint. The inflammation can spread from the tissue to the cartilage, and eventually to the bones as well [1].

RA is progressive, meaning the symptoms worsen as the disease develops. There are four stages of RA: early stage RA, moderate stage RA, severe stage RA, and end-stage RA. However, not all cases of RA progress through all four stages of the disease. Early stages of RA impact the smaller joints, such as the fingers and toes [2]. As progression continues, the inflammation will spread to larger joints such as the knees, elbows, wrists, ankles, and hips [2].

Early stage RA occurs when patients experience inflammation and swelling of the joints. Common symptoms include tender, warm, and swollen joints, joint stiffness, fatigue, fever, and loss of appetite. The signs and symptoms in early stages of the disease are comparable to those of other various disorders. This, along with the fact that symptoms may come and go, make RA difficult to diagnose early on. During moderate stage RA, patients experience inflammation in the joint cartilage, which covers and protects the ends of bones at the site of a joint. As cartilage becomes damaged, pain and other symptoms will advance and mobility may be reduced.

Severe stage RA occurs when the inflammation has spread from the joint and cartilage to the bone as well. Symptoms will progress, causing more pain, inflammation, and swelling. Muscle weakness or wasting can present itself with due to a decline in muscle use. Those who have reached this stage may also experience erosion of the bones due to a lack of protection from joints and cartilage [2].

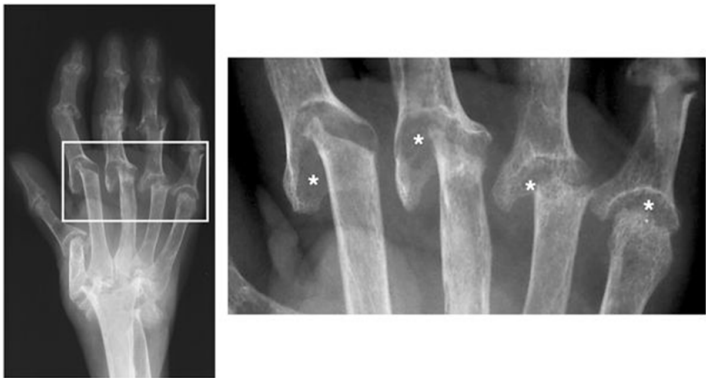

Figure 1a: Shows a hand radiograph of an RA patient with bone erosion in the fingers. The box drawn around the finger joints shows the area of the hand in which bone erosion has occurred [3].

Figure 1b: Shows a magnified version of the radiograph. The asterisks represent specific locations of visible bone erosion [3].

End-stage RA is the last stage of RA. In end-stage RA, the joints are destroyed and no longer function. The purpose of a joint is to allow movement by bearing weight between bones in the body. Therefore, once the joint is damaged and can no longer provide support, the surrounding bones become damaged as well. Some cases may lead to ankylosis, or bone fusion, causing stiffness or loss of movement in the area [2]. Not all individuals diagnosed with RA will advance to the more severe stages of the disease during their lifetime. Some may experience periods of remission, during which no symptoms appear [2].

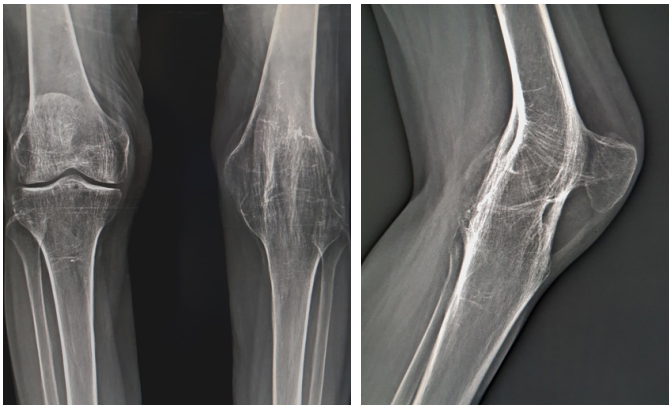

Figure 2a: Portrays a leg radiograph of a patient with ankylosis of the left knee from a frontal view. Ankylosis in this image involves the femorotibial and the femoropatellar joints [4].

Figure 2b: Portrays a lateral view of the ankylosis of the left knee [4].

RA impacts approximately 1.5 million people across the United States. It is most commonly diagnosed in individuals between the ages of 30 and 60, especially in women. There are three times as many diagnosed cases of RA in women than in men [1]. However, there are other genetic and environmental risk factors involved as well. Heredity is a significant risk factor, as approximately 50% of individuals diagnosed with RA have family history of the disease. Numerous environmental factors such as tobacco smoke exposure, UV exposure, and obesity can also contribute to development of RA [6]. Of the environmental factors, there seems to be the strongest correlation between tobacco smoke exposure and the development of RA [7].

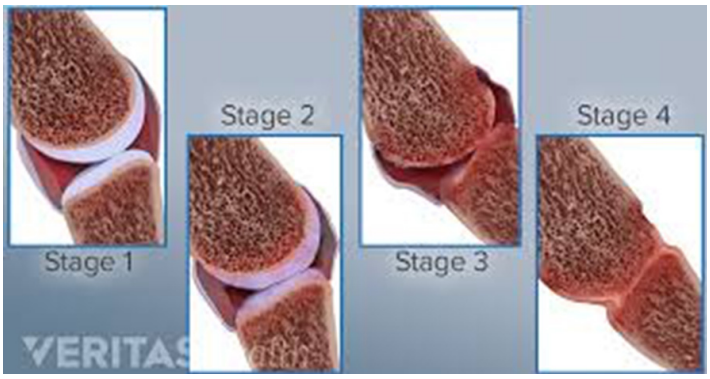

Figure 3: Demonstrates the progression of RA as the joint deteriorates, leaving no protection for the bones. Stage 1, or early stage RA, shows inflammation and swelling at the site of the joint. Stage 2, or moderate stage RA, shows the inflammation spreading to the cartilage, covering the ends of the bones. Stage 3, or severe stage RA, shows the inflammation spreading to the bones. Bone erosion at the end of the bones is also visible. Stage 4, or end stage RA, shows the complete destruction of the joint, meaning there is no longer protection of the bones at the joint site. Ankylosis is visible at the end of the bones in the stage 4 image [5].

