Review Article

Regenerative mechanisms of stem cells and their clinical applications for degenerative eye diseases

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There are different types of treatment for eye diseases. Although the majority of eye diseases are curable with primary treatments and surgery, some of degenerative eye damages need regeneration that is not gained by conventional procedures. Stem cells, such as mesenchymal stem cells, human embryonic stem cell-derived retinal pigmented epithelium, and inducible pluripotent stem cells, are now considered one of the most important and safe methods for regeneration of various damaged tissues or organs. However, how will stem cell therapy contribute to regeneration and overcome degenerative eye diseases? This review discusses the regenerative mechanisms, clinical applications, and advantages of different types of stem cells for restoring degenerative eye diseases.

Key words: Eye diseases, mesenchymal stem cells, regeneration, stem cells

How to cite this article: Zhang B, Gao S, Liu S, Gong X, Wu J, Zhang Y, *et al.* Regenerative mechanisms of stem cells and their clinical applications for degenerative eye diseases. J Res Med Sci 2024;29:42.

INTRODUCTION

Treatment of eye diseases, especially retinal degenerative disorders, has remained a significant concern for ophthalmologists. Clinically, there is no effective therapeutic procedure to restore some types of eye diseases, such as loss of visual system connectivity in retinal degenerative diseases. Therefore, there is an essential need to find a replacement method for effective and safe treatment of eye diseases with minimal side effects. Stem cells become a promising technology for the treatment of eye disease. These unspecialized cells have the potential to be differentiated into any cell of an organism.[1] The high capacity for self-renewal and differentiation has made stem cells a unique candidate for regenerative therapies. Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are among the most promising and popular stem cells for cell-based therapies.[2] They are multipotent stem cells with multilinear differentiation ability, high migratory and immunomodulatory capacities, and low immunogenicity activity.[3] A growing number of *in vivo* and *in vitro* studies have reported the potential of MSCs to restore some types of eye diseases.[4,5] Therefore, MSCs are considered a promising and cutting-edge technology to help patients with some types of eye diseases. There are a limited number of articles that reported the effect of stem cells, particularly MSCs, and their mechanisms for treating eye diseases. In the following sections, we will review stem cell types based on their origin and differentiation abilities, general mechanisms of MSCs' action in the repairing process, and their potential for eye disease treatment.

METHODOLOGY

Relevant literature was searched through databases

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_358_23

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Submitted: 03-Jun-2023; **Revised:** 14-Jan-2024; **Accepted:** 18-Mar-2024; **Published:** 30-Jul-2024

such as PubMed and Scopus with the following keywords: stem cells, regenerative medicine, eye diseases, stem cell transplantation, and regenerative therapy for eye diseases. As a result, 96 relevant papers that evaluated the mechanistic and therapeutic approach of stem cells for eye diseases during 1995–2020 were selected.

MESENCHYMAL STEM CELL TYPES

There are several types of stem cells found in human tissues according to their origin and developmental potential, including adult stem cells (ASCs), germline stem cells, and embryonic stem cells (ESCs).[6] Stem cells can also be divided into five main groups based on their differentiation ability, including unipotent, oligopotent, multipotent, pluripotent, and totipotent stem cells.[1] While unipotent stem cells (e.g., dermatophytes) are only able to form one cell type, totipotent stem cells (e.g., zygote) have the capacity to divide and differentiate into all cells of the body organs and extraembryonic tissues. Pluripotent stem cells (e.g., inducible pluripotent stem cells [iPSCs] and ESCs) can form cells of all germ layers, but they do not differentiate into extraembryonic tissues (e.g., placenta).[1,7] Oligopotent stem cells (e.g., myeloid stem cells) can differentiate into several cell types. In addition, multipotent cells, such as MSCs and hematopoietic stem cells (HSCs), can differentiate into a narrower spectrum of specific cells.

