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A new approach in the treatment of retinopathies and optic nerve atrophy using mesenchymal stem cells

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Abstract

Background: The tissue engineering is the evolving science that combines cells, biomaterials and biochemical factors aimed at restoring, maintaining and substituting different types of tissue. An important role is played by the use of the stem cells in various fields of medicine, including ophthalmology, namely in cases of retinopathies and optic nerve atrophy.
Conclusions: Current treatment of the optic nerve atrophy is based on the etiological causes or late complications. Considering the availability of advanced therapies, stem cell therapy offers a new approach in the treatment of the atrophy of the optic nerve. Being easy to harvest and cultivate, mesenchymal stem cells are most commonly used in regenerative medicine, they can be induced to differentiate into cartilage, tendons, adipose tissue and other cell lines. Mesenchymal stem cell harvesting has no ethical issues compared to embryonic stem cell harvesting. The major histocompatibility factor II is not expressed on the surface of mesenchymal stem cells, and this great advantage allows their use in autologous or allogenic form. Mesenchymal stem cells produce growth factors with paracrine action that are thought to activate endogenous repair mechanisms, due to these properties mesenchymal stem cells have been used in several clinical studies in optic nerve disorders where immunomodulatory and neuroprotective properties have been demonstrated. All of the properties mentioned above stand for the clinical use of mesenchymal stem cells in case of optic nerve atrophy.
Key words: stem cells, retinopathy, optic nerve atrophy.

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Introduction

The retinal diseases and the optic nerve atrophy are more frequent causes of decreased visual acuity and blindness [1]. There are multiple causes of the retinopathies and of the optic nerve atrophy: inflammatory and vascular pathologies of the optic nerve and retina, glaucoma, atherosclerosis of the vessels of the head and neck, pathologies of the central nervous system, intoxications of various etiology, hereditary diseases. Optic nerve atrophy is caused by the irreversible apoptosis of retinal neuronal cells. In the absence of curative treatment for these degenerative pathologies, current therapies focus mainly on the etiological cause or late complications. However, most treatments have low specificity. Given the availability of advanced therapies, stem cell-based therapies offer a new approach in the treatment of retinal and optic nerve pathologies [2].

Being easily harvested and cultured, mesenchymal stem cells are the most widely used stem cells in regenerative medicine [3]. Mesenchymal stem cells can be induced to differentiate into bone, cartilage, fat, tendon and other cell lineages, depending on conditions and growth factors [4, 5]. Mesenchymal stem cells are easy to isolate and expand rapidly after a short rest period [6].

The harvesting of mesenchymal stem cells is free of ethical problems, compared to the harvesting of embryonic stem cells [7]. It is also considered that mesenchymal stem cells are "immunoprivileged" because the Major Histocompatibility Factor II is not expressed on their surface [8], this great advantage allows the use of mesenchymal stem cells in autologous or allogeneic form [9].

Furthermore, mesenchymal stem cells produce several growth factors with paracrine action that are believed to activate endogenous repair mechanisms [10-14]. Due to these properties, mesenchymal stem cells have been used in several preclinical studies in optic nerve disorders and retinopathies, where immunomodulatory, neuroprotective and tissue repair properties have been demonstrated [15-17]. These properties support the clinical use of mesenchymal stem cells. In neurodegenerative disorders, the use of mesenchymal stem cells is an opportunity for tissue repair and regeneration [18].

This synthesis aims to review the published clinical studies on the indications, dosage and results of stem cell therapy in case of retinal pathology and in case of optic nerve pathology.

Results and discussion

The material was synthesized based on clinical studies in which mesenchymal stem cells were used in cases of retinopathies and optic nerve atrophy.

For the advanced selection of bibliographic sources, the following filters were applied: stem and eye, optic nerve atrophy, retina, the materials published from 2004 to 2022 were analyzed. After examining the titles of the articles found, only papers containing relevant information on the use of stem cells in retinopathies and optic nerve atrophy were considered. The information was systematized, highlighting both the contemporary aspects of the use of mesenchymal stem cells in retinal and optic nerve pathologies, as well as the results obtained following the performance of published clinical studies. In the analyzed clinical studies, autologous stem cells from bone marrow or adipose tissue were used, the main route of administration of mesenchymal stem cells was intravitreal injection, followed by intravenous administration.

