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MINIREVIEWS

Mesenchymal stem cell therapy in retinal and optic nerve diseases: An update of clinical trials

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Abstract

Retinal and optic nerve diseases are degenerative ocular pathologies which lead to irreversible visual loss. Since the advanced therapies availability, cell-based therapies offer a new all-encompassing approach. Advances in the knowledge of neuroprotection, immunomodulation and regenerative properties of mesenchymal stem cells (MSCs) have been obtained by several preclinical studies of various neurodegenerative diseases. It has provided the opportunity to perform the translation of this knowledge to prospective treatment approaches for clinical practice. Since 2008, several first steps projecting new treatment approaches, have been taken regarding the use of cell therapy in patients with neurodegenerative pathologies of optic nerve and retina. Most of the clinical trials using MSCs are in Ⅰ/Ⅱ phase, recruiting patients or ongoing, and they have as main objective the safety assessment of MSCs using various routes of administration. However, it is important to recognize that, there is still a long way to go to reach clinical trials phase Ⅲ-Ⅳ. Hence, it is necessary to continue preclinical and clinical studies to improve this new therapeutic tool. This paper reviews the latest progress of MSCs in human clinical trials for retinal and

optic nerve diseases.

Key words: Mesenchymal stem cells; Cell therapy; Optic nerve diseases; Clinical trials; Retinal diseases

Core tip: Advances in the knowledge of neuroprotection, immunomodulation and regenerative properties of mesenchymal stem cells (MSCs) are contributed by several preclinical studies of various neurodegenerative diseases. It has provided opportunity to perform the translation of treatment approach to the clinical practice. Several clinical trials in patients with retinal and optic nerve diseases have been developed since 2008. Most of them using MSCs are in Ⅰ/Ⅱ phase. However, there is still a long way to go to reach clinical trials Phase Ⅲ-Ⅳ. Hence, it is necessary to continue with preclinical and clinical studies to improve this new therapeutic tool.

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INTRODUCTION

Retinal dystrophies, diabetic retinopathy, age related macular degeneration and optic nerve diseases are chronic and degenerative ocular pathologies which lead to irreversible visual loss. Retinal degeneration is a leading cause of incurable low vision and blindness worldwide[1]. Most retinal and optic nerve diseases are caused by irreversible apoptosis of retinal neural cells or adjacent supporting tissue. Because there is no curative treatment for these degenerative diseases, current therapies mainly focus on the aetiology cause or at specific situations, such as late complications. However, most of them have low efficacy. Since the advanced therapies availability, cell-based therapies offer a new all-encompassing approach[2].

Mesenchymal stem cells (MSCs) are multipotent and self-renewing stem cells derived from bone marrow, adipose tissue, and other mesenchymal tissues, which can be induced to differentiate into bone marrow, cartilage, muscle, lipid, myocardial cells, glial cells and neurons[3,4]. MSCs have some features that make them useful in cell therapy research. These are easy to isolate and expand rapidly after a short period of dormancy[5]. They are free of ethical issues associated with the harvesting of embryonic stem cells[6]. Also, it is considered that MSCs are "immunoprivileged" because they do not express Major Histocompatibility Complex class Ⅱ (MHC-Ⅱ) on their surface, associated with transplant rejections[7], and this advantage allows its use as an autologous or allogenic form[8]. Furthermore, MSCs produce several growth factors with paracrine actions that are believed to modulate the microenvironment of diseased tissues, promote survival and activate endogenous repair mechanisms[9].

Due to this features MSCs have been used in several preclinical studies of retinal and optic nerve diseases, where they have demonstrated their properties of immunomodulation, neuroprotection and tissue repair[10-13]. These properties support the clinical use of MSCs as an opportunity for tissue repair and regeneration in several neurodegeneratives disorders. To remember, the stages of clinical trials for drugs in development can be divided into four phases. The main purpose of the first clinical stage, phase Ⅰ, is to observe the tolerance and pharmacokinetic characteristics of the drug in the human body and to provide evidence to establish the phase Ⅱ administration protocol. The purpose of phase Ⅱ clinical trials is to evaluate the efficacy and safety of the drug in patients with the target indication. In phase Ⅲ, the efficacy and safety of the drug in patients with the target indication is further validated, providing the basis of the evidence used for review during the drug registration and application process. The phase Ⅳ clinical trial, which takes place during the post marketing period, provides further evidence regarding the drug's efficacy and any emerging adverse reactions under conditions of real-life use in large numbers of patients[14].

