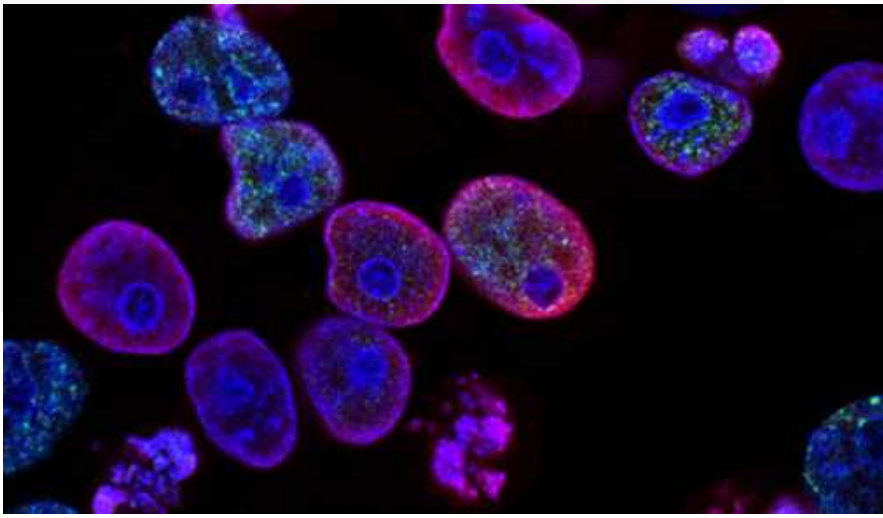
INFINITY
Medicina Regenerativa

EVIDENCE OF
MEDICAL USES OF STEM CELLS

CONTENT



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HEART DISEASES

REFRACTORY ANGINA

Patients with angina, in whom symptoms persist after conventional treatment and who are not candidates for surgery, stem cell therapy has emerged as an instrument with positive impact on standard therapy.

In the year 2017, a review was published in which 13 clinical studies were included, with 1061 patients and 12 months of follow-up on average. The authors concluded that "although the available data are not yet conclusive, given the scarcity of therapeutic alternatives, we believe that stem cell therapy is a viable option to add to the conventional treatment of refractory angina" (1).

A meta-analysis published in 2018, with 304 patients reported improvement in total exercise time and the frequency of angina attacks at three, six and twelve months, as well as a reduction in mortality at two years (2).

A second meta-analysis published in March 2019, which included 526 patients controlled for 14 months, found that, compared to those who received conventional treatment, patients who received stem cells had fewer serious adverse effects, less mortality, less angina crisis and less antianginal medication (3).

A third meta-analysis of 2019, with 269 decrease in mortality from all causes and the patients and 15 months of follow-up on frequency of angina, increase in exercise time, average, reports the following results: with no increase in reactions adverse (4).

CARDIOMYOPATHY
(ISCHEMIC AND NON-ISCHEMIC)

Many patients with heart failure are exposed to a long process of destruction of the heart muscle, which does not allow restoring heart function, despite optimal medical and surgical management.

According to a review of 5 clinical studies published between 2017 and 2018, in which 605 patients were included, the authors report that cell therapy is safe, causes immunomodulatory effects, is related to improvement of functional capacity and adds clinical benefits to the patient's standard therapy. They conclude that the results are promising and advise to continue strengthening the level of evidence (5-9).

A meta-analysis published in May 2019, which included 20 investigations and 1418 patients, evaluated for 21 months on average, shows the following result: compared with controls, stem cells improved indicators of cardiac function (LVEF and LVESV, by its acronym in English), walking distance, functional classification of heart failure, quality of life and mortality. There were no differences with the control group regarding serious adverse events and hospitalizations (10).

In a recent review of 9 studies, which included 612 patients with heart failure, improvement of clinical and paraclinical parameters was found, evaluated for 9 months on average. The authors conclude that stem cells are an effective therapy for the treatment of heart failure, improving the prognosis and exercise capacity of patients (11).