ECSs are a group of pluripotent stem cells with high differentiation ability to almost all cell types. However, they are not suitable for cell-based therapy due to ethical issues and the risk of tumorigenic potential.[8] Human iPSCs are a type of pluripotent stem cells that can be generated directly from a somatic cell by reprogramming. Although the generation of patient-specific iPSCs and their engineered differentiation into target cells is a promising technology for disease modeling and drug screening, high potential tumorigenesis of iPSCs is the biggest obstacle for clinic applications.[9,10]

MSCs are a class of ASCs and the most promising stem cell types for cell-based therapies because they are free from teratoma formation and ethical issues.[11] MSCs have high self-renewal and differentiation capacities to produce many types of specialized cells of the body, such as heart muscle cells, osteoblasts, liver cells, chondroblasts, endothelial cells, lung epithelial cells, adipocytes, and nerve cells.[2,12,13] Although these cells can be isolated from nearly all tissues or organs, MSCs originated from adipose tissue (Ad-MSCs), bone marrow (BM-MSCs), umbilical cord (UC-MSCs), and human amniotic membrane/fluid (hA-MSCs) are the most common form of stem cells that have been considered for eye disease treatment.[14] These cells can be divided into several main groups, including MSCs, vascular precursor cells (i.e., $CD34^+$ cells, hematopoietic cells, or endothelial progenitor cells), and adipose stromal cells [Figure 1].

Bone marrow was thought to be the only source of stem cells until the 1990s.[15] It is a rich source of MSCs and other stem cell types, such as HSCs. BM-MSCs are the most common

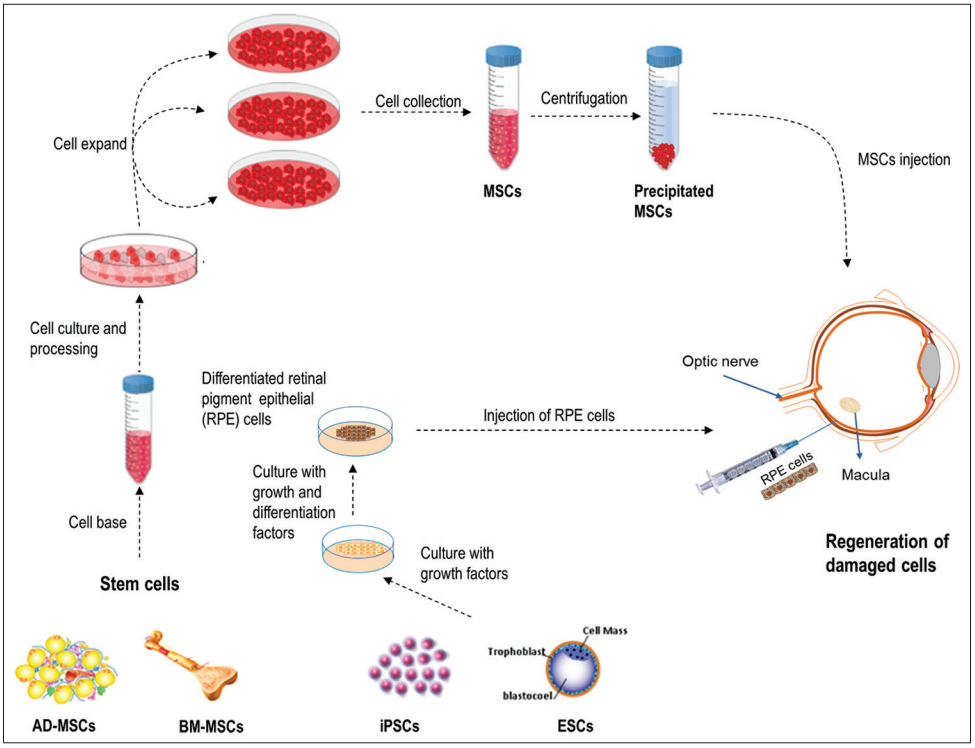

Figure 1: Schematic cell processing for stem cell therapy for eye diseases

cell source to control HSPCs homeostasis and bone tissue regeneration.[16] Recent evidence has revealed that these cells not only play fundamental roles in hematopoiesis regulation but also have the capability of differentiating into a wide variety of cells (e.g., cardiomyocytes, skeletal muscle cells, chondrocytes, osteoblasts, tenocytes, adipocytes, and endothelial cells).[17,18] Given the high self-renewal and differentiation capacities of BM-MSCs, they are now considered an ideal candidate for eye disease treatment.