In this review, we summarize the latest progress of MSCs in human clinical trials for retinal and optic nerve diseases.

TISSUE SOURCES OF MSCS

Bone marrow is the first isolation source of MSCs following by umbilical cord and adipose tissue[15]. Although bone marrow is the best source of obtaining MSCs, there are some aspects that reduced their use: Limited growth rate, differentiation capability depending on the donor age, and risk inherited to sample collection[15]. Regarding to umbilical cord source to obtain MSCs, it is required an optimal protocol such as, time of recollection and process less than 16 h, as well as, volume collection higher than 30 mL to get a success culture[16]. MSCs obtaining by adipose tissue source have a similar morphology and phenotype to the bone marrow source, but these cells have a higher capability of proliferation and adipose tissue samples are easier to collect from liposuction procedures[17].

CRYOPRESERVATION OF MSCS

Cryopreservation consists on the interruption of cellular metabolism regulated by processes of freezing and thawing, maintaining a good functional and structural cellular state. To preserve a biological sample as long as possible, without losing their properties, cells are immersed in liquid nitrogen at extremely low temperature

(-196 ℃), stopping the metabolic activity of the cells[18].

Cryopreservation has been performed primarily for the purpose of preserving the hematopoietic stem cell populations for transplantation. Currently, the use of this procedure has been extended, allowing the preservation of the biological potential, and to retain the biological age at time of cryopreservation. In autologous patients, MSCs are collected and cryopreserved for later clinical use. In allogeneic patients, cryopreservation permits banking of cells for human leukocyte antigen typing and matching, facilitating the logistical transport of cellular products to transplant centers, and allowing enough time for the screening of transmissible diseases in the donated cells before transplantation[19].

CLINICAL TRIALS USING MSCS

Today, there are ongoing clinical trials of advanced therapies' using MSCs in various retinal and optic nerve diseases. In these clinical trials the main route of administration is the intravitreal injection following by subretinal implant and then intravenous route. In all these studies it is used autologous stem cells from bone marrow or adipose tissue. On Table 1 it is shown all clinical trials finished and ongoing registered in clinicaltrials.gov and the International Clinical Trials Registry Platform, until today (Last search performed on 18 May 2016).

Clinical trials in retinal dystrophies: Retinitis pigmentosa and stargardt's disease

Retinitis pigmentosa (RP) includes some inherited diseases which are characterized by a classic pattern of difficulties in dark adaptation and night blindness in adolescence, loss of mid-peripheral visual field in young adulthood and central vision later in life due to the severe loss of rod and cone photoreceptors[20]. The RP is one of the leading hereditary degenerative retinal diseases, affecting 1 in 4000 individuals[20]. RP is characterized by the classic triad of decreased arteriolar diameter, pigment spicules deposits in the mid periphery of the retina and pallor of the papilla[20].

Stargardt's disease (SD) is the most common form of inherited juvenile macular degenerations. Its prevalence worldwide is estimated to be 1 in 10000 individuals[21]. Patients initially present with reduced central vision. The pathology is defined by the accumulation of lipofuscin in the apical zone of the RPE cells. The patients present decreased vision to legal blindness and secondary choroidal neovascularization, with bilateral gradual involvement of vision[21].

There are nine clinical trials that use MSCs to treat this kind retinal dystrophies (6 for RP, 2 for SD and RP and 1 for RP and other diseases) (Table 1). Although most clinical trials are in recruitment phase, there are two completed to treat retinitis pigmentosa, both were held at Hospital das Clinicas (Medical school Ribeirao Preto, Sao Paulo) - (NCT01068561 phase Ⅰ, NCT01560715 phase Ⅱ). The cells used were autologous bone marrow-derived MSCs, which were administered through intravitreal injection containing 10 × 10^6 cells/0.1 mL. The MSCs were obtained through aspiration of 10 mL bone marrow tissue from the posterior iliac crest and were separated by Ficoll-Hypaque gradient centrifugation. Regarding to the clinical trial NCT01068561 (phase Ⅰ), there is a case reported[22]. The case is about one recruited patient of this study, who had macular oedema associated with RP, which showed complete resolution of the oedema 7 d after injection, and the effect remained for one month of follow-up with optical coherence tomography. They concluded that the adult stem cells can restore the blood ocular barrier due their paracrine effects or by osmotic gradient allowing the absorption of macular oedema[22]. The trial NCT01560715 (phase Ⅱ) is completed and also have published results[23], they concluded that the therapy with intravitreal use MSC can improve the quality of life of patients with RP, although the improvement is lost with time. Patient's improvement has been evaluated with vision-related quality of life test (NEI VFG-25) before therapy and 3 and 12 mo later. There was a statistically significant improvement 3 mo after treatment, whereas by 12th month there was no significant difference from baseline[23].