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HEPATIC DISORDERS

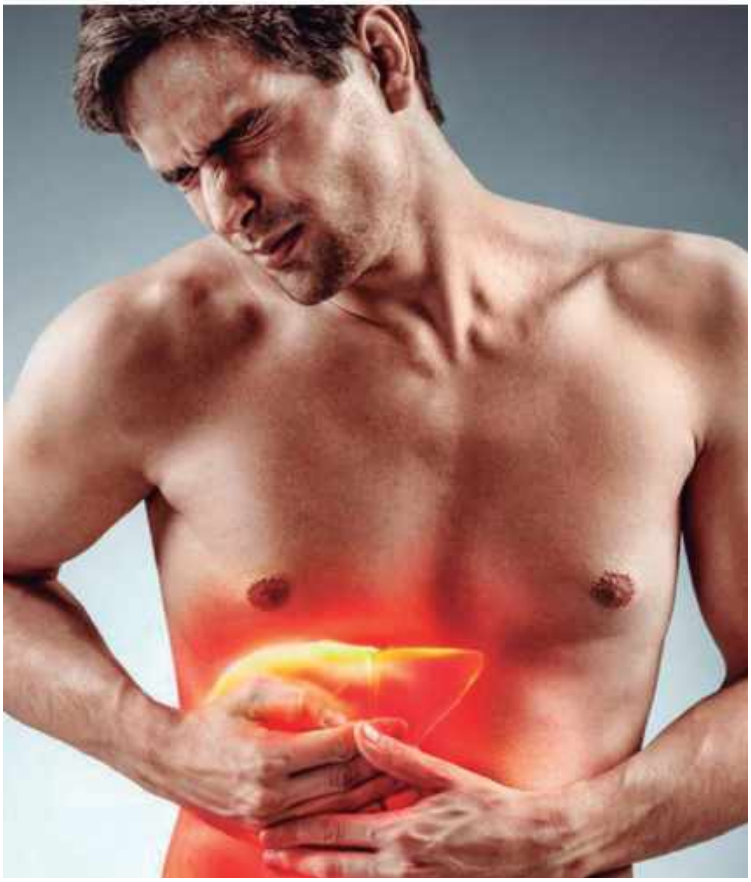
CIRRHOSIS

In many patients with cirrhosis and terminal states of liver failure, liver transplantation is not a realistic option, due to the shortage of donors, complications related to immunosuppression, complexity and high costs of surgical intervention. The application of stem cells is currently positioned as a safe option and the best candidate to reverse liver failure and improve the quality and life expectancy of these patients, since it is the only therapeutic tool that has been shown to be capable of repair.

In 2015, a meta-analysis of 7 clinical trials was published with patients with terminal cirrhosis due to hepatitis B, C or alcoholic, in which 233 patients who received placebo or conventional treatment were compared, with 256 patients who were added with cells mother. Resuvlts: there were histological, biochemical and liver function changes in favor of the group treated with cells. Conclusion "Stem cell transplantation significantly improved liver function, becoming at this moment the most promising therapeutic approach" (1).

In 2016, a study was published in which 65 patients with decompensated hepatitis B cirrhosis were divided into a control group that received the standard treatment and another group that received umbilical cord stem cells. After six months of follow-up, the authors registered the following results: in the group transplanted with stem cells there was inhibition of the proliferation of T and B lymphocytes, activation of the Treg cells, an increase in the production of anti-inflammatory cytokines and reduction of the proinflammatory ones; therefore, they conclude that stem cells reduce inflammation and cell damage, decreasing the probability of liver failure (2).

Also in 2016, an investigation was published in 72 patients with alcoholic cirrhosis. One group received the standard treatment and another group the standard plus stem cells (two doses). They underwent control biopsies at 6 months and follow-up of adverse events for 12 months. The results were the following: in the group treated with stem cells there was reduction of hepatic fibrosis between 25% and 37%; there was also significant improvement in the liver function indicators; the proportion of adverse events was not different between the groups. The authors concluded that the stem cells were safe and were associated with histological and functional improvement (3).



A recently published clinical trial reports that 20 cirrhotic patients who received stem cells had improvement on the MELD scale (which measures liver disease status), INR, serum albumin and bilirubin levels, at 3 and 6 months after transplantation the cells (4).

It is worth mentioning that in a recent review of liver disease by alcohol (ranging from fatty liver / steatosis to cirrhosis and liver cancer) the authors conclude that cell therapy seems promising in the treatment, for its ability to migrate to the liver, differentiate into hepatocytes and release growth, anti-inflammatory and immunomodulatory factors in the organ (5).