As a result of analyzing the information identified by the Google Search engine, from the PubMed databases according to the search criteria, 127 articles and 24 clinical trials were found on clinicaltrials.gov that address the problem of retinopathies and optic nerve atrophy. After the primary review of the titles, 40 publications and 24 clinical trials were considered relevant and were included in this review article.

Retinitis pigmentosa is one of the main hereditary degenerative retinal diseases, affecting 1 in 4000 people. Retinitis pigmentosa is characterized by low arteriolar diameter and pallor of the papilla [19-20]. Stargardt disease is the most common form of hereditary juvenile macular degeneration. The worldwide prevalence is 1 in 10000 people [21].

Initially, patients present a decrease in central vision. The pathology is defined by the accumulation of lipofuscin in the apical area in the cells of the pigmented epithelium of the retina. The clinical manifestations are a decrease in visual acuity up to blindness, secondary choroidal neovascularization with a gradual bilateral decrease in vision [21].

There are currently 9 clinical studies using mesenchymal stem cells to treat this type of retinal dystrophy (6 for retinitis pigmentosa, 2 for Stargardt disease and retinitis pigmentosa, 1 for retinitis pigmentosa and other pathologies).

Although most clinical trials are in the recruitment phase, there are two completed trials that include retinitis pigmentosa. Both performed at Hospital das Clinicas, Sao Paolo. (NCT01068561 phase I, NCT01560715 phase II). Autologous MSCs harvested from the bone marrow were used, which were injected intravitreally containing 10x106 cells/0.1ml. MSCs were obtained by aspirating 10 ml of bone marrow tissue from the posterior iliac crest and were separated by Ficoll-Hypaque centrifugation.

In the NCT01068561 study (phase I) there is one reported case [22]. The patient presented macular edema associated with retinitis pigmentosa. The macular edema resolved within seven days after mesenchymal stem cells injection, and the result was maintained for one month, a fact demonstrated by optical coherence tomography. It was concluded that adult stem cells have the ability to restore the ocular blood barrier due to paracrine effects or through an osmotic gradient that allows the absorption of macular edema [22].

The NCT01560715 study (phase II) is completed, from the published results it was concluded that therapy with intravitreal administration of mesenchymal stem cells can improve the quality of life of patients with retinitis pigmentosa.

The results were evaluated with a test that assesses the quality of life related to sight (NEI VFG-25) before therapy, 3 and 12 months later. There was considerable improvement 3 months after treatment, while at 12 months there was no significant difference from baseline [23].

A phase I clinical trial with autologous mesenchymal stem cells from bone marrow in retinitis pigmentosa patients is underway at the Virgen Hospital in Arrixaca, Spain. This clinical trial continues to recruit patients.

There are some clinical studies involving patients with diabetic retinopathy and age-related macular degeneration. Diabetic retinopathy is a prevalent microvascular complication in diabetes and remains the main cause of blindness in able-bodied people (20-74 years). Approximately 30% of all patients with diabetes have signs of diabetic retinopathy, and 30% of them may have sight-threatening retinopathy (severe retinopathy or macular edema) [24, 25]. Current standard treatment for the management of these disorders is mainly based on laser therapy or antiangiogenic therapy, both of which are associated with unavoidable ocular and systemic effects [25]. Age-related macular degeneration is a chronic, progressive retinal pathology and a leading cause of vision loss worldwide in people older than 60 years [26]. The prevalence of this pathology is increasing as an exponential consequence of the aging of the population. Significant progress has been made in the management of age-related macular degeneration with the introduction of anti-angiogenesis therapy [27]. However, antiangiogenic treatment does not stop progression or treat age-related macular degeneration. Thus, new approaches in the treatment of age-related macular degeneration, such as stem cell therapy, are needed. The use of bone marrow-derived stem cell therapy in diabetic retinopathy has been evaluated [28, 29] and there are five ongoing clinical trials (NCT01518842, IRCT 201111291414N29, NCT01736059, ChiCTR-ONC-16008055 and NCT01920867), and in case of age-related macular degeneration there are four clinical trials (NCT02016508, NCT01920867, NCT01736059 and NCT01518127). Following the NCT01736059 study, results were published in patients with age-related macular degeneration [30]. In these clinical trials, bone marrow mesenchymal stem cells were collected from the patient's