At the hospital Virgen de la Arrixaca, Murcia (Spain), it is being carried out a phase Ⅰ clinical trial with autologous bone marrow stem cells in patients with RP. This clinical trial continues recruiting patients. Regarding to the other clinical trials for RP and Stargardt's disease (NCT01531348, NCT017336059, NCT01914913, NCT02280135, NCT027 09876 and NCT01518127), they are on phase Ⅰ or Ⅰ/Ⅱ, and they are recruiting patients (Table 1).

Clinical trials in diabetic retinopathy and age macular degeneration

Diabetic retinopathy (DR) is a prevalent microvascular complication of diabetes, and remains the leading cause of preventable blindness in working-aged people (20-74 years)[24]. About 30% all diabetics have signs of diabetic retinopathy, and 30% of these might have vision-threatening retinopathy, defined as severe retinopathy or macular edema[25]. The current standard treatment for management of these disorders relies mainly on laser therapy, which is inherently destructive, or antiangiogenic therapy, both associated with unavoidable ocular/systemic side-effects[25].

Age-related macular degeneration (AMD) is a progressive chronic disease of the central retina and a leading cause of vision loss worldwide, it accounts for 8% of all blindness worldwide and is the most common cause of blindness in developed countries[26], particularly in people older than 60 years. Its prevalence is likely to increase as a consequence of exponential population ageing. There have been significant advances in the management of exudative AMD with the introduction of anti-angiogenesis therapy, and patients now have effective treatment options that can prevent blindness and, in many cases, restore vision[27]. However antiangiogenic treatment doesn't stop the progression nor serves to treat dry AMD.

Table 1 Clinical trials for retinal and optic nerve diseases

Clinical trial	Condition	Cells	Route of administration	Dose	Estimated enrollment	Recruitment status	Study phase	Country	Start date
NCT01068561[1]	Retinosis pigmentaria	ABMSC	Intravitreal injection	10×10^6 cells/0.1 mL	5	Completed	I	Brazil	2010
NCT01531348	Retinosis pigmentaria	ABMMSC	Intravitreal injection	1×10^6 cells/0.1 mL	10	Enrolling by invitation	I	Tailandia	2012
NCT01560715[2]	Retinosis pigmentaria	ABMSC	Intravitreal injection	10×10^6 cells/0.1 mL	50	Recruiting	II	Brasil	2012
NCT01736059[3]	Retinosis pigmentaria, AMD, DR,VO	ABMSC	Intravitreal injection	3.4×10^6 cells/0.1 mL	15	Enrolling by invitation	I	EEUU	2012
NCT01914913	Retinosis pigmentaria	ABMSC	-	-	15	Recruiting	I / II	India	2014
NCT02280135	Retinosis pigmentaria	ABMSC	Intravitreal injection	30×10^6 cells/0.1 mL	10	Recruiting	I	Spain	2014
NCT02709876	Retinosis pigmentaria	ABMSC	Intravitreal injection	-	50	Recruiting	I / II	Arabia	2014
NCT01518127	Stargardt's disease and AMD	ABMSC	Intravitreal injection	10×10^6 cells/0.1 mL	10	Recruiting	I / II	Brazil	2011
NCT01736059[3]	Stargardt's disease,AMD, DR, VO, RP	ABMSC	Intravitreal injection	3.4×10^6 cells/0.1 mL	15	Recruiting	I	EEUU	2012
Carta al editor Act. Opht[4]	Diabetic retinopathy	ABMSC	Intravitreal injection	18×10^7 cells/0.5 mL	1	Completed	I	Germany	2008
NCT01518842	Diabetic retinopathy	ABMSC	Intravitreal injection	2×10^4 cells/0.1 mL	30	Unknown	I / II	Brasil	2011
IRCT201111291414N29	Diabetic retinopathy	ABMMSC	Intravenous	2×10^6 cells/kg	20	Ongoing	I / II	Iran	2011
NCT01736059[3]	Diabetic retinopathy, VO, HRD	ABMSC	Intravitreal injection	3.4×10^6 cells/0.1 mL	15	Recruiting	I	EEUU	2012
ChiCTR-ONC-16008055	Diabetic retinopathy	ASMSC	-	-	30	Recruiting	I / II	China	2013
NCT01518127	AMD, Stargardt's disease	ABMSC	Intravitreal injection	10×10^6 cells/0.1 mL	10	Recruiting	I / II	Brasil	2011
NCT01736059[3]	AMD, DR, VO, HRD	ABMSC	Intravitreal injection	3.4×10^6 cells/0.1 mL	15	Recruiting	I	EEUU	2012
NCT02016508	AMD	ABMSC	Intravitreal injection	-	1	Unknown	I / II	Egypt	2013
NCT02024269	AMD	AASC	Intravitreal injection	-	-	Withdrawn	I	EEUU	2013
NCT00787722	Neuromielitis óptica	AHSC	Intravenous	-	10	Recruiting	I	EEUU	2008
NCT01364246	Neuromielitis óptica	UC-MSC	Intravenous	-	20	Unknown	I / II	China	2010
NCT01339455	Neuromielitis óptica	AHSC	Intravenous	-	3	Ongoing	I / II	Canada	2011
NCT02249676	Neuromielitis óptica	ABMMSC	Intravenous	2×10^6 cells/kg	15	Recruiting	II	China	2014
NCT02638714	Optic nerve atrophy	AHSC	-	-	100	Ongoing	I / II	Jordania	2013
NCT01834079	Optic nerve atrophy	ABMSC	Intrathecal	10×10^7 cells/dose	24	Recruiting	I / II	India	2014
ChiCTR-TRC-14005093	Traumatic optic neuropathy	UC-MSC	Endonasal	-	70	Recruiting	I / II	China	2014
NCT02330978	Glaucoma	ABMMSC	Intravitreal injection	1×10^6 cells/0.1 mL	10	Recruiting	I	Brasil	2014
NCT02144103	Glaucoma	AASC	Subtenon injection	0.5 mL	16	Enrolling by invitation	I	Russia	2014
NCT01920867[5]	Retinal diseases, Macular degeneration, HRD, OND, glaucoma	ABMSC	Retrobulbar, subtenon, intravenous, intravitreal and intraocular injection	1.2×10^{12} cells/15 mL	300	Recruiting	I	Estados Unidos	2013