RA impacts approximately 1.5 million people across the United States. It is most commonly diagnosed in individuals between the ages of 30 and 60, especially in women. There are three times as many diagnosed cases of RA in women than in men [1]. However, there are other genetic and environmental risk factors involved as well. Heredity is a significant risk factor, as approximately 50% of individuals diagnosed with RA have family history of the disease. Numerous environmental factors such as tobacco smoke exposure, UV exposure, and obesity can also contribute to development of RA [6]. Of the environmental factors, there seems to be the strongest correlation between tobacco smoke exposure and the development of RA [7].

There is no known cure for RA; however, there are various treatment methods that can alleviate symptoms caused by the disease and allow remission of symptoms. The principal goals of these treatments are to reduce pain, inflammation, and joint damage to allow more mobility and improve quality of life. Starting treatment earlier yields more favorable results for RA patients. It allows for higher chances of remission and less joint damage. Medications, therapy, and surgery are all common ways that RA is currently treated, and treatment can vary among individuals based on the severity of symptoms. The three most commonly recommended drug classes for RA treatment include: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids,

and disease modifying anti-rheumatic drugs (DMARDs) [8]. The treatment plan arranged for a patient depends on the severity of the disease and the goal of treatment.

NSAIDs are commonly used among RA patients as an anti-inflammatory and analgesic. There are various over-the-counter NSAIDs including ibuprofen and naproxen, along with an extensive list of prescription NSAIDs. NSAIDs are typically used as the first-resort treatment for symptomatic relief in early stages of RA. Most NSAIDs are known to act successfully as a pain reliever at significantly lower doses than what is necessary to act successfully as an anti-inflammatory. A benefit of using NSAIDs is that there are so many different forms of the drug type. If one form in particular is not alleviating symptoms, another form can be prescribed. There are also side effects that can occur due to NSAID use, including: gastrointestinal disturbance and renal dysfunction [8].

Unlike NSAIDs, Corticosteroids are a class of steroidal drugs. Corticosteroids function as synthetic hormones to decrease inflammation and regulate immune system activity throughout the body. Examples of corticosteroids include prednisone, methylprednisone, and Medrol. Of these, prednisone is the most commonly prescribed by doctors as a treatment for RA. Low doses of prednisone are characteristically successful in maintaining inflammation and immunoregulatory activity. The daily standard dose of prednisone is 5 to 10 mg. 15 to 20 mg daily is considered a higher dose of prednisone, and is only required in RA patients with life-threatening conditions. However, these higher doses skyrocket a patient's chances of steroid toxicity and development of unwanted side effects. Intra-articular corticosteroids are another variation of corticosteroids that have the ability to control inflammation in the localized area of a joint while allowing patients to continue their treatment plans [8].

DMARDs are a class of disease-modifying drugs that target the immune system to slow the progression of RA. A patient diagnosed with RA will likely be advised to use some form of DMARD, as it can alter the course of the disease unlike NSAIDs and other medications. DMARDs function by blocking inflammation in the joints to allow joint protection. Without the use of DMARDs, RA would continue on its normal course of spreading inflammation throughout the joint site. Numerous DMARDs can be used by RA patients, but Methotrexate is the most commonly prescribed. Many benefits accompany the use of Methotrexate in comparison to other DMARDs such as: rapid effectivity, simple administration, and it is relatively inexpensive. Common side effects include nausea and vomiting, hair loss, painful urination, fever, and sore throat. Other, more serious side effects may also occur depending on the specific type of DMARD being administered [8].

The primary goal of physical and occupational therapy as an RA treatment to increase functionality and mobility of the joints [8]. Therapy is often recommended in addition to medications for a well-rounded treatment plan. Physical therapy for RA patients involves advancing physical strength of the individual by exercising the joints, muscles, and bones. This helps to avoid muscle wasting and maintains activity levels in the joint for mobility. Keeping patients active and with weight maintenance is also important to reduce stress in the joints [9]. Occupational therapy focuses on activities of daily living and ability to complete simple tasks. As mobility declines in RA patients, it's crucial that they are aware of various ways to perform tasks differently. Individuals may feel hopeless or unenthusiastic about their situation, which is why the support of therapy is essential [9].

Surgical approaches are not commonly used in RA patients as a treatment, but some individuals may decide to have surgery to reduce pain caused by the deteriorating joint and to improve mobility and functionality [8]. The two main RA treatment surgeries are joint replacements and arthrodesis. A joint replacement includes the removal of an inflamed or damaged joint, and its replacement with a prosthesis of that joint. Joint replacements are typically completed on larger joints such as the knees, hips, or shoulders, but may also be completed in smaller joints such as the fingers or toes. There are many risks that accompany a joint replacement, along with a lengthy recovery process, which is why the surgery is often a last resort for patients. Arthrodesis is the fusion of two bones after the arthritic joint is removed. This treatment severely limits mobility in the area, as the joint that provides flexibility is no longer present. However, patients experiencing severe symptoms may opt to receive this surgery in order to reduce the pain experienced [10].

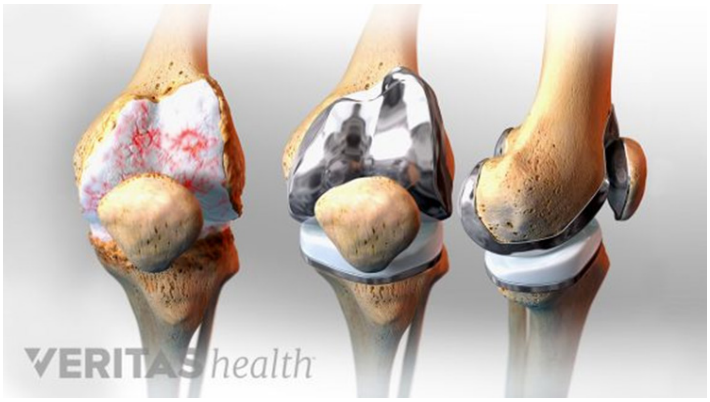

Figure 4: Shows a total joint replacement of an RA impacted knee. The knee on the left side of the image shows the inflamed knee of an RA patient before a joint replacement. The knee in the middle of the image shows a frontal view of an artificial knee after a total joint replacement surgery. The knee on the right side of the image shows a posterior view of an artificial knee after total joint replacement surgery [10].