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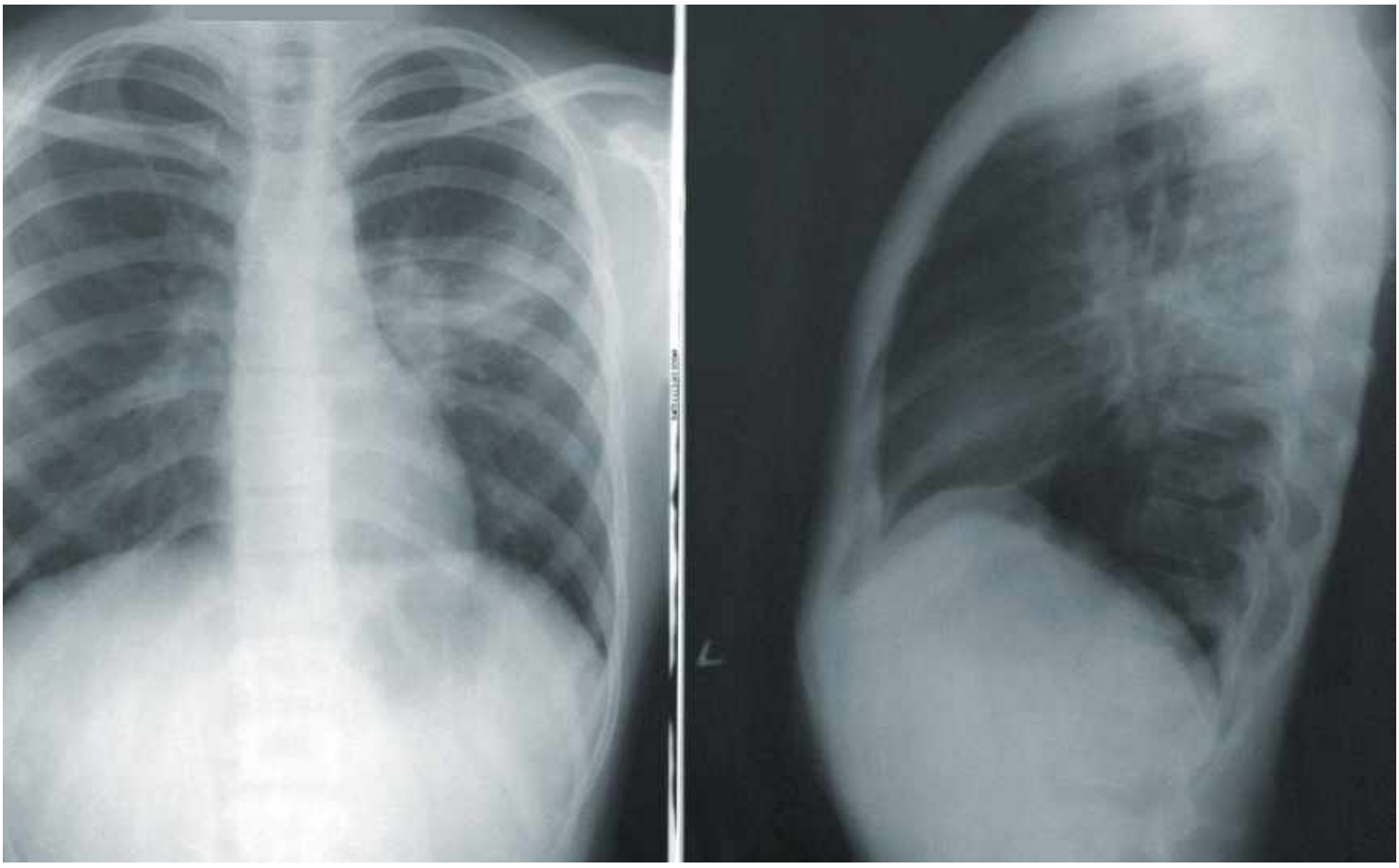
PULMONARY DISORDERS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

From the time it was shown in human lung cultures that the stem cells inhibit the formation of fibrous tissue and increase the normal repair of the lung, studies were started in animals and then in humans. Recent clinical trials confirm the safety of the use of stem cells in patients with chronic lung diseases and, although it is advisable to improve the level of clinical evidence, the results are promising in diseases such as COPD and pulmonary fibrosis (1, 2).

In 2013, a clinical trial was published in which 62 patients with moderate to severe COPD were randomized to receive stem cells or placebo in order to evaluate the safety of the cells. After two years of control, the authors concluded that the application of stem cells are safe and, since there was a significant reduction in inflammation indicators in the group that received the stem cells, they call for an intensification of the exploration of the therapeutic role of these cells (3).



In a review of the year 2017, of 4 investigations with 86 patients suffering from COPD of different degrees, after an average follow-up of 15 months, the authors concluded that stem cells have shown a good adjuvant role in the clinical scenario. The trials that used stem cells combined with other conventional treatments found that patients obtained a greater benefit in pulmonary function and quality of life tests, as well as reductions in the systemic markers of inflammation (4).

Another review of 15 registered studies (completed or ongoing) through 2017 in the ClinicalTrials.gov database, which included 803 patients with COPD, discusses the potentially beneficial properties of stem cells in this condition and the authors conclusion that stem cell transplantation is a clinical alternative to diseases such as COPD, for various reasons including its anti-inflammatory and immunomodulatory actions, in addition to the safety of the application (5).

Recent studies have confirmed that stem cells modulate the immune response in patients with COPD (6).

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OSTEO ARTICULAR DISORDERS

OSTEOARTHRITIS

Osteoarthritis, chronic tendinopathies and fractures with bone loss, have been the most studied by regenerative medicine, which is currently positioned as a safe option and a good candidate to overcome functional limitation and pain chronic to those who are condemned some of these patients, since it is the only therapeutic tool where tissue repair capacity has been demonstrated.