Last search performed in Clinicaltrials.gov and the International Clinical Trials Registry Platform, 18 May 2016. [1]Case reported[22]; [2]Case reported[23]; [3]Case reported[30]; [4]Case reported[28]; [5]Case reported[36,37]. ABMSC: Autologous bone-marrow stem cells; ABMMSC: Autologous bone-marrow mesenchymal stem cells; ASMSC: Autologous stromal mesenchymal stem cells; AASC: Autologous adipose stem cells; AHSC: Autologous hematopoietic stem cells; UC-MSC: Umbilical cord mesenchymal stem cells; AMD: Age-related macular degeneration; DR: Diabetic retinopathy; HRD: Hereditary retinal diseases; OND: Optic nerve diseases; RP: Retinitis pigmentosa; VO: Vein occlusions.

Thus, new approaches like stem cell therapy are needed.

The use of bone marrow derived stem cells (BMDSC) therapy for the DR has been evaluated[28,29] and there are five ongoing clinical trials (NCT01518842, IRCT 201111291414N29, NCT01736059, ChiCTR-ONC-16008055 and NCT01920867) (Table 1). In relation to this therapy for the AMD, it has been evaluated in four (4) ongoing clinical trials (NCT02016508, NCT01

920867, NCT01736059 y NCT01518127). One of them (NCT01736059) has published results in the AMD patients[30]. Bone marrow stem cells used in these clinical trials was harvested from the patient's own iliac crest (autologous use) with an average final volume of 50 mL (20-100 mL). Then, mononuclear cells were separated by Ficoll-gradient centrifugation. The dose of cells is between 2×10^4-1.8×10^8 suspended in 0.1 mL buffered saline solution. A trial using adipose derived stems cells (ADSC) has been withdrawn prior to enrollment (NCT02024269), however they don't explain the reasons.

Results of stem cell-treatment for the DR are limited to the report on two patients. A 43-year-old patient with very advanced atrophy of the retina and optic nerve caused by the DR and vision limited to defective light perception, after cell treatment patient have improvement but no signs of any side-effects, such as inflammation or infection[28]. The other reports a patient with macular oedema associated with macular ischemia, and describe the decrease of macular oedema and the improvement of retinal function after intravitreal injection of BMDSC[29].