RA has no current cure; however, an early diagnosis and effective drug regimen can significantly reduce symptoms and slow the progression of the disease while improving the quality of life for patients. Because there is no cure, patients will likely be following a treatment plan throughout their entire lifetime. In order for treatments to work correctly, it is also important for patients to be educated about their treatments

Over the past decade, therapies and treatments for RA have

drastically improved, as new medications and methods have been discovered. However, no currently used treatments have the ability to completely stop progression of RA or cure RA patients. Therefore, researchers are now shifting to study therapies regarding tissue repair, such as stem cell therapy. Stem cells are a relatively new form of treatment, and its effectiveness has not yet been proven [11].

Stem cells are cells that exist within the body and are capable of becoming various types of cells. There are numerous types of stem cells including: adult stem cells (ASCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) [12].

ASCs, also called somatic stem cells, are undifferentiated cells found in tissues and organs that exist amongst other differentiated cells. An ASC renews itself or generates new cells that can specialize to maintain and repair the tissue in which it exists. ASCs can be found in the majority of tissues throughout the body, including the brain, bone marrow, peripheral blood, blood vessels, muscle, skin, heart, gut, liver, placenta, umbilical cord, ovarian epithelium, testes, and others. However, the amount of stem cells found in each area is typically limited, along with the amount of division that occurs after extraction. There are various types of ASCs, which are classified based on where they originate or the type of cells they will become after differentiation. The types of ASCs include hematopoietic stem cells, mesenchymal stem cells (MSC), neural stem cells, epithelial stem cells, and skin stem cells. hematopoietic stem cells differentiate into any blood cell type through a process called hematopoiesis. MSCs are found in various adult tissues including bone marrow, umbilical cord blood, dermis, and other locations. MSCs can give rise to bone cells, cartilage cells, fat cells, and stromal cells. Neural stem cells are located in the brain and most commonly develop into neurons. However, they may also develop into astrocytes or oligodendrocytes, which are two forms of non-neural cells. Epithelial stem cells derive from the lining of the digestive tract, specifically the intestinal crypt. These types of stem cells can develop into absorptive cells, goblet cells, Paneth cells, or enteroendocrine cells. Skin stem cells originate in the adult epidermis and hair follicles. The stem cells located in the epidermis are known as epidermal stem cells, and specialize into keratinocytes. Once keratinocytes develop, they create a protective layer at the surface of the skin which aids in the prevention of things such as dehydration and infection. Although these stem cells may originate from a particular area of the body, research shows that they can experience transdifferentiation, and become cell types other than what is expected based on where they are located [13].

ESCs are stem cells derived from the inner cell mass of embryos that have been fertilized in vitro. Extraction of ESCs occurs 3-6 days after an in vitro fertilization, but before implantation in the uterus. During this time period, the embryo is experiencing the blastocyst stage. These stem cell types are pluripotent, meaning they can become nearly any form of specialized tissue in the body [12]. There is great potential for ESCs to regrow cells for transplantations. However, use of ESCs poses an ethical dilemma as stem cell extraction causes destruction to the early embryo. While ESCs have the potential to save lives, they also take away the chance of that particular embryo developing into a human being. Due to this, there is significant controversy surrounding the use of ESCs [14].

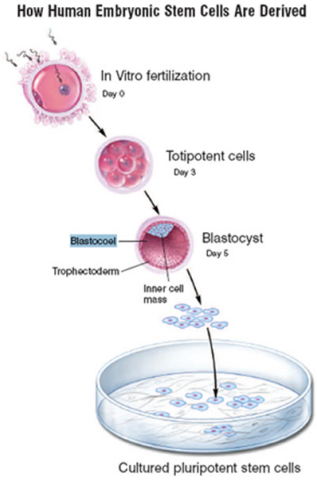

Figure 5: Demonstrates the timeline and process of ESC extraction after in vitro fertilization has occurred. In Vitro fertilization occurs at day 0. Following fertilization, the cells are totipotent by day 3. The cells continue to develop, and are in the blastocyst stage at day 6. Cells from the inner cell mass of the blastocyst are extracted, and the cultured pluripotent stem cells are developed outside of the body [13].

The final stem cell category is iPSCs, which serve as an intermediate form of stem cells between ASCs and ESCs. iPSCs are adult stem cells that are transformed in the laboratory to display ESC-like traits. ASCs are manipulated to express specific genes and factors that are present in ESCs. iPSCs are also considered pluripotent, similarly to ESCs [12]. The introduction of iPSCs to stem cell research is significant because they allow the benefit of pluripotency, while not harming embryos through the process of extraction. However, this discovery is relatively recent in the stem cell field, and requires further testing and research before implementation as a clinical therapy [13].

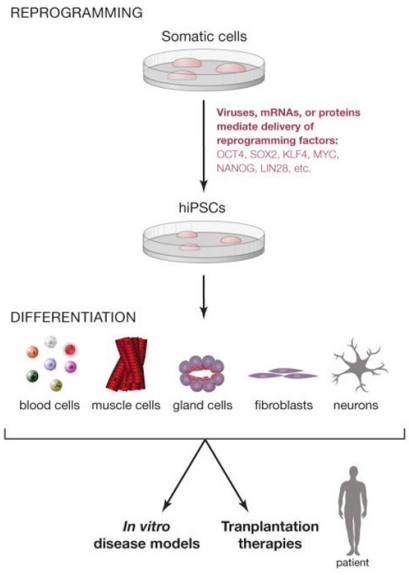

Figure 6: Displays the transformation process from adult somatic cells to iPSCs through laboratory manipulation. After somatic ASCs are extracted, they are reprogrammed through the addition of various reprogramming factors to the cells via viruses, mRNAs, or proteins. Once reprogrammed into iPSCs, the stem cells are pluripotent and have the ability to differentiate into multiple cell types including: blood cells, muscle cells, gland cells, fibroblasts, and neurons. After differentiation occurs, the cells can potentially be used for disease treatment or transplantation in patients [15].

