MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt22311

Major clinical findings of cellular therapy for intravitreal use in ischemic retinopathy and macular degeneration: a systematic review

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DOI: https://doi.org/10.54448/mdnt22311
Received: 05-15-2022; Revised: 07-25-2022; Accepted: 08-09-2022; Published: 08-24-2022; MedNEXT-id: e22311

Abstract

Introduction: In the scenario of eye diseases, diabetic retinopathy and retinal vein occlusion are the two most common ischemic retinopathies in the world. Ischemia is caused by retinal vascular diseases due to decreased blood perfusion and the appearance of areas of retinal non-perfusion. Also, age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in people over 65 years of age in industrialized countries. By 2020, around 200 million people will be affected by AMD worldwide. **Objective:** the present systematic review study aimed to highlight the main clinical findings of the treatment of ischemic retinopathy and age-related macular degeneration through cell therapy with bone marrow stem cells. **Methods:** The rules of the Systematic Review-PRISMA Platform were followed. The search was carried out from March 2022 to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** It was found 235 articles involving retinitis pigmentosa, macular degeneration, and bone marrow stem cell therapy. A total of 51 were fully evaluated and 28 studies were included and developed in a systematic review in the results field. The symmetrical Funnel Plot does not suggest a risk of bias between the small sample size studies. It was concluded that intravitreal injection of bone marrow-derived stem cells in a patient with retinal vascular occlusion sequelae demonstrated that the procedure is feasible and safe to be performed in humans as there were no signs of infection, inflammation, or development of intraocular tumor formation. Also, neurotrophic effects correlate with vasculature preservation, suggesting that bone marrow-derived stem cells can be used in the treatment of diseases such as retinal degenerations and vasculopathy that currently lack effective treatment. The authors concluded that stem cells can protect retinal cells from degeneration and also suggested that they were able to replace some types of lost retinal neurons.

Keywords: Eye diseases. Ischemic retinopathies. Age-related macular degeneration. Cellular therapy. Bone Marrow stem cell.

Introduction

In the scenario of eye diseases, diabetic retinopathy and retinal vein occlusion (RVO) are the two most common ischemic retinopathies in the world [1-3]. Ischemia is caused by retinal vascular diseases due to decreased blood perfusion and the appearance of areas of retinal non-perfusion. The ischemic retina produces vascular endothelial growth factor (VEGF) and high concentrations of VEGF in the vitreous can further aggravate retinal ischemia and hypoxia (edema and even vision loss) [4].

RVO consists of central retinal vein occlusion and branch retinal vein occlusion, leading to macular edema (MS), hemorrhage, the appearance of retinal non-perfusion and even causing anterior segment neovascularization, especially in RVO, which is similar to what was found in DR [1,2]. When the macular region is affected by retinal ischemia, patients have varying degrees of macular ischemia. In this sense, anti-vascular endothelial growth factor (anti-VEGF) therapies have been recommended as a first-line treatment for

diabetic retinopathy and RVO, which improves retinal ischemia and hypoxia by blocking the VEGF pathway [4].

In addition, age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in people over 65 years of age in industrialized countries. By 2020, around 200 million people will be affected by AMD worldwide. The disease accounts for approximately 9% of all cases of blindness [5,6].

Hereditary retinal dystrophies (degenerations) affect 1 in 3500 individuals and are characterized by progressive night blindness, visual field loss, optic atrophy, arteriolar attenuation, altered vascular permeability, and progressive central vision loss with complete blindness [7]. The molecular genetic analysis of these diseases has identified over 110 different genes that have been identified so far responsible for triggering these entities [8,9]. Many of these mutations are associated with enzymatic and structural components of the phototransduction machinery including rhodopsin [10], cGMP phosphodiesterase [11], peripherin [12], and RPE65 [13].

Despite these observations, there is still no effective treatment to delay the progression or reverse these diseases [13-15]. Adult bone marrow is known to contain a population of stem cells (HSCs) that can be divided into lineage-positive (Lin+) and lineage-negative (Lin-) subpopulations according to their potential to differentiate and form blood elements [16]. The Lin- subpopulation contains a variety of progenitor cells including those capable of becoming vascular endothelial cells [17].