iliac crest in an average volume of 50 ml. Then, mononucleated cells were separated by Ficoll gradient centrifugation. The dose of cells was between $2x10^4$-$1.8x10^8$ suspended in 0.1 ml of buffered saline. A clinical study using stem cells obtained from adipose tissue was withdrawn, the reasons were not elucidated (NCT02024269).

The results of stem cell treatment for diabetic retinopathy are limited to the report of two patients. A 43-year-old patient with advanced retinal and optic nerve atrophy caused by diabetic retinopathy, vision – limited to defective light perception. After treatment with mesenchymal stem cells the patient showed improvement and did not show side effects such as inflammation or infection [28]. In this study, a patient with macular edema associated with macular ischemia is included, after intravitreal injection of mesenchymal stem cells from the bone marrow, the decrease of macular edema and the improvement of retinal function were described [29]. Clinical results of mesenchymal stem cell therapy in age-related macular degeneration describe two patients with 20/200 visual acuity. After intravitreal injection of mesenchymal stem cells, visual acuity changed to 20/80 and 20/160. In the patient with visual acuity 20/80, the result was maintained for 6 months. In the case of the second patient with visual acuity 20/160, it returned to the initial values of 20/200. After performing fluorescein angiography, in the case of both patients, a slight increase in extrafoveal geographic atrophy was detected in both eyes, a fact that can be attributed to disease progression [24].

Optic neuropathies are characterized by the degeneration of the optic nerve and can be caused by pathologies, such as glaucoma, autoimmune diseases, infections, trauma, ischemia or infections. In adults, glaucoma is the most common cause of vision loss followed by nonarteritic anterior ischemic optic neuropathy [30-32]. Traumatic optic neuropathy is a cause of vision loss and currently has no reliable treatment [33]. Neuromyelitis optica or Devic's disease is an autoimmune demyelinating pathology that causes optic neuritis, prevalence 1-3 per 100000 [31, 34]. Currently, the treatment consists of administration of corticosteroids and immunosuppressive drugs [32, 35].

There are two phase I clinical trials using mesenchymal stem cells to treat glaucoma (NCT02330978 and NCT02144103). Both clinical trials are currently recruiting patients. One clinical trial is taking place at the University of Sao Paolo, Brazil (NCT02330978), and the other at the Burnasyan Federal Medical Center, Russian Federation (NCT02144103). In the clinical study carried out in Brazil, autologous mesenchymal stem cells, derived from the bone marrow, are injected intravitreally. In the clinical study carried out in the Russian Federation, autologous mesenchymal stem cells are introduced into the subtenon space. Mesenchymal stem cells are taken from the adipose tissue on the anterior abdominal wall. There are currently no published data from these studies. In the SCOTS clinical trial (NCT01920867), conducted at the John Hopkins Hospital, United States of America, a case of autoimmune optic neuropathy was reported [36]. The patient underwent vitrectomy and injection of autologous mesenchymal stem cells from the bone marrow in one eye, and injection of autologous mesenchymal stem cells from the retrobulbar, subtenon and intravitreal bone marrow was performed in the other eye. Thus, the improvement of visual acuity was noticed.

A case of idiopathic optic neuropathy was also included in this study. The patient, in the right eye, was injected with autologous MSCs from the bone marrow in the retrobulbar, subtenon and intravitreal space, and in the left eye vitrectomy was performed, followed by direct injection of autologous MSC cells from the bone marrow, followed by the intravenous injection of them. After this procedure, a considerable improvement in visual acuity was observed, and the result was maintained for 12 months postoperatively [36].