Moreover, the only clinical results of MSCs therapy for the AMD[30] describes two patients who start from a visual acuity (VA) of 20/200. After intravitreal injection, they had an improvement with its new VA of 20/80 and 20/160. The patient with VA 20/80 kept it during first six months and the other patient with VA 20/160 worsened to its initial state of 20/200. A slight growth of extrafoveal geographic atrophy in both eyes of both patients was detected by fluorescein angiography. The results of electroretinography showed a slight worsening of the macular function of both eyes that could be attributed to the disease progression. In analysis by OCT hyperdense deposits were evident within the retinal layers after a month of therapy that correspond in size with $CD34^+$ cells, however, more studies are needed to prove whether it corresponds to intraretinal incorporation of $CD34^+$ cells. The results suggest that this cell therapy in patients with the AMD, especially in advanced stages, would not stop the progression[30].

Clinical trials of MSCs for optic neuropathies

Optic neuropathies are characterized by damage to the optic nerve and they can be due to various causes, such as glaucoma, autoimmune diseases, inflammation, infections, traumas, ischemia or compression. Glaucoma is the most common cause of optic nerve-related visual loss in adults, followed by nonarteritic anterior ischaemic optic neuropathy (NAION)[31]. The treatment for glaucoma is based on drugs and surgery that reduce intraocular pressure, whereas there is no treatment for NAION, nor to reverse the process nor for its recurrence[32]. Traumatic optic neuropathy is a cause of severe visual loss and it has no reliable treatment[33]. Neuromyelitis optica, also known as Devic's disease, is an autoimmune, demylienating disorder which causes optic neuritis. Its prevalence is about 1-3/100000[34]. Nowadays neuromyelitis optica treatment is based in corticosteroids and plasma exchange for the acute attacks and immunosuppressant drugs for the maintenance therapy[35].

Currently, there are two clinical trials at phase Ⅰ using MSCs to treat glaucoma (NCT02330978 and NCT02144103), both of them are recruiting patients at the moment. One of them is being held at Medical School Ribeirao Preto, University of São Paulo, Brazil (NCT02330978), and the other one in Burnasyan Federal Medical Biophysical Center, Russia (NCT02144103). The Brazilian one uses an intravitreal injection of 10^6 autologous bone marrow derived mesenchymal stem cells (BMMSCs) to assess the safety of the procedure and how it improves visual field and visual acuity. The Russian one uses a sub Tenon administration of autologous adipose-derived regenerative cells that have been extracted from the patient's front abdominal wall. There are still no published results of these studies.

In the SCOTS clinical trial (NCT01920867), held at the Johns Hopkins Hospital, United States, there is one case reported of autoimmune optic neuropathy[36]. They made a vitrectomy and intra-optic injection of autologous bone marrow stem cells (BMSCs) in one patient's eye and retrobulbar, sub Tenon and intravitreal injection in the other eye, improving the visual acuity, macular thickness and fast retinal nerve fiber layer thickness. In this clinical trial there is also a case reported of idiopathic bilateral optic neuritis[37]. The patient received a retrobulbar injection, sub Tenon injection and intravitreal injection of autologous BMSCs for the right eye (OD), and vitrectomy and direct intra-optic nerve injection of autologous BMSCs for the left eye (OS), followed by intravenous infusion. After this procedure, there was an improvement in visual acuity in both eyes and remained stable at the 12 mo post-operative[37].

For neuromyelitis optica there is one active clinical trial at Foothills Medical Centre, University of Calgary, Canada (NCT01339455), two recruiting patients at Northwestern University, United States (NCT00787722), one ongoing clinical trial in Tianjin Medical University General Hospital, China (NCT02249676), and one with unknown status at Nanjing University Medical College Affiliated Drum Tower Hospital, China (NCT01364246). Most of them, active and recruiting clinical trials, use immunosuppressive treatment followed by an autologous hematopoietic stem cells transplantation. While the Nanjing University uses human umbilical cord mesenchymal stem cells transplantation. In this clinical trial (NCT01364246), 5 patients were followed for 18 mo including evaluation of Expanded Disability Status Scale (EDSS) levels, clinical course, magnetic resonance imaging (MRI) characteristics and adverse events. and they reported an improvement in the symptoms and signs of neuromyelitis optica in four out of five patients treated[38]. There is another clinical trial for secondary progressive multiple sclerosis with evidence of optic nerve involvement (NCT00395200), in which patients were treated with autologous bone marrow stem cells transplantation and that resulted in an increase in visual acuity, visual evoked response latency, and optic nerve

area[39]. Some individual cases with neuromyelitis optica treated with allogeneic hematopoietic stem cells have been reported[40].