These endothelial progenitor cells (EPC) mobilize from the bone marrow and respond to a variety of signaling molecules and can reach sites of angiogenesis in the ischemic peripheral vasculature, myocardium, or areas of induced ocular injury [18-25].

Therefore, the present systematic review study aimed to highlight the main clinical findings of the treatment of ischemic retinopathy and age-related macular degeneration through cell therapy with bone marrow stem cells.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis: www.prisma-statement.org/) were followed.

Data Sources And Research Strategy

The search for this systematic review was based on the keywords (MeSH Terms): "*Eye diseases. Ischemic retinopathies. Age-related macular degeneration. Cellular therapy. Bone Marrow stem cell*". The search was carried out from March 2022 to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, the combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality And Risk Of Bias

The quality of the studies was based on the GRADE instrument. The quality of scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

It was found 235 articles involving retinitis pigmentosa, macular degeneration, and bone marrow stem cell therapy. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the topic of this article, leaving a total of 87 articles. Of these articles, a total of 51 were fully evaluated and 28 studies were included and developed in a systematic review in the results field. A total of 128 studies did not meet the GRADE (**Figure 1**), and 36 studies were excluded because they had a high risk of bias. Considering the Cochrane tool for risk of bias, the overall assessment did not result in significant risk of bias studies (**Figure 2**).

Figure 2 presents the results of the risk of bias in the studies using the Funnel Plot (Effect Size - Cohen's Test). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). The graph showed symmetrical behavior, not suggesting a significant risk of bias in the studies with small sample sizes that are shown at the bottom of the graph.

Age-Related Macular Degeneration

Age-related macular degeneration is responsible for severe visual loss and is the leading cause of legal blindness in patients over 50 years of age in most developed countries [1,2].

Age-related macular degeneration is a degenerative eye disease characterized clinically, in the early stages, by changes in the retinal pigment epithelium and the presence of drusen, without clinically significant impairment of visual function in most cases

Figure 1. Article selection (Systematic Review, N=28 studies).

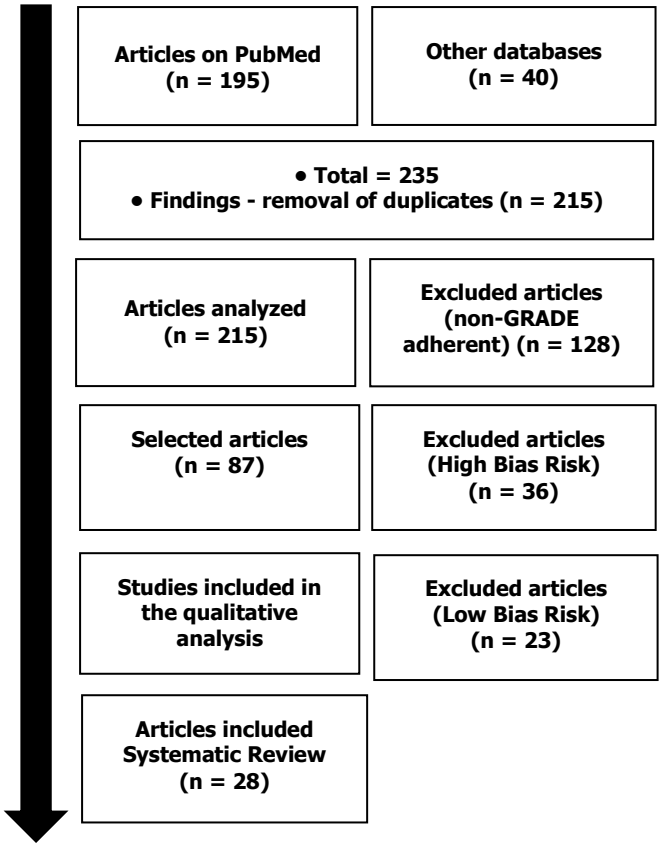
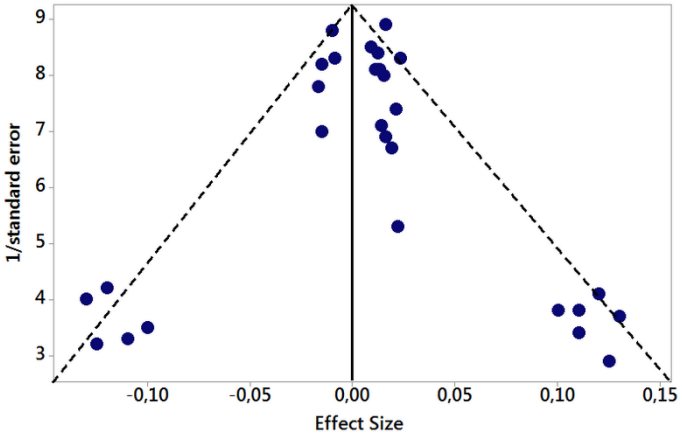