Adipose tissues are a reliable source of MSCs that can be used for cell-based therapies. Ad-MSCs exhibit the same typical characteristics as BM-MSCs but have some advantages over BM-MSCs. Firstly, Ad-MSC isolation is easier and cheaper and requires minimally invasive procedures than BM-MSCs.[19] Secondly, higher yields of Ad-MSCs can be obtained from subcutaneous sources. Thirdly, Ad-MSCs may be more suitable for allogenic transplantation than BM-MSCs because they can maintain their phenotype longer in culture and exhibit a greater proliferative capacity.[20,21]

Furthermore, autologous Ad-MSCs are not associated with graft rejection after transplantation. In this respect, Ad-MSCs can also differentiate into all three developmental germ layers, including endoderm, mesoderm, and ectoderm.[22] For these reasons, Ad-MSCs have become the most attractive source of MSCs for regenerative medicine.

The UC is another interesting source of MSCs because isolating MSCs from Wharton's jelly or UC blood is painless and noninvasive compared to MSCs harvested from other tissues.[23] Moreover, UC-MSCs can be collected abundantly from discarded UC materials without ethical concerns and harm to the mother or infant. Recent evidence has shown that UC-MSCs not only have low tumorigenicity or immunogenicity properties but also display higher proliferation capacities than other types of MSCs.[24] These cells can maintain their phenotype and genetic stability even after a long-term *in vitro* culture. They also have a prolonged survival rate and a high ability to modulate immune responses after transplantation. Some studies demonstrated the long-term safety of UC-MSCs' engraftment.[25] For these reasons, human UC-MSCs have become an interesting source of stem cells for treating different diseases.

The human placenta, especially the amniotic fluid and amniotic membrane, can be considered a rich and alternative source of MSCs for clinical applications. The process of hA-MSCs' collection is easy, safe, and painless, with minimized ethical issues.[26] Similar to UC-MSCs, hA-MSCs are going to be popular in the context of clinical application because of their noninvasive isolation producers, high immunomodulatory potential, large-scale supply, rapidly increasing differentiation properties, genome stability, nontumorigenic behavior, and minimized ethical concerns.[27-29]

MECHANISMS OF MESENCHYMAL STEM CELL HOMING AND REGENERATIVE ACTIVITIES

Mesenchymal stem cells' migration

Tissue repair and maintenance are the most essential functions of MSCs that induce the recomposition of injured organs. They are a rich source of various growth factors and cytokines, making them unique for cell therapy in regenerative medicine.[30] The migratory capacity or homing ability of MSCs is the first and critical stage of the regeneration process. They can migrate into injured sites, differentiate into their local components, and help tissue regeneration by secreting chemokines, cytokines, and growth factors.[31] According to previous studies, various chemical factors, chemokines, and growth factors are involved in MSCs' delivery into the injured tissue sites. The stromal-derived factor-1 (SDF-1)/CXC motif chemokine receptor-4 (CXCR-4) axis is critical for MSCs' recruitment to the site of injury.[32] CXCR-4 expression increases in response to increased concentration of SDF-1.[33] The expression of these proteins is enhanced after tissue injury.[34,35] Some *in vitro* and *in vivo* studies reported that overexpression of SDF-1 and CXC-4 proteins significantly promotes the migration of MSCs and tissue regeneration.[33,36] These data indicate that upregulation of SDF-1 and CXC-4 proteins may be a potential strategy to enhance the migratory capacity of MSCs and accelerate tissue regenerating efficiency. There are also other factors, such as osteopontin (OPN), C-C chemokine receptors, and growth factors that regulate MSCs' migration and homing to the site of injury.[31,37] These factors are overexpressed in response to an injury and inflammation. Research has shown that overexpression of OPN is associated with increased migration and survival ability of MSCs.[38] Moreover, OPN increases integrin β1 expression in MSCs and consequently promotes MSCs' migration through the ligation to integrin β1.[39] Growth factors not only induce MSCs' migration to the site of injury but also play a critical role in regulating their proliferation and differentiation. Currently, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor β1 (TGF-β1), hepatocyte growth factor (HGF), platelet-derived growth factor, HGF and placental growth factor (PGF) are the best-known growth factors involved in tissue repair.[31] Furthermore, some mechanical factors (e.g. matrix stiffness, microgravity, and shear stress) regulate MSCs' migration to the site of injury. Thus, the microenvironment of MSCs plays a crucial role in their migration. Abnormal changes in the extracellular matrix (ECM) are an alarm for cellular damages that release signals to recruit circulating MSCs.[40]

Mechanisms of mesenchymal stem cells in tissue repairing

After migrating MSCs into injured tissues, they promote regenerating damaged tissues through direct differentiation to local cells or paracrine activities. MSCs' activities in the repairing process are mediated via cell-cell interaction, secretion of various angiogenic factors, promotion of the survival of the resident cells, niche regulation, modulation of immune responses, and activating tissue-specific progenitor cells.[41,42] Overall, angiogenesis, differentiation abilities, immunomodulatory and anti-apoptotic properties, and anti-fibrotic activities are important underlying mechanisms by which MSCs induce tissue regeneration.