Preclinical Studies

As a novel treatment methods are discovered, it is necessary for studies to be completed on the safety and effectiveness of the drug or therapy before the treatment is applied to humans in clinical trials. Pre-clinical studies are commonly carried out on animals, typically rats or mice, in a laboratory setting. Through these studies, researchers are able to gauge the relative safety of the treatment to living animals that may display similar characteristics of diseases to humans. Pre-clinical studies provide scientists with a baseline of the effectiveness of the specific treatment, along with potential methods of administration and appropriate dosage. This is a significant step in the development of a new treatment, as treatments will not be applied to humans without proper research to support the safety and potential effectiveness to treat specific diseases.

Researchers can induce RA in animals such as rats or mice through various techniques. The most common modes of induction are collagen-induced arthritis (CIA) and adjuvant-induced arthritis (AIA) [16]. CIA is the most widely utilized arthritis model in preclinical studies, during which subjects are injected with doses of complete Freund's adjuvant (CFA) and type II collagen (CII). The amount of injections required depends on the type of subject being used. For example, mice normally undergo two injections before symptoms are experienced, while only one injection is necessary for rats. After injection, subjects will begin to develop RA-like symptoms such as inflammation in the joint region and degradation of cartilage and bone. However, a significant difference between CIA and RA is that no rheumatoid factor exists in CIA [17].

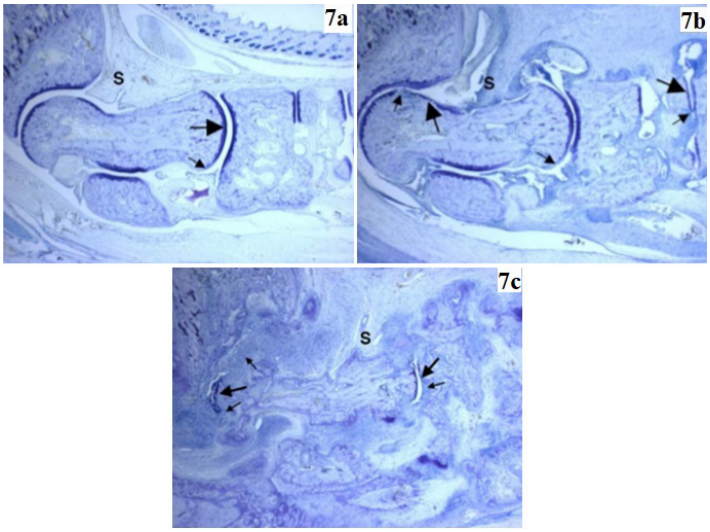

Figure 7a: Shows a photomicrograph of a rat ankle at a magnification of 16x. This ankle displays a normal synovium (denoted by S), cartilage (denoted by large arrow), and bone (denoted by small arrow). The joint has not yet developed arthritis, as no pannus or bone destruction have occurred [18].

Figure 7b: Shows a photomicrograph of a rat ankle at a magnification of 16x. This ankle displays a joint that has developed arthritis 17 days after the CIA-causing injection. A slightly inflamed synovium (denoted by S), moderate inflammation and damage to the cartilage (denoted by large arrows), and moderate pannus and bone destruction (denoted by small arrows) have developed in the ankle [18].

Figure 7c: Shows a photomicrograph of a rat ankle at a magnification of 16x. This ankle displays a joint that has developed arthritis 34 days after the CIA-causing injection. An inflamed synovium (denoted by S), severe inflammation and damage to the cartilage (denoted by large arrows), and severe pannus and bone destruction (denoted by small arrows) have developed in the ankle [18].

AIA is another commonly practiced method of arthritis introduction. AIA produces symptoms similar to those of RA including: inflammation and swelling in the joints, synovial tissue proliferation, and damage to cartilage and bone surrounding joints. When comparing the characteristics of CIA and AIA, the symptoms of AIA tend to be less severe and have shorter lasting effects [19]. Both of the previously mentioned arthritis-inducing models, along with others, are applied to rodents in preclinical research studies. The similarity between the characteristics of RA in animals and humans allows researchers to create a guideline for how stem cell therapy can apply to humans [16].

MSCs are a form of multipotent stem cells that can differentiate into several forms mesenchymal tissue. A main source of MSCs is adult bone marrow tissue. Bone marrow mesenchymal stem cells (BM-MSCs) are a type of stem cell that has been found to successfully suppress CIA and autoimmune diseases in animal subjects. Along with bone marrow, adipose tissue is another main source of human MSCs, whose immunomodulatory characteristics have been found effective in preclinical arthritis studies [20].

A study reviews human adipose-derived MSCs (hASCs) and their ability to treat and suppress symptoms resulting from CIA. Through the study, researchers discovered that hASCs were able to reduce many of these symptoms including: edema, erythema, swelling, joint inflammation and destruction, cartilage and bone erosion, and others. The subjects that received hASC injections also experienced reduced levels of proinflammatory cytokines and amplified levels of anti-inflammatory cytokines [20]. Observing the changes in expression of inflammatory cytokines with the use of hASCs is a very significant for the data collection of the study, as it shows one of the methods through which symptoms such as inflammation are reduced. Overall, the data collected through this experiment demonstrates that hASC usage is a potentially beneficial treatment method for RA [20].

Based on completed studies, researchers have determined that stem cell therapy using MSCs as a treatment method for RA generates beneficial results in animal models [16]. These findings should be taken into consideration to create guidelines for stem cell therapy

to treat RA in humans. Studying various treatment methods that yield beneficial results in preclinical studies will allow scientists and researchers to maximize benefits throughout clinical studies. While preclinical studies are beneficial in collecting data on stem cell therapy as a treatment for RA, it must not be assumed that the disease and its treatment will yield identical responses in animal models and the human body.

Clinical Trials

Mesenchymal stem cells and their regenerative ability in autoimmune disorders are widely observed through clinical trials. There are various types of MSCs, each of which originate from different locations. Researchers have discovered that, compared to other stem cell lineages, MSCs are more easily isolated and readily available for use. MSCs also maintain their ability to differentiate as they grow both in vivo and in vitro, which is an important quality when using stem cells as a treatment method for diseases. MSCs also function as anti-inflammatory and immunosuppressive agents, which are essential MSC characteristics, as RA is an autoimmune disease with inflammation being one of the primary symptoms [21]. Therefore, MSCs are a promising treatment method for RA.