The conventional treatment of osteoarthritis shows only modest clinical benefits, while several studies report that intra-articular injection of stem cells with growth factors results in evident recovery of cartilage, with clinical improvement (pain, functional limitation and quality of life), and radiological More than 40 published clinical trials report that intra-articular injection of stem cells with growth factors results in evident recovery of cartilage and clinical parameters (pain and functional limitation), imaging, arthroscopy and quality of life (1,2).

A meta-analysis of the year 2019, which included 33 investigations and 724 patients with osteoarthritis, shows that there was significant improvement in pain and joint function, accompanied by regeneration of the articular cartilage (3).

TENDINOPATHIES

In sports injuries that involve the tendons and chronic tendinopathies traditionally management includes analgesics, anti-inflammatory, physiotherapy and surgery, typically with partial results/responses and many undesirable side effects. Conversely, most published clinical studies show that intralesional application of stem cells improves pain, joint performance and structural defects of the injured tendon (4-6).

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DIABETES MELLITUS
TYPES 1 AND 2

It is accepted that the cause of diabetes mellitus type 1 (DMl) is the self-destruction of pancreatic beta cells, while in type 2 diabetes (DM2) occurs a chronic inflammation of low grade, which causes dysfunction of beta cells and insulin resistance (1).

The remarkable immunomodulatory and anti-inflammatory properties of stem cells attracted the attention of researchers and clinicians, which explains the numerous clinical trials completed or underway, whose purpose has been to evaluate the safety and effectiveness of stem cells in the treatment of DMl and DM2 (2).

In 2016, a clinical trial of patients with DM2 was published, distributed in a group that received conventional treatment and another to which stem cells were added. At the 3-year follow-up in the group that received stem cells, neither acute nor chronic adverse effects were found and glycemia, glycosylated hemoglobin, (-peptide, beta-cell function and the incidence of diabetic complications (nephropathy, neuropathy and retinopathy). The benefits began to be noticed at 3-6 months (3).

A review of 16 clinical studies published between 2010 and 2018, of 426 patients with OM 1 or 2 and average follow-up time of 16 months, concluded: "Despite the heterogeneity of the investigations, the results are positive and, with the exception of one, all the studies reported a decrease in the requirements for insulin and / or oral anti-d iabetics"(4).

Another review of clinical trials of the use of stem cells for the treatment of DMI (4 studies) and DM2 (3 studies) concluded that "in DMI, despite the favorable results, there are doubts about the effectiveness. On the contrary, the consistent positive metabolic effects give hope for the treatment of DM2 with stem cells "(5).

Finally, a meta-analysis of the year 2019, of 6 investigations with 266 patients with DM2 treated with stem cells, aged between 45 and 58 years and average follow-up time of 16 months, concludes that "therapy with mother cells has beneficial effects in DM2 "(6).

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AUTOIMMUNE DISEASE

RHEUMATOID ARTHRITIS (RA)

In some patients, conventional RA therapy is associated with little response or intolerance; in such cases, stem cells have become a novel therapeutic option. In a controlled clinical trial, published in 2017, with 53 patients suffering from refractory RA, the safety and tolerability of different doses of stem cells were evaluated. At 3 months of follow-up, it was reported that intravenous infusion of stem cells was, in general, well tolerated and without evidence of toxicity related to cell dose; in addition, there was a trend towards clinical improvement, which is why the authors invite us to continue exploring the promising benefit of stem cells in these cases (1).

In 2019, one study reported the effects of intravenous administration of stem cells in nine patients with refractory RA, who were monitored for 12 months. The authors found a significant reduction in markers of inflammation, increase in immunomodulatory cells and improvement in the clinical scales of activity and symptoms of disease (2).

The ability of stem cells to restore in patients with RA the lost balance between cells and pro-inflammatory and anti-inflammatory factors is confirmed in a systematic review also published in 2019 (3).

ANKYLOSING SPONDYLITIS (AS)