Angiogenesis capacity

Angiogenesis is among the main mechanisms of stem cell activity. This mechanism is associated with neovascularization and expression of angiogenic factors that interact with endothelial cells and stimulate their proliferation, tissue healing, or regeneration.[43] The cross-talk between stem cells and endothelial cells is an important step in angiogenesis. Recent evidence has shown that MSC-derived proangiogenic factors promote the angiogenic behavior of endothelial cells after binding to the relevant receptors on the endothelial cells.[44] This interaction induces or inhibits different intracellular signaling pathways associated with promoting angiogenesis.[45] Stem cells secrete extracellular vesicles, multiple cytokines, and growth factors that accelerate angiogenesis and local cell proliferation and subsequently help tissue repair.[43] VEGF, fibroblast growth factor (FGF), HGF, PGF, monocyte chemotactic protein 1, angiopoietin-1 (Ang1), Ang2, and SDF-1 are among the most important proangiogenic factors secreted by MSCs. These factors play a critical role in blood vessel formation and the regeneration process. These paracrine factors also recruit and activate resident or circulating stem cells and progenitor cells, improving blood vessel formation to support damaged tissues.[46]

Differentiation abilities

The self-renewal and differential abilities of stem cells to produce various cell types make them an invaluable candidate for tissue regeneration. Stem cells directly differentiate into mature endothelial cells and improve tissue regeneration. Besides, they stimulate resident progenitor cells to proliferate and differentiate into mature cells by secreting various growth factors and cytokines.[47] Nevertheless, the paracrine effect of MSCs in the regeneration process seems more significant than their direct differentiation regarding the limited survival and differentiation ability of MSCs posttransplantation at the lesion site or ischemic microenvironment.[48] Research has shown that MSCs-derived growth factors effectively stimulate microvascular endothelial cell proliferation and differentiation and are responsible for therapeutic effects.[17] In support of this hypothesis, some studies showed that various cell types respond to growth factors released from MSCs. Therefore, they regulate various cellular responses (e.g., proliferation, migration, survival, and gene expression).[49-51]

Immunomodulatory properties

The immunomodulatory ability of stem cells is a key mechanism of their action in modulating the inflammatory niche and the regeneration process. Although inflammation is necessary for tissue repair and regeneration,[52] uncontrolled accumulation of leukocytes or immune cells at the injury site may be associated with elevated secretion of pro-inflammatory mediators, overproduction of reactive oxygen species (ROS), oxidative damage, and apoptosis of adjacent cells. Therefore, modulation of the immune response at the injury site is a key factor for tissue healing and regeneration. Studies show that MSCs exhibit their immunomodulatory effect by direct cell-to-cell contact. For this purpose, they also secrete immunosuppressive mediators such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), soluble human leukocyte antigen G5, programmed death-ligand 1, nitric oxide, inducible nitric oxide synthase, IL-10, IL-6, heme oxygenase-1, and growth factors (e.g. TGF-β and HGF).[53] MSCs can interact with almost all the innate and adaptive immune system cells, such as natural killer cells, monocytes or macrophages, dendritic cells, neutrophils, and T- and B-lymphocytes, and modulate their responses.[54,55] Cytokines and growth factors secreted by MSCs can suppress immune responses by inhibiting the proliferation and maturation of B- and T-cells and dendritic cells and enhancing the generation of regulatory B- and T-cells.[56,57] MSCs also promote the activity and migration of other immunoregulatory cells, such as myeloid cells, to the injured site and subsequently increase the immunosuppression and sustain the immunomodulatory ability of MSCs for a longer period. Besides, MSCs stimulate the differentiation of macrophages toward anti-inflammatory M2 phenotype via the secretion of metabolic reprogramming factors such as IDO following exposure to IFN-γ,[58] PGE2, IL-1, and overexpression of CD40L on cell surfaces.[59,60] Activated M2 macrophages are a main source of anti-inflammatory cytokine IL-10, while the M1 phenotype generates high levels of pro-inflammatory cytokines.[61]