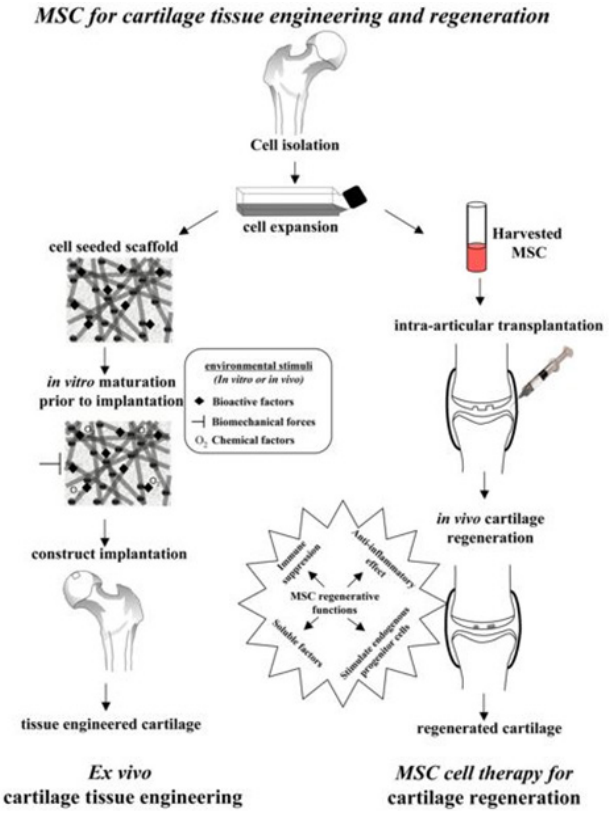

Figure 8: Demonstrates the use of MSCs for cartilage tissue engineering and regeneration. The two potential paths for cartilage tissue engineering and regeneration using MSCs are ex vivo and in vivo. The processes of both ex vivo and in vivo first require cell isolation and cell expansion. Ex vivo cartilage tissue engineering then involves scaffold and in vitro maturation at with specific environmental stimuli before construct implantation. In vivo cartilage regeneration involves transplanting the harvested MSCs into the joint to allow cartilage growth. The MSC regenerative functions such as immune suppression and anti-inflammatory effect are essential to the in vivo cartilage regeneration [21].

BM-MSCs are a form of mesenchymal stem cells derived from the bone marrow. BM-MSCs play an essential role in hematopoiesis and hematopoietic stem cells (HSCs) within the bone marrow [22]. However, BM-MSCs can also be isolated from the bone marrow allowing them to differentiate into multiple other cell lineages such as bone, fat, and cartilage [23]. BM-MSCs, along with other stem cell lineages, have been studied as a treatment for RA and other various autoimmune diseases because of their immunomodulatory abilities [22].

However, there are also consequences in BM-MSC use. They have a higher degree of viral infection than other forms stem cells, they decline in their ability to differentiate and proliferate over time, and the extraction methods required are invasive [24]. In order for BM-MSCs to be isolated, bone marrow must first be extracted from the human body. During the bone marrow extraction procedure, an incision is made and a needle is used to pass through the bone and into the bone marrow where a sample of the liquid bone marrow is collected. Stem cells can then be isolated from the sample and cultured [25].

Umbilical cord tissue-derived MSCs (UC-MSCs) represent an alternate category of MSCs that have been studied as a treatment method for RA and other joint pathologies. When compared to BM-MSCs, researchers have discovered that UC-MSCs provide more benefits in certain aspects. While there is a decline in proliferative and differentiation capabilities throughout the aging process in BM-MSCs, this decline does not occur in UC-MSCs [24]. According to a report by Wu et al, which studied UC-MSC use in humans, UC-MSCs have much greater proliferation capabilities than MSCs extracted from the bone marrow [26]. The isolation of UC-MSCs is also less invasive, and considered by some to be more ethical than that of BM-MSCs. Growth of the human umbilical cord is initiated at 4-8 weeks of gestation. The umbilical cord continues to develop in the amniotic cavity throughout fetal development, and expands to a length of approximately 50-60 cm. Throughout the course of delivery, the umbilical cord can be isolated and UC-MSCs can be extracted [27]. UC-MSC properties also allow cryopreservation, which allows the stem cells to be frozen at their peak biological potential. This method creates availability for UC-MSC use both at the time of extraction and in the future [28].

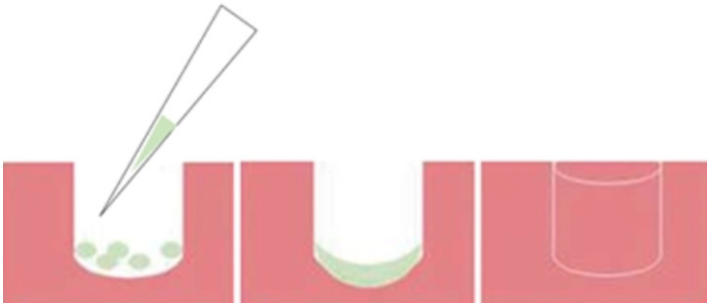

Figure 9a: Graphic displaying the in vitro use of UC-MSCs through the regeneration of cartilage tissue [24].

One study focused particularly on UC-MSCs and their ability of to serve as a treatment for RA by examining the long-term outcomes

of treatment through a clinical trial. The UC-MSC lineage is not the most common treatment method in clinical studies; however, researchers found it to be safe and beneficial. Prior to treatment, patients received a dose of dexamethasone in 100 mL of saline to avoid potential allergic reactions. 40 mL of a UC-MSC product was then administered to patients intravenously. The product contained 2 x 10^7 cells/mL. The treatment plan also included the continuation of DMARDs as medications as well [29].