Figure 2. The symmetrical Funnel Plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph (N=28 studies).



until central or extensive forms of atrophy occur. geographic or formation of choroidal neovascularization, subretinal exudation, and macular fibrous scar with marked loss of vision [3,4].

There is an increase in prevalence at older ages; thus, in the study by Ferris et al (27), 1.6% of age-related macular degeneration was diagnosed in the population between 52 and 64 years of age and 27.9% in patients over 75 years of age. The dry, atrophic, geographic, or non-neovascular form, is characterized by the presence of an atrophic area, geographic contours in the macular area, where the great vessels of the choroid are observed and the absence of a choroidal neovascular membrane (CNM), occurs in the vast majority of cases (79%) of age-related macular degeneration has a slow evolution.

When the choroidal neovascular membrane and/or disciform scar accompanies these background abnormalities, we have the "wet", exudative, disciform, or neovascular form that occurs in 15.3% of age-related macular degeneration cases [28-32]. This form, although it has a lower prevalence than the dry form, is responsible for about 80% of blindness from a legal point of view due to age-related macular degeneration [33-35].

There is no effective therapy for the atrophic form of AMD, which affects more than 90% of patients with this condition [36]. For the remaining 10%, laser photocoagulation therapy, photodynamic therapy with verteporfin, and intravitreal antiangiogenics allow relative stabilization of vision in about 2/3 of eyes, despite high costs [27-29]. Therefore, prevention is the best strategy, since AMD reduces the individual's ability to perform daily activities that require clear central vision, and is associated with a high risk of depression and Social dependence, which represents an important socioeconomic impact on the patient state [31].

Ischemic Retinopathy

Visual loss resulting from ischemic retinopathy is due to loss of blood supply to the inner retina. Among the diseases that can lead to retinal ischemia, the most serious is retinal arterial occlusion. The ophthalmic artery is the first branch of the internal carotid artery and enters the orbit below the optic nerve through the optic canal. The central retinal artery is the first intraorbital branch of the ophthalmic artery, which enters 8-15mm behind the eyeball to supply the retina. Branches of the short posterior ciliary arteries from the ophthalmic artery supply the choroid. Anatomical variants include cilioretinal branches of the short posterior ciliary artery, which provide additional supply to the macula from the choroidal circulation (the cilioretinal artery is present in approximately 14% of the population) [32-37].

Another condition that leads to retinal ischemia with visual loss is an arteriolar and capillary occlusion in severe and terminal stages of diabetic retinopathy and retinal venous occlusion. In these advanced stages of these conditions, there is retinal ischemia including the macular region with irreversible visual loss. The treatments available for these conditions only aim to reduce the complications resulting from the formation of choroidal neovascularization, but without the possibility

of functional improvement [36,37].

To date, there is no treatment available to functionally restore or improve vision in patients with ischemic retinopathy [35-38]. Clinical use of cell therapy in retinal diseases. Recently Jonas et al. [39,40] performed an intravitreal injection of bone marrow-derived stem cells in a patient with retinal vascular occlusion sequelae and demonstrated that the procedure is feasible and safe to be performed in humans as there were no signs of infection, inflammation or development of intraocular tumor formation.