Anti-apoptotic properties

In addition to the anti-inflammatory and immunomodulatory effects of MSCs, they protect normal cells against early apoptosis at the injury site. However, the exact mechanisms of the anti-apoptotic properties of MSCs are not well understood. Some studies have demonstrated that MSCs inhibit cellular apoptosis and restore tissue homeostasis through secreting B-cell lymphoma 2 (BCL2), various

growth factors (e.g., VEGF, HGF, IGF, TGF-β, and FGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF).[62-64] A recent study has reported that local transplantation of MSCs inhibited apoptosis of corneal cells by increasing the expression of the anti-apoptotic molecule *Bcl-2* and attenuating the expression of pro-apoptotic genes *Bax* and *p53*.[65] Furthermore, MSCs' transplantation significantly inhibited the production of pro-inflammatory cytokines and molecules associated with endoplasmic reticulum stress and apoptosis, including *Atf4*, *Bip*, and *p21*.[65] It has been demonstrated that *in vitro* treatment with amniotic epithelial stem cell conditioned medium decreases the expression of caspase-3, caspase-8, Bax, and Annexin V proteins and increases the relative BCL-2/Bax ratio in oligodendrocyte cells.[66] Therefore, these data indicate that apoptosis inhibition may be the main mechanism of MSCs' action in regenerative therapies.

Anti-fibrotic effect

Stem cells also promote tissue regeneration by suppressing fibrosis. Fibrosis, a phenomenon associated with proliferation and accumulation of fibroblasts and ECM formation, is a pathologic condition accompanied by overproduction of ROS, oxidative stress, inflammatory lesions, morphological damage, and apoptosis of adjacent cells.[67] Recent studies have demonstrated that MSCs can migrate to the site of injury or inflammation and reduce collagen deposition and myofibroblast differentiation via inhibiting pro-inflammatory factors, SMAD/TGF-β, and PPARγ/Wnt/β-catenin signal pathways.[68,69] In addition, molecules and growth factors secreted by stem cells enhance autophagosome activity in accumulated fibroblasts and reduce fibrosis by inhibiting the PI3K/mTORC1 pathway.[70] Research has shown that Ad-MSCs' transplantation limits pulmonary fibrosis and preserves tissue architecture by enhancing HGF and PGE2 secretion and minimizing TNF-α and TGF-β1 in host cells.[71,72] Intravenous injection of MB-MSCs has also significantly decreased skeletal muscle fibrosis and accumulation of calcium/necrotic fibers primarily via secreting matrix metalloproteinase-1 as a main anti-fibrotic protein. Based on the mentioned points, MSCs play a critical role in tissue repair and regeneration through multiple mechanisms, including immunomodulation via anti-inflammatory properties, mitigation of ROS production and oxidative stress, induction of angiogenesis, suppression of apoptosis and fibrosis, activation of local progenitor stem cells, and direct differentiation to adult cells.

CLINICAL TRIALS FOR REGENERATIVE THERAPY OF EYE DISEASES BY STEM CELLS

Recent experimental and clinical studies have reported the potential role of stem cells, especially MSCs, in the regeneration or treatment of eye diseases.[73,74] For example, Otani *et al*.[75] found that HSCs containing endothelial precursors stabilize and rescue retinal blood vessels in mice with retinal degenerative disease. Another study showed that BM-MSCs' transplantation significantly reduced mice's apoptotic outer nuclear layer cells.[76] In another recent study, pluripotent BM-MSCs not only preserved rod and cone photoreceptors but also improved visual function in rats with retinitis pigmentosa (RP) disease.[77] These findings indicate that stem cells are a promising tool for treating and regenerating eye diseases, especially degenerative diseases. However, clinical applications of stem cells for eye diseases depend on stem cell types and type and the severity of the eye diseases. Several studies recommended using HSCs in treating eye-related diseases [Table 1]. Autoimmune-related retinopathy (ARRON) is an inflammatory rare disease in which immune cells attack proteins in the retina, affect the optic nerve, and subsequently cause vision loss. The disease may affect the nerves in the ear and cause reduced hearing or