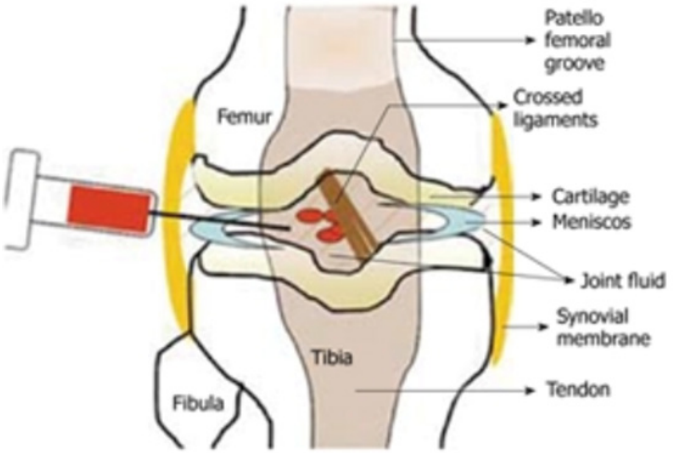

Figure 9b: Graphic displaying the procedure of an in vivo use of UC-MSCs through an intra-articular injection at the site of a knee joint [24].

In order to determine the long-term impact of UC-MSC plus DMARD treatment, researchers collected various data before treatment, 1 year after treatment, and 3 years after treatment. Normal blood routine examinations and proper functionality of the liver and kidney demonstrated the safety of the treatment. Patients receiving the treatment also experienced a reduction in inflammatory markers and RA serological markers. The 28-joint disease activating score (DAS28) is another assessment used to determine the effectiveness of the treatment [29]. The DAS28 measures RA activity by assessing 28 joints for traits such as swelling and tenderness [30]. A decline in DAS28 was observed both 1 year after treatment and 3 years after treatment.

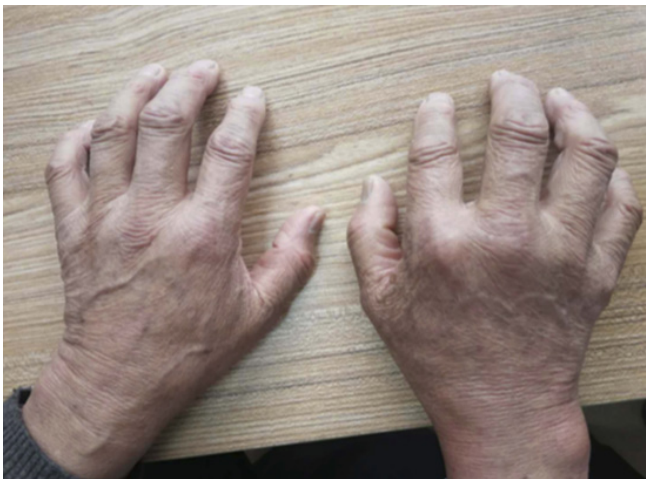

Figure 10a: Shows the hands of a 68-year-old male diagnosed with RA. He cannot hold his fingers straight out due to symptoms of RA [29].

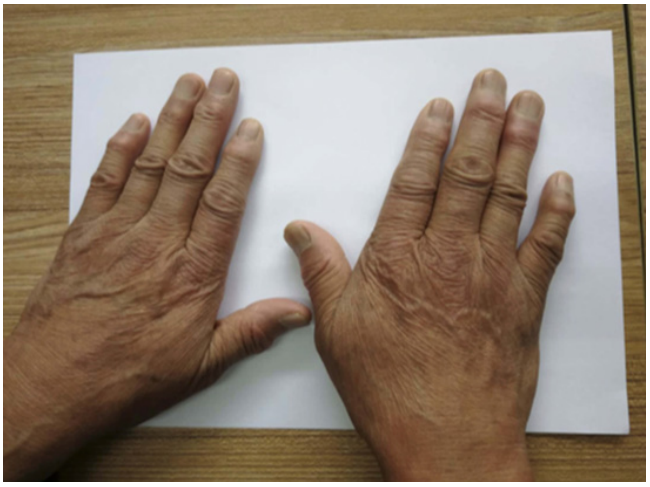

Figure 10b: Shows the hands of the same 68-year-old male 3 years after treatment with UC-MSCs. He can now stretch his fingers out and lay his hands on a flat surface due to a decrease in RA symptoms [29].

Another clinical trial studied the impact of human umbilical cord blood-derived MSCs (hUCB-MSCs) in RA patients through an intravenous infusion. The hUCB-MSCs differ from the previously discussed UC-MSCs in both their location of origin and the preparation of stem cells. hUCB-MSCs are isolated from the umbilical vein directly following delivery, and are combined with a Hetasep solution to separate the red blood cells from nucleated cells through aggregation. The hUCB-MSC differentiation and proliferation characteristics are tested before stem cell administration to RA patients. Each patient participating in the clinical received an intravenous infusion of hUCB-MSCs at a dose of 2.5 x 10^7 cells, 5 x 10^7 cells, or 1 x 10^8 cells over a 30 minute period of time. The safety of the clinical study and stem cell administration were monitored over for up to 4 weeks after the infusions. The effectiveness of disease treatment was also observed through the swollen and tender joint counts, DAS28 assessment, a pain visual analog scale (VAS), and a health assessment questionnaire (HAQ) [31].

The clinical trial results indicate that patients can tolerate a dose of up to 1x10^8 cells of hUCB-MSCs through an intravenous infusion, as administration at this dose caused no major toxicity or other safety issues up to 4 weeks after administration of the infusion. Figure 10 shows the results of the various measures that were observed throughout the study to determine the effectiveness of the treatment. The subjects of the study experienced an average decrease in each of these measures from the baseline assessment to the assessment 4 weeks after infusions. Overall, the patients experienced a decrease in swollen and tender joints and pain, demonstrating that the use of hUCB-MSCs is an effective treatment method for RA [31].

Through clinical studies, scientists and researchers have determined that the use of UC-MSCs and hUCB-MSCs are generally safe and effective in humans. UC-MSCs and hUCB-MSCs also reap certain benefits that other cell lineages lack, such as steady proliferative and differentiation abilities over time, ease of stem cell extraction,

and the opportunity to use cryopreservation [24,31]. UC-MSC differentiation success has also been observed both in vivo and in vitro, allowing a wider range of use [24]. Researchers determined that the use of UC-MSCs along with DMARDs produces beneficial long-term responses in RA patients. It is also important to note the safe doses and methods used during this study to yield successful outcomes [29]. Researchers also determined that the use of hUCB-MSCs via intravenous infusions are another safe and effective way to implement stem cell therapy for RA patients [31]. These are each methods that should be further researched to determine the most beneficial treatment method.