For neuromyelitis optica there is an active clinical trial at Foothills Medical Center, University of Calgary, Canada (NCT01339455), two patients recruited at Northwestern University, United States (NCT00787722), an ongoing clinical trial in Tianjin Medical University General Hospital, China (NCT02249676) and one with unknown status at the Affiliated Hospital of Nanjing University, China (NCT01364246). Most active and recruitment clinical trials use immunosuppressive treatment followed by autologous hematopoietic stem cell transplantation. Nanjing University uses human umbilical cord mesenchymal stem cell transplantation. In this clinical trial (NCT01364246), 5 patients were followed for 18 months, including assessment of the Extended Disability Status Scale (EDSS), clinical course, magnetic resonance imaging (MRI) features, and adverse events, and reported an improvement in symptoms and signs of neuromyelitis optica in four out of five treated patients [34]. There is another clinical trial for secondary progressive multiple sclerosis with evidence of optic nerve damage (NCT00395200), in which patients were treated with autologous bone marrow stem cell transplantation, which resulted in an increase in visual acuity [35]. Some individual cases of neuromyelitis optica treated with allogeneic hematopoietic stem cells have also been reported.

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

Advances in the knowledge of the neuroprotective, immunomodulatory and regenerative properties of MSC are continuously generated by several *in vitro* and *in vivo* preclinical studies on animal models with different neurodegenerative diseases, including optic nerve atrophy and retinopathies. This fact gave the possibility to carry out the translation of treatment approaches in clinical practice.

Since 2008, several steps have been taken, designing new treatment approaches, regarding the use of cell therapy in patients with degenerative pathologies of the optic nerve and retina. These are phase I or I/II clinical trials, whose main objective is to evaluate the safety of mesenchymal stem cells using different routes of administration, in which the main route used is intravitreal injection. However, of the 24 clinical trials registered on clinicaltrials.gov, there are only 2 completed clinical trials, 3 ongoing, 15 in patient recruitment, 3 in unknown status, and 1 clinical trial has been withdrawn without informing about the reasons for this decision. Most of the results published so far are reduced to 6 cases reported in various retinopathies and optic nerve atrophy, but the number of patients is small.

Moreover, most of these clinical trials use autologous cells, obtained by bone marrow aspirates, so that the final content to be administered is a concentrate of mononuclear cells, which contains a very small percentage of mesenchymal stem cells (0.1%) [15], only four clinical trials used a specific concentration of mesenchymal stem cells without adding another cell type. Surprisingly, although adipose tissue-derived MSCs are easier to obtain and in higher concentration [17], there are only 2 clinical trials using this type of cells and one of them was withdrawn without explanation. Regarding the use of allogeneic MSCs, it is limited to 2 clinical trials, using umbilical cord-derived MSCs, however, it is not known whether patients will receive immunosuppressive therapy. Regarding the cell dose used in different clinical trials, there is a large variation from one to another. There is no consensus regarding the calculation of cell dose for the use of these cells by intravitreal injection. In clinical trials using aspirated mononuclear cells, the doses are usually high (between 3×10^6 cells / 0.1 ml and 30×10^6 cells/0.1 ml), while in clinical trials using a purified concentrate of mesenchymal stem cells the doses are smaller (1×10^6cells/0.1 ml). However, the information collected by clinicaltrials.gov and the international clinical trial registration platform does not specify the cell dose calculation.

Conclusions

It is important to know the development of cell therapy in relation to its use in clinical practice. However, it is also important to recognize that there is still a long way to go to reach phase III-IV clinical trials. One of the factors needed to proceed is the establishment of unified criteria for the dose to be used, another important factor is the use of only CSM without the addition of other cells, mesenchymal stem cells are immunoprivileged cells. Therefore, it is necessary to continue preclinical and clinical studies to improve this new therapeutic tool.

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TT conducted literature review, obtained raw data and wrote the manuscript; AP and VN revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The project was approved by the Research Ethics Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (Protocol No14, 15.03.2019).

Conflict of interests
No competing interests were disclosed.