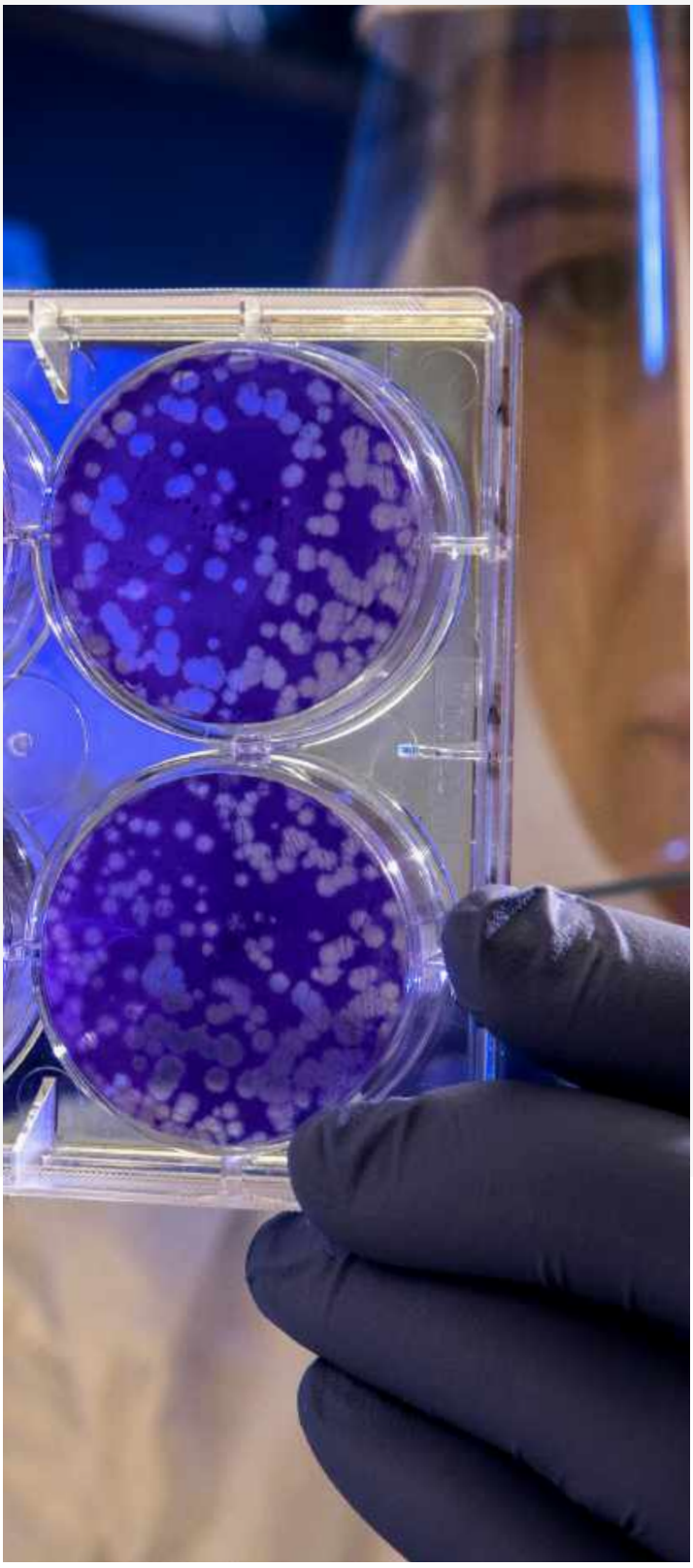
It is a spondylo-arthropathy chronic that especially affects the spine and is also caused by a disorder of the immune system; its conventional treatment is unsatisfactory and with a high incidence of undesirable effects. Since 2014, intravenous application of stem cells has been reported in 31 patients with refractory or intolerant AS to conventional medication. During the 20 weeks, safety, clinical condition based on activity scales and magnetic resonance studies were evaluated. The authors conclude that stem cells are a feasible, safe and promising option in the treatment of AS (4).

For this year 2019 an extensive review of the possible mechanisms involved in AS is published, the current treatment alternatives, the theoretical basis of the mechanism of action of the stem cells, as well as the clinical evidence of their benefit; the authors conclude that there is evidence that stem cells can improve signs and symptoms of the disease, since they control the events that give rise to the disease and promote the regeneration of damaged tissue (5).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

The LES is one of the autoimmune diseases that has greater support of benefit and safety in animal models and in humans. With the reservation that should be had when the clinical evidence is still limited, the results of the clinical studies of safety and effectiveness give rise to optimism. This is indicated by studies of the molecular mechanisms by which these cells may be beneficial, as well as reports of survival, clinical improvement and tolerability in patients with various autoimmune diseases (6-8).

In an investigation of the predictive factors of clinical response to the administration of stem cells to 69 patients with SLE refractory to standard treatment, the authors found that there was clinical remission with decreased activity of the disease at 1, 3, 6 and 12 months of follow-up (9).



SYSTEMIC SCLEROSIS (SS)

It is a rare autoimmune disease, which attacks the skin and any internal organs and can have a severe course; their treatment options are very limited and medications that can be useful have a narrow margin of safety. Cell therapy emerges as an option that is not only safe but also capable of correcting many of the inflammatory and immune system disorders that characterize the disease (10).

We reviewed the data of 60 patients with SS, reported in 8 clinical studies published between 2008 and 2018. In all of them, safety was confirmed and significant benefits were obtained with the application of stem cells, in some cases with follow-up up to 5 years (11,12).

A study related to stem cells and SS, published in 2019, deserves comment. Blood was collected from 6 patients (between 23 and 58 years old) with aggressive forms of SS, before and up to 14 months after applying stem cells, with the purpose of investigating changes in their immune profile. During the follow-up period, positive changes were found in subpopulations of lymphocytes and in the secretion of mediators of immune response, indicating immunomodulation associated with clinical improvement (13).