	Baseline	Week 4	*p* value
Female, *n* (%)	7 (77.8)		
Age, mean ± SD, yr	57.4 ± 10.0		
Disease duration, mean ± SD, yr	9.5 ± 8.7		
BMI, mean ± SD, kg/m^2	25.2 ± 0.9		
Rheumatoid factor, positive, *n* (%)	6 (66.7)		
Anti-CCP, positive, *n* (%)	4 (44.4)		
Previous medication			
MTX users, *n* (%)	9 (100.0)		
Dose, mean ± SD, mg/wk	14.2 ± 0.9		
Corticosteroid users, *n* (%)	7 (77.8)		
Dose, mean ± SD, mg/day[a]	3.1 ± 0.8		
Swollen joint count, mean ± SD, *n*	2.4 ± 2.7	0.7 ± 0.8	.1038
Tender joint count, mean ± SD, *n*	11.8 ± 16.7	2.0 ± 3.1	.0888
DAS28-ESR, mean ± SD	4.53 ± 1.35	2.93 ± 1.22	.0158
Pain VAS (0–100), mean ± SD, mm	64.8 ± 20.2	46.9 ± 29.1	.0885
HAQ (0–5), mean ± SD	0.69 ± 0.63	0.54 ± 0.58	.3706

Figure 11: Compares the baseline data collected before infusions to the results of the clinical trial 4 weeks after infusions of the 9 participants in the clinical study. The subjects were 77.8% female, and had an average age of 57.4 years old. The subjects were diagnosed with RA an average of 9.5 years prior to the study. The average BMI of the patients was 25.2. 66.7% of the participants were Rheumatoid factor positive, and 44.4% of the participants were Anti-CCP positive. All of the participants previously used MTX as a treatment method at an average dose of 14.2 mg/week. 77.8% of the participants used corticosteroids at an average dose of 3.1 mg/day. The swollen joint count average decreased from an average of 2.4 at the baseline assessment to an average of 0.7 at the assessment 4 weeks after infusions. The tender joint count decreased from an average of 11.8 at the baseline assessment to an average of 2.0 at the assessment 4 weeks after infusions. The DAS28 decreased from an average of 4.53 at the baseline assessment to an average of 2.93 at the assessment 4 weeks after infusions. The pain VAS decreased from an average of 64.8 at the baseline assessment to an average of 46.9 at the assessment 4 weeks after infusions. The HAQ decreased from an average of 0.69 at the baseline assessment to an average of 0.54 at the assessment 4 weeks after infusions [31].

Stem Cell Therapy for RA vs. Other Treatments

Currently, there is no cure for RA. Upon diagnosis, an individual may be prescribed drugs such as NSAIDs, DMARDs, or corticosterois. However, these drugs only function to relieve patients of symptoms such as pain and inflammation [32]. Physical and occupational therapy are also recommended to maintain or improve mobility at affected joints, as well as keeping patients motivated to improve their situation [8]. These treatment methods focus on improving the quality of life, while also aiming for reduced RA activity or remission [33]. Surgery is another treatment option that is typically considered after the disease has progressed to a moderate or severe state. Two surgical approaches used for RA patients include joint replacements and arthrodesis. While these surgieries may be beneficial in reducing the pain and inflammation at the joint, there are various complications that can occur as well [10]. Joint replacements include an extensive recovery period, and may lead to infections, malfunctioning prosthesis, or nerve injury. There are also more risks involved for obese or elderly patients [34]. Arthrodesis also reduces pain in patients, but severely restricts mobility in the process [10]. While quality of life is an important aspect for patients experiencing RA, scientists and researchers have continued to explore other options that may eventually lead to a cure. One of these options is stem cell therapy.

Stem cell therapy is a treatment option that has the potential to improve the quality of life for RA paitents, while solivng many other issues as well. Two main qualities of stem cells two are proliferation and differentiation capabilities, which allow stem cells to regenerate damaged bone or cartilage tissue in RA-affected joints [11]. MSCs also have anti-inflammatory and immunosuppressive characteristics, which allow the stem cells to restrict further progression of the disease and decrease inflammation at the site of the joint. When these aspects of the disease are targeted, other syptoms including pain, swelling, and tenderness begin to improve as well.

Another factor that contributes to an individuals choice of treatment methods is cost. Drug treatments such as NSAIDs, DMARDs, and corticosteroids are less expensive and often covered (or partially covered) by health insurance or Medicare [35]. Joint replacements are also partially covered by insurance, but because surgery is a much larger expense, patients are typically required to pay out of pocket for 10-20% of the total treatment cost [36]. For example, the knee is a very commonly affected joint in patients with RA, and individuals with knee damage due to arthritis may choose to have a total knee replacement (TKR) surgery. On average, a TKR costs over $50,000, meaning that patients could be required to pay anywhere between $5,000 to $10,000 out of pocket [37]. Stem cell therapy is an alternative treatment method for RA, which often removes the need for surgical repair of a joint. Stem cell treatment for one knee costs approximately $5,000 per knee. Treatment costs for both surgical repairs and stem cell repairs vary based on the affected joint. Stem cell therapy is not typically covered by insurance, so the full cost is paid out of pocket. However, as researchers continue to study the safety and effectiveness of stem cell therapy, insurance companies may begin to cover the cost [38].

Therefore, stem cell therapy may soon become a more affordable treatment method while promoting a greater degree of recovery than other treatment method options.

Conclusion

Rheumatoid arthritis is an autoimmune disease that causes pain, inflammation, and swelling of the joints. It is a progressive disorder that can eventually lead to cartilage and bone damage [1]. There are various treatment methods that are currently used to alleviate the pain and other symptoms of RA. These include NSAIDs, DMARDs, corticosteroids, and other drugs, along with physical therapy, occupational therapy, and surgical repairs [8]. Stem cells are a relatively new discovery in the world of medicine, and are being studied in their use as a treatment method for patients with RA. MSCs display various beneficial characteristics such as ease of extraction, quick growth, differentiation capabilities, and immunosuppressive and anti-inflammatory capabilities [21].