Regarding the clinical use of cell therapy in retinal diseases, Jonas et al. [39] performed intravitreal injection of bone marrow-derived stem cells in a patient with retinal vascular occlusion sequelae and demonstrated that the procedure is feasible and safe to perform in humans as there were no signs of infection, inflammation, or development of intraocular tumor formation. However, it is imperative to standardize in Brazil and the world the procedures for the preparation and application of intravitreal cells from the stroma-medullary fraction for the treatment of retinopathies [40-43].

As an example, Otani et al. [44] reported that Lin-HSCs injected directly into the eye could activate astrocytes and participate in the development of angiogenesis in neonatal rats or adult rats with injury-induced neovascularization. These authors also reported that bone marrow-derived stem cells (Lin-HSCs), when injected intravitreal 2 weeks postnatally, could completely prevent retinal vascular degeneration seen in mouse models of retinal degeneration (type rd1 and rd 10).

In this same study, it was observed that this vascular rescue correlated with a neuronal rescue. It was shown that the inner nuclear layer remained close to normal and the outer nuclear layer containing the photoreceptors was significantly preserved with salvage of cells containing predominantly cones. In the electroretinographic (ERG) study, responses were present in the rats that underwent treatment and absent responses in the control group [45]. Another finding in this study was that the analysis of the genomes of the treated and untreated eyes revealed an increase in the expression of apoptotic genes. These findings demonstrate that neurotrophic effects correlate with vasculature preservation, suggesting that bone marrow-derived stem cells can be used in the treatment of diseases such as retinal degenerations and vasculopathy that currently lack effective treatment [45].

Furthermore, Chiou et al. [46] isolated and cultured bone marrow-derived stem cells with differentiation potential. After 2 and 4 weeks of culture in hepatocyte induction media, adipogenic and chondrogenic, stem cells were found to differentiate into cartilage, bone, adipocytes, and hepatocyte-like cells. It was also demonstrated in this study that these cells could differentiate into neural precursor cells, as well as their plasticity in differentiating into retinal cells and photoreceptor lineages, suggesting their potential for the treatment of retinal degenerations.

In addition, Banin et al. [47] studied the potential of using embryonic stem cells in the treatment of retinal degenerative diseases and their potential to differentiate into retinal cells, and their survival and integration after transplantation. They observed that the cells showed differentiation into retinal cells and that the subretinal medium for placing the cells was the one that offered the best result compared to the intravitreal and subretinal medium in rats. Another important finding in this study was the non-development of teratoma in any sample. The authors, therefore, suggested the use of stem cells in the treatment of degenerative diseases of the retina.

Besides, Meyer et al. [48,49] demonstrated that embryonic stem cells after intravitreal implantation incorporated into the retinal layers, undergoing differentiation, assuming the appearance of retinal neurons in morphological terms. In addition to this finding, they demonstrated in this study that samples that received the stem cells showed a greater survival of retinal cells, especially photoreceptors. The authors concluded that stem cells can protect retinal cells from degeneration and also suggested that they were able to replace some types of lost retinal neurons.

Das et al. [50], in a review on the use of stem cells to treat degenerative diseases of the retina, highlighted the rationale of using this therapeutic modality as an alternative with possibilities not only to increase the survival of degenerated cells, but also the repositioning of the cells damaged by the degenerative process.

Finally, Minamino et al. [51] demonstrated that bone marrow-derived stem cells can differentiate into retinal cells and described a new option for the intravitreal injection of stem cells technique by previously performing laser photocoagulation of the retina. In the group that received photocoagulation, stem cells survived longer and also showed greater specificity for binding to retinal cells.

Conclusion

It was concluded that intravitreal injection of bone marrow-derived stem cells in a patient with retinal vascular occlusion sequelae demonstrated that the procedure is feasible and safe to be performed in humans as there were no signs of infection,

inflammation, or development of intraocular tumor formation. Also, neurotrophic effects correlate with vasculature preservation, suggesting that bone marrow-derived stem cells can be used in the treatment of diseases such as retinal degenerations and vasculopathy that currently lack effective treatment. The authors concluded that stem cells can protect retinal cells from degeneration and also suggested that they were able to replace some types of lost retinal neurons.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethics approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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