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INFLAMMATORY BOWEL DISEASE (IBD)

It is accepted that IBD is caused by an attack to the gut microbiota itself, due to an alteration of the immune response in a person with genetic predisposition; therefore, treatment has focused on the control of inflammation and normalization of the immune system, which is why stem cells have been used to treat this condition. In Crohn's disease (CD), which is a classic inflammatory bowel disease, it has been found that the infusion of allogeneic stem cells is safe and more effective than conventional treatment. In fact, clinical studies, including controlled clinical trials and meta-analysis, show that the infusion of stem cells are safe and effective in the treatment of CD, including the severe perianal form. The cure rates seen in patients, including perianal fistulas due to CD, without the surgical risks and the secondary result of incontinence, extended research to other forms of IBD, such as ulcerative colitis. Since the first report of success in the cure of recto-vaginal fistula through the injection of stem cells, in 2003, 11 phase I to Ill studies, including 365 patients, have demonstrated the safety and efficacy of stem cells in Crohn's disease (1).

On the other hand, in 2010 the first controlled study was published including 42 patients with ulcerative colitis, monitored for 24 months. The stem cells reduced the activity of autoimmune inflammation and stimulated the repair process of the intestinal mucosa, increasing the duration of the remissions and reducing the frequency of hospitalizations (2).

Between 2008-2018, 20 phase / Ill investigations were published, with 519 patients with ulcerative colitis and follow-ups between 3 months and 5 years, with remission rates of 45% to 100% (3).

More recently (2019), the following results of a phase Ill clinical trial were published with 212 patients with I BD, randomized to receive or not receive stem cells: remission rates at six months (50% vs. 34%) and annually (56% vs. 39%). There was no increase in the incidence of adverse events in the group that received stem cells (4).

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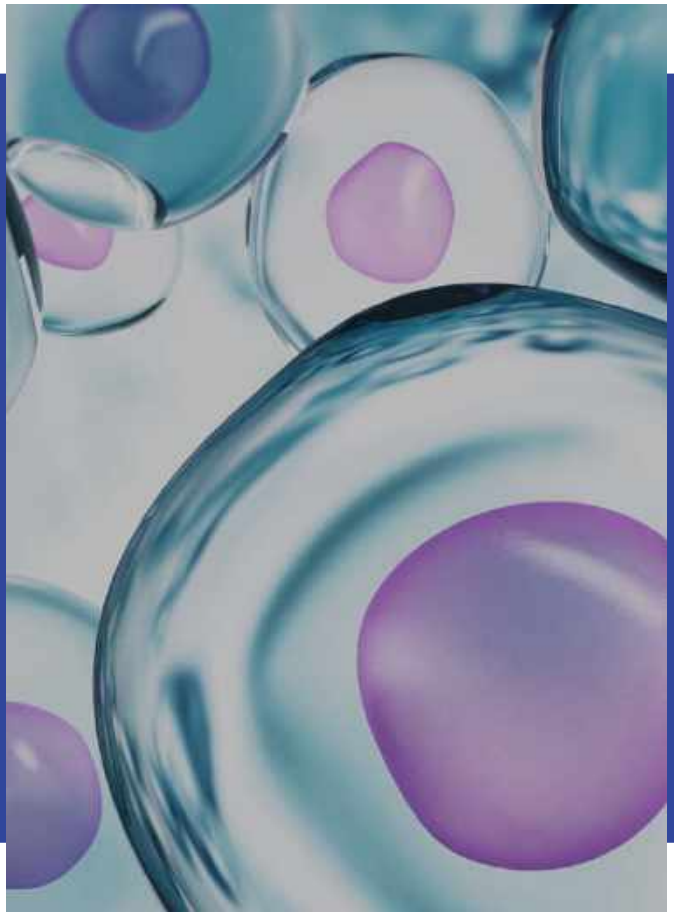
MALIGNANT HEMATIC DISEASES, GRAFT-VERSUS-HOST DISEASE

Among malignant blood diseases, in which it is known that allogeneic hematopoietic cell transplantation significantly reduces the risk of relapse and death, are acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma and non-Hodgkin's lymphoma. Unfortunately, many patients who need a stem cell transplant do not find a compatible donor or do not get a good response, so it became necessary to explore other alternatives. Stem cells from the umbilical cord tissue are currently the source of stem cells richer, more accessible, and less expensive and with less risk of inducing rejection, which makes this subtype of stem cell in the most promising and safe source for the cells. Transplants with these indications (1).