Table 1: Clinical use of autologous hematopoietic stem cells in eye diseases

Disease	Country	Years	Phase	Evaluation after cell therapy	NCT number
ARRON	USA	2006–2013[1]	I	Standard Snellen acuity clinical testing and improvement visual fields are done by using Humphrey automated machine with 30-2 program or using kinetic visual fields on the Goldmann perimeter (time frame: 5 years after transplant)	NCT00278486
Retina cell	Brazil	2012–2018[2]	I	Safety and efficacy of intravitreal injection of auto-BMHSCs. Change in size of FAZ at 48 weeks. Change in central foveal thickness and BCVA at 48 weeks. Not show any side effect	NCT01518842
ER	USA	2008–2018	III	The difference between the number of observed and expected failures is approximately normally distributed with independent increments and may be used for interim monitoring using standard group sequential boundaries. The toxicity-associated death rate and the percentage of patients for whom an adequate yield of stem cells cannot be harvested will be monitored across all treatment groups collectively. Toxicities will be descriptively summarized	NCT00554788
NMO	Canada	2011–2017	I/II	The proportion of surviving patients who are relapse-free at three years after transplant. Evaluated change in RNFL by OCT over trial	NCT01339455

HSCTs=Hematopoietic stem cell transplantation; RNFL=Retinal nerve fiber layer; NMO=Neuromyelitis optica; ARRON=Autoimmune-related retinopathy; ER=Extraocular retinoblastoma; BCVA=Best-corrected visual acuity; BMHSCs=Bone marrow-derived hematopoietic stem cells; OCT=Optical coherence tomography; NCT=National Clinical Trial number

Table 2: Clinical use of autologous bone marrow-derived mesenchymal stem cells in eye diseases

Disease	Locations	Years	Phase	Evaluation after cell therapy	NCT number (clinicaltrials.gov)
ONA	India	2013–2016	I/II	Reduction in degeneration of the optic nerve with improvement in vision. Increase in visual function. Improvement in idiopathic intracranial hypertension	NCT01834079
AMD	Egypt	2013–2015	I/II	Assessment of visual function changes from the baseline. assessment will include change in the mean of BCVA, OCT imaging, fluorescein angiography, slit-lamp examination with fundus photography, electroretinographic evidence (mfERG) showing enhanced activity in the location	NCT02016508
AMD	Brazil	2012–2017	I	ETDRS VA change. Primary safety outcome included VA loss of 15 or more ETDRS letters after treatment	NCT01518127
AG	Brazil	2014–2016	I	Primary outcomes are types and severity of adverse effects. Secondary outcomes are changes in visual field, VA, OCT, and retinal ganglion cells' function	NCT02330978
ONA	Jordan	2013–2019[3]	I/II	Reduction in degeneration of the optic nerve using the visual field assessment with the Humphrey automated and Goldmann manual perimeters. Improvement in visual function using the documentation of VA using the Snellen chart	NCT02638714
ONA	USA Emirates	2016–2020	II	Visual fields will be evaluated with automated perimetry during postprocedure visits as needed and specifically at 6 months and 12 months. Visual fields are a key measurement in patients with peripheral vision loss. OCT imaging revealed thickness of the retinal nerve fiber layer, the optic nerve and/or macula during the postprocedure visits as needed and specifically at 6 and 12 months - if available	NCT03011541
NAION	USA	2013–2018[4]	II	Following therapy in SCOTS, 80% of patients experienced improvement in Snellen binocular vision with 20% remaining stable; 73.6% of eyes treated gained vision and 15.9% remained stable in the postoperative period. There was an average of 3.53 Snellen lines of vision improvement per eye with an average 22.74% and maximum 83.3% improvement in LogMAR acuity per eye. The average LogMAR change in treated eyes was a gain of 0.364. Improvements typically manifested no later than 6 months postprocedure	NCT01920867
RP	Jordan	2014–2020[5]	I/II	Evolution of ETDRS VA change. Quality of life: Questionnaire VFQ-25. Color vision: Ishihara color test	NCT02709876
RP	Brazil	2011–2013[6]	II	There was a statistically significant improvement ($P<0.05$) in the quality of life of patients 3 months after treatment, whereas by the 12th month there was no statistically significant difference from baseline	NCT01560715
RP	Brazil	2010–2011[7]	I	Intravitreal injection of autologous BM-derived mononuclear cells in eyes with advanced retinitis pigmentosa or cone-rod dystrophy was associated with nondetectable structural or functional toxicity over a period of 10 months	NCT01068561
RP	Thailand	2012–2017	I	Change from baseline in laser flare, cell measurements, and visual function tests. No side effect after cell therapy	NCT01531348
RP	Spain	2014–2017	I	Rate of serious and nonserious adverse events related to the use of BM mononuclear cells in patients with RP. Evaluated quality of life: Questionnaire VFQ-25, VA, IOP, ERG, and VEP after 12 months	NCT02280135
Retinopathy	USA	2012–2019[8,9]	I	Therapy was well tolerated with no intraocular inflammation or hyperproliferation. BCVA and full-field ERG showed no worsening after 6 months. Clinical examination also showed no worsening during follow-up except among age-related macular degeneration subjects in whom mild progression of GA was noted in both the study eye and contralateral eye at 6-month follow-up, concurrent with some possible decline on multifocal ERG and microperimetry. Cellular *in vivo* imaging using adaptive optics OCT showed changes suggestive of new cellular incorporation into the macula of the hereditary macular degeneration study eye	NCT01736059
BD	Iran	2007–2013[10]	I	Results showed a total failure of the procedure, essentially due to the late and advanced state of vasculitis. However, the autoimmune/inflammatory reaction was greatly controlled by the procedure	NCT00550498