Traumatic optic neuropathy is being studied in a clinical trial in China, by the Cell Biotherapy Center, Daping Hospital, Third Military Medical University (ChiCTR-TRC-14005093). Currently, they are recruiting patients and will use human umbilical cord derived mesenchymal stem cells transplantation. There are still no results.

There are also clinical trials for optic neuropathies, without considering what caused it. One of them is currently active (NCT02638714) and is held by Stem Cells of Arabia, Jordan. The patients will be treated with a transplantation of purified adult autologous bone marrow derived $CD34^+$, $CD133^+$, and $CD271^+$ stem cells due to their diverse potentialities to differentiate into specific functional cell types to regenerate damaged optic nerves, supporting tissues and vasculature. They will use clinical-grade purification system (CliniMACS) and Microbeads to purify the target cell populations. There is another clinical trial on optic atrophy, currently recruiting patients (NCT01834079) in Chaitanya Hospital in Pune, India. Patients will receive three intrathecal injections of 100 million autologous bone marrow derived mononuclear cells per dose at intervals of 7 d. There are no results posted yet of these studies.

DISCUSSION

Advances in the knowledge of neuroprotective, immunomodulative and regenerative properties of MSCs are continuously generated by several preclinical studies *in vitro* and *in vivo* in animal models of various neurodegenerative diseases, including optic nerve and retinal diseases. It has given the opportunity to perform the translation of treatment approaches to the clinical practice. Since 2008, several first steps, projecting new treatment approaches, have been taken regarding the use of cell therapy in patients with neurodegenerative pathologies of optic nerve and retina. It is about Phase Ⅰ or Ⅰ/Ⅱ clinical trials, which have as main objective the safety assessment of MSCs using various routes of administration, where the main route used is the intravitreal injection.

Nevertheless, of the 24 clinical trials registered on clinicaltrials.gov, there are only 2 clinical trials finished, 3 are ongoing, 15 are in recruiting patients phase, 3 are in unknown state and 1 clinical trial has been withdrawn without knowing the reasons for this decision. Most of the results published to date, are reduced to 6 cases reported in various retinal/optic nerve pathologies, their number of patients is very low, and these are exceptional cases, so, there is not enough evidence to get any valid and scientific conclusion.

Furthermore, most of these clinical trials use autologous cells, obtaining by bone marrow aspirates, so the final content to be administered is a concentrate of mononuclear cells, containing a very small percentage of MSCs (0.1%)[15], only four clinical trials use a specific concentration of MSCs without added another cell type. It is surprising that, although MSCs derived from adipose tissue are easier to obtain and in a higher concentration[17], there are only 2 clinical trials using this cell type, and one of them has been withdrawn without explanation. Regarding the use of allogenic MSCs, is limited to 2 clinical trials, which use MSCs derived from umbilical cord, however, it is not known whether their patients will receive immunosuppressive therapy.

Regarding to cell dose used in various clinical trials, there is a great variation from one to another. There is no consensus regarding the calculation of cell dose for the use of these cells through intravitreal injection. The clinical trials which use mononuclear cells aspirate, the doses are usually high (between 3×10^6 cells/0.1 mL and 30×10^6 cells/0.1 mL), whereas clinical trials using a concentrated purified of MSCs, doses are lower (1×10^6 cells/0.1 mL). However, the information collected by clinical trials.gov and the International Clinical Trials Registry Platform not specify the cell dose calculation or the cell production process.

CONCLUSION

It is important to know the development of cell therapy in relation to its use in the clinical practice. However, it is also important to recognize that, there is still a long way to go to reach clinical trials phase Ⅲ-Ⅳ. One of the factors necessary to move forward is to establish unified criteria for the dose to be used, another important factor is the use of only MSCs without another cells added, because MSCs are immunoprivileged cells, and do not produce rejection. It is also important to use more frequently allogeneic MSC associated with cryopreservation processes. It can be the key to a better bioavailability of these cells, getting greater advantages of MSCs derived from adipose tissue, which are easier in obtaining and production. Therefore, it is necessary to continue preclinical and clinical studies to improve this new therapeutic tool.

Limitations

Most of the clinical trials using MSCs are in Ⅰ/Ⅱ phase, recruiting patients or ongoing. The information available in clinicaltrials.gov about the procedure obtaining cells or the dose used in each clinical trial is not described in all cases. Hence, there are not enough published results to have scientific evidence about the use of these cells in retinal and optic nerve diseases.

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