MSCs also have the ability to be expanded and preserved after isolation, which allows immediate or future use of the stem cells in patients [24]. Due to these many benefits observed through the use of MSCs in pre-clinical studies and clinical studies, MSCs are considered the most promising stem cell type for the treatment of RA and similar diseases [21]. Researchers have conducted studies supporting the use of multiple types of stem cells, including BM-MSCs, hASCs, UC-MSCs, and UCB-MSCs. While there are studies that support the use of each type of MSC as a beneficial treatment method, there is still more research to be completed to determine which type of MSC is the most effective in treating RA.

References

1. https://www.arthritis.org/better-living-toolkit/rheumatoid-arthritis
2. https://www.healthline.com/health/rheumatoid-arthritis/stages-and-progression
3. Schett, G. Erosive arthritis. Arthritis Res Ther. 2007; 9: S2.
4. https://radiopaedia.org/cases/ankylosis-of-the-knee-joint?lang=us
5. https://www.arthritis-health.com/types/rheumatoid/rheumatoid-arthritis-ra-diagnosis
6. https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648
7. Deane KD, Demoruelle MK, Kelmenson LB, et al. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017; 31: 3-18.
8. https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/
9. https://www.rheumatoidarthritis.org/treatment/
10. https://www.healthline.com/health/types-rheumatoid-arthritis
11. https://www.medicalnewstoday.com/articles/325583#stem-cell-for-ra
12. https://www.unmc.edu/stemcells/educational-resources/types.html
13. https://stemcells.nih.gov/info/basics/1.htm
14. https://www.eurostemcell.org/embryonic-stem-cell-research-ethical-dilemma
15. Hockemeyer D, Jaenisch R. Induced Pluripotent Stem Cells Meet Genome Editing. Cell Stem Cell. 2016; 18: 573-586.
16. Liu L, Chi W Wong, MengluHan, et al. Meta-analysis of preclinical studies of mesenchymal stromal cells to treat rheumatoid arthritis. EBioMedicine. 2019; 47: 563-577.
17. Brand D D, Latham K A, Rosloniec E F. Collagen-induced arthritis. Nature News. 2007; 2: 1269-1275.
18. https://bolderbiopath.com/study/collagen-induced-arthritis-cia-rat/
19. https://www.creative-biolabs.com/drug-discovery/therapeutics/adjuvant-induced-arthritis-aia-rodent-model.htm.
20. Zhang L, Wang XY, Zhou PJ, et al. Use of immune modulation by human adipose-derived mesenchymal stem cells to treat experimental arthritis in mice. Am J Transl Res. 2017; 9: 2595–2607.
21. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Research & Therapy. 2008; 10: 223.
22. Pontikoglou C, Deschaseaux F, Sensebé L, et al. Bone Marrow Mesenchymal Stem Cells: Biological Properties and Their Role in Hematopoiesis and Hematopoietic Stem Cell Transplantation. Stem Cell Reviews and Reports. 2011; 7: 569-589.
23. Berthelot J-M, Goff BL, Maugars Y. Bone marrow mesenchymal stem cells in rheumatoid arthritis, spondyloarthritis, and ankylosing spondylitis: problems rather than solutions? Arthritis Research & Therapy. 2019; 21: 239.
24. Arufe MC. Umbilical cord as a mesenchymal stem cell source for treating joint pathologies. World Journal of Orthopedics. 2011; 2: 43.
25. Baghaei K, Hashemi SM, Tokhanbigli S, et al. Isolation, differentiation, and characterization of mesenchymal stem cells from human bone marrow. Gastroenterol Hepatol Bed Bench. 2017; 10: 208-213.
26. Wu K-H, Chan C-K, Tsai C, et al. Effective Treatment of Severe Steroid-Resistant Acute Graft-Versus-Host Disease With Umbilical Cord-Derived Mesenchymal Stem Cells. Transplantation. 2011; 91: 1412-1416.
27. Iwatani S, Yoshida M, Yamana K, et al. Isolation and Characterization of Human Umbilical Cord-derived Mesenchymal Stem Cells from Preterm and Term Infants. Journal of Visualized Experiments. 2019; 143.
28. Harris D. Umbilical Cord Tissue Mesenchymal Stem Cells: Characterization and Clinical Applications. Current Stem Cell Research & Therapy. 2013; 8: 394-399.
29. Wang L, Huang S, Li S, et al. Efficacy and Safety of Umbilical Cord Mesenchymal Stem Cell Therapy for Rheumatoid Arthritis Patients: A Prospective Phase I/II Study. Drug Design, Development and Therapy. 2019; 13: 4331-4340.
30. https://www.nras.org.uk/the-das28-score.
31. Park EH, Lim H-S, Lee S, et al. Intravenous Infusion of Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Rheumatoid Arthritis: A Phase Ia Clinical Trial. Stem Cells Translational Medicine. 2018; 7: 636-642.
32. Bortoluzzi A, Furini F, Generali E, et al. One year in review 2018: novelties in the treatment of rheumatoid arthritis.

Clinical and Experimental Rheumatology. 2018; 36: 347-361.
33. Bortoluzzi AA, Furini FA, Generali EA, et al. One year in review 2017: novelties in the treatment of rheumatoid arthritis. Clinical and Experimental Rheumatology. 2017; 35: 721-734.
34. Bronson WH, Fewer M, Godlewski K, et al. The Ethics of Patient Risk Modification Prior to Elective Joint Replacement Surgery. The Journal of Bone and Joint Surgery-American Volume. 2014; 96: e113.
35. Yazdany J, Dudley RA, Chen R, et al. Coverage for High-Cost Specialty Drugs for Rheumatoid Arthritis in Medicare Part D. Arthritis & Rheumatology. 2015; 67: 1474-1480.
36. https://www.stemcures.com/stem-cell-therapy-cost-for-spine-and-joints.
37. Evans M. What Does Knee Surgery Cost? Few Know, and That's a Problem. Wall Street Journal. 2018; 21.
38. https://www.healthline.com/health/stem-cell-therapy-for-knees.