On the other hand, the most common complication in patients undergoing some transplants is graft-versus-host disease, known as "graft rejection," which can affect any organ and occur suddenly or slowly; some medications may reduce the risk, but the incidence of rejection remains high. Because stem cells regulate the immune response, the use of such cells in patients undergoing solid organ transplants and blood cells for malignant blood diseases has been investigated. Current evidence shows a clear trend in favor of stem cells, with respect to the risk of relapse and survival of patients.

Although the evidence is still not considered conclusive, a clear trend in favor of stem cells is established, with respect to the risk of relapse and survival of patients (2-5).



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INFINITY Medicina Regenerativa

NEURODECIENERATIVE DISEASES

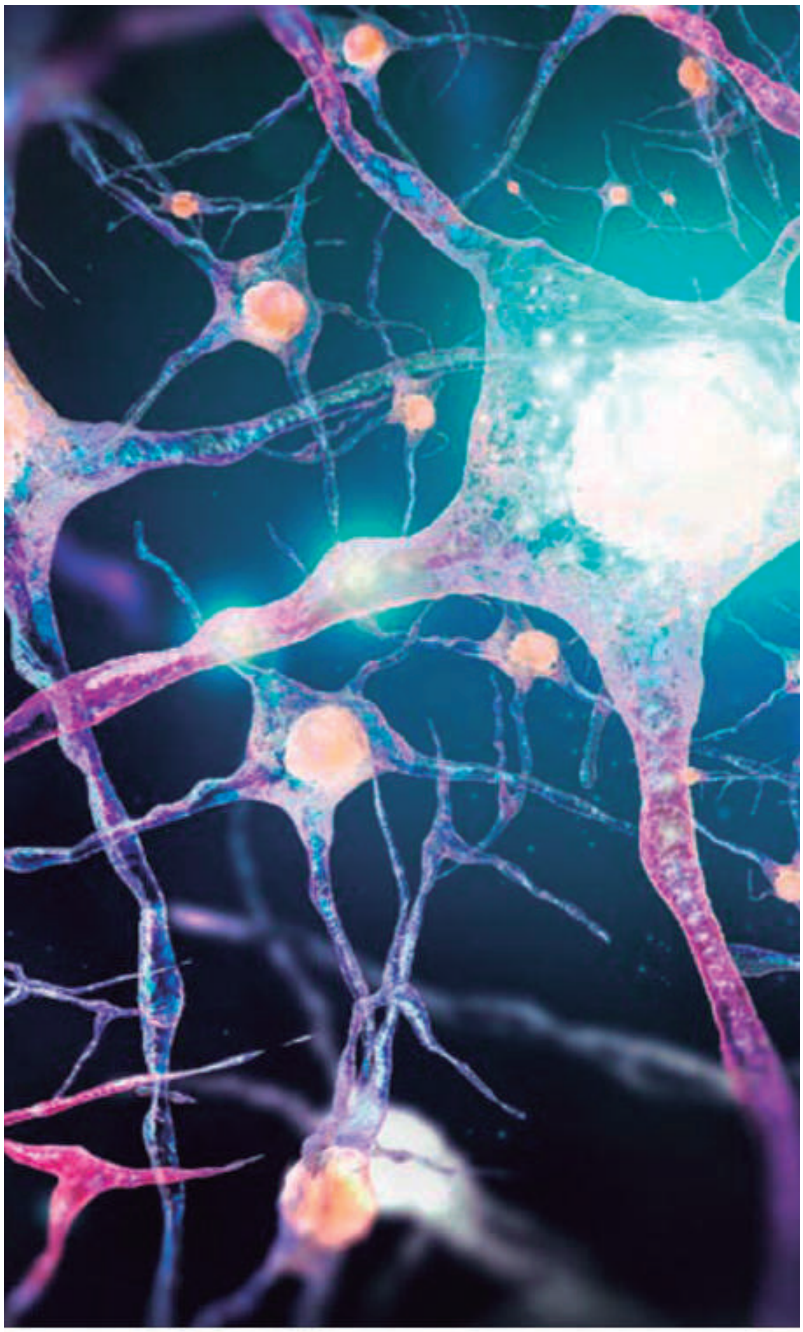
In recent years there has been great interest in establishing the role of stem cell therapies in several neurodegenerative diseases. More than in the differentiation to neurons and the replacement of dead neurons, research is currently focused on exploiting the paracrine properties of neuroprotection, control of inflammation and modulation of the immune system by transplanted stem cells (1). Although it is necessary to reinforce, through controlled clinical trials currently under way, evidence of safety / efficacy, dose, cell type, administration routes, etc., the available information shows slowing of the progression of diseases such as multiple sclerosis, amyotrophic lateral sclerosis and Parkinson's disease.

The safety and effectiveness of stem cell based regenerative medicine for the treatment of multiple sclerosis has reached such a level of evidence that recently the American Society for Bone Marrow and Blood.

Transplants has recommended including severe forms of this disease among the indications of autologous hematopoietic stem cell transplantation, which opens the doors of the clinic to explore the role of stem cells of other types (2).

On the other hand, a review of 19 phase I/ II studies on amyotrophic lateral sclerosis (ALS), which includes 380 patients, confirms safety (not severe adverse events) and the feasibility of intravenous and intracerebral application of stem cells, although the results of effectiveness still cannot be considered conclusive (3,4). By mid-2019 there were 50 studies registered in ClinicalTrials on ALS + stem cells.

The ability of stem cells to repair the damage caused by Parkinson's disease (PD) has been demonstrated in vitro, and the safety and effectiveness studies of stem cell treatment in animal models of the disease are conclusive, to the point that has authorized to move to research on human beings. Until now, the clinical evidence can be summarized as follows: i) The safety studies of the application in humans leave no doubt: we are facing a therapeutic tool with a very low rate of undesirable effects and not related to what could be considered serious adverse effects; ii) Evidence from studies of effectiveness, although not yet decisive, is becoming stronger and stem cells are emerging as a therapy associated with improvement of the clinical condition, radiological images and neuropsychological scores of the patients with PD (5-7).



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FRAILTY AND AGING

As age advances, there is an inevitable and progressive increase in debilitating and painful diseases; so aging and its associated diseases represent a huge cost to the health system and, as the problem will obviously grow, there is a need to find the mechanisms responsible for aging and develop new therapeutic strategies aimed at controlling it. Frailty is a clinical entity that is independent of the morbidity and disability of the patient, increases with age and has been defined as a systematic and progressive decline in physiological reserves and an increase in vulnerability to minor stressors (l); its main clinical manifestations are flaccidity and reduction of muscle mass and strength, slowness of mobility, reduction of physical activity and fatigability, among others, becoming an important predisposing factor to falls, disabilities and hospitalizations of elderly people. Due to the anti-inflammatory and immunomodulatory effects of stem cells, regenerative medicine has aroused great interest, as an option to repair the damage caused by the frailty syndrome. The safety of allogeneic stem cells from a young donor or from an umbilical cord has already been validated in numerous preclinical and clinical studies of senile frailty (2).

At the end of 2017, a controlled study of safety and efficacy in frailty patients treated with stem cells was published. The safety of the procedure and improvement of the walking distance at six minutes, lung function tests, cognition and the physical component of quality of life were confirmed, and the concentrations of some markers of inflammation were reduced (3).

A recent publication (year 2019) made a systematic review of the phenomena that determine the frailty, the fundamentals of the use of stem cells in this condition and the clinical trials that evaluate the treatment of frailty with stem cells. According to the reports of 5 clinical studies completed or underway, which have included 208 patients between 55 and 96 years, monitored for approximately 12 months, the authors reach the following conclusion: "Frailty urgently requires attention. Stem cell therapy has great potential because, although challenges persist, a single intravenous infusion of allogeneic stem cells has proven safe, well tolerated and effective for the modulation of immunity and inflammation and shows a tendency to improve physical functions and the quality of life"(4).

It is interesting to mention that at a symposium of the National Institute of Aging (NIA) of the United States, aimed at analyzing the problem of frailty in clinical practice, the role of stem cells in fragility was discussed. Stem cell dysfunction was identified as one of the biological targets linked to aging and, therefore, should be the object of intervention in the prevention or treatment of frailty (5). These recommendations are supported by a recent review where they show that stem cells possess properties capable of controlling or reversing many of the biochemical phenomena that cause frailty.

Although the authors acknowledge that it is necessary to improve the level of clinical evidence, based on the data presented in this review, the modulation of chronic inflammation by stem cells is a prom1s1ng strategy to prevent and delay not only the frailty, but some other clinical conditions frequently associated with it, such as chronic lung disease, cardiovascular disease, diabetes and osteoarthritis (6).

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SKIN DISORDERS AND AESTHETIC MEDICINE

The following are the cases in which there is solid and consistent evidence of the benefits of regenerative medicine.

- Chronic skin wounds, often associated with diabetes or obesity. A meta-analysis of clinical trials that have investigated the effect of stem cells in the treatment of diabetic foot ulcers found that stem cell therapy was a safe procedure and was associated with significant improvement, independent of the size of the ulcer and the age of the patient. This is the reason why many authorities consider cell therapy as a novel and effective alternative treatment, of course accompanied by conventional medical and surgical measures (1-4).

- Regenerative medicine has become a new strategy for facial rejuvenation and filling of unwanted furrows and lines, elimination of scars and signs of acne, vitiligo, among others (5).

- Given the regenerative mechanisms of stem cells and that have been shown to release factors that promote hair growth and hair regeneration, alopecia has become a target of regenerative medicine, with variable beneficial results and minimal undesirable effects (6).

A recent review on the subject indicates that "the application of stem cells constitutes one of the most promising and potentially effective therapies for the treatment of different causes of alopecia" (7).

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