VA=Visual acuity; BCVA=Best-corrected VA; ETDRS=Early treatment diabetic retinopathy study; OCT=Optical coherence tomography; FERG=Flash electroretinogram; FVEP=Flash visual evoked potentials; VFQ-25=Visual Function Questionnaire-25; ONA=Optic nerve atrophy; NAION=Nonarteritic ischemic optic neuropathy; RP=Retinitis pigmentosa; BD=Behcet's disease; AG=Advanced glaucoma; AMD=Age-related macular degeneration; MFERG=Multifocal electroretinogram; BM=Bone marrow; LogMAR=Logarithm of the minimum angle of resolution; IOP=Intraocular pressure; ERG=Electroretinogram; VEP=Visual evoked potentials; GA=Geographic atrophy; NCT=National Clinical Trial number

deafness. A recent study has revealed that HSCs can mitigate the progression of ARRON syndrome.[78] Macular edema associated with ischemia diabetic maculopathy or ischemia central retinal vein occlusion is another eye disease without any proven treatment for this condition. Siqueira *et al*.[79] showed the safety and efficacy of intravitreal injection of autologous BM-derived hematopoietic stem cells (BM-HSCs) in patients with retinal dystrophy. Another clinical trial study reported that intravitreal injection of BM-HSCs improved macular edema in patients with RP.[80] Further clinical trials investigating the safety and efficacy of intravitreal auto-BMHSCs are ongoing. In this respect, the results of these trials will facilitate an understanding of the potential role of auto-BMHSCs for ischemic retinopathy.[81,82] Table 1 summarizes some clinical trials that used autologous HSCs in eye diseases.

Recent evidence has also reported the therapeutic effect of BM-MSCs in different eye diseases [Table 2]. For instance, some ongoing clinical trials have been focused on using BM-MSCs for the treatment of eye diseases such as optic nerve atrophy (ONA), RP, Behcet's disease, advanced glaucoma, and age-related macular degeneration [Table 2]. ONA is a serious condition in which the optic nerve and subsequently central and peripheral vision are harmfully affected.[83] ONA may occur as a result of multiple conditions, including optic neuritis, tumors or aneurysms, toxic and nutritional neuropathies, and trauma, and in response to systemic diseases such as diabetes. Symptoms of ONA vary diversely but mainly include blurred vision and a reduction in optic sharpness and color visualization. Since ONA is an irreversible process, current medical strategies focus on finding the underlying cause, preventing further vision loss, and protecting the other healthy eye. In this regard, a single-arm and single-center trial study has been conducted to assess the safety and efficacy of BMSCs through a 24-month follow-up period.[84] Anticipated outcomes of this study were defined as an overall improvement of vision, restoration of functions to damaged optic nerves, and improvement in patients' quality of life.

In another clinical trial, a patient whose normal visual acuity decreased to between 20/350 and 20/400 in the right eye and to 20/70 in the left eye underwent a right eye vitrectomy with injection of BM-MSCs into the optic nerve of the right eye and retrobulbar and subtenon, followed by intravitreal injection of BM-MSCs in the left eye. After 15-month BM-MSCs posttransplantation, the patient's visual acuity had improved to 20/150 in the right eye and 20/20 in the left eye. Furthermore, bilateral visual fields improved significantly in this patient. Macular thickness and fast retinal nerve fiber layer thickness were significantly improved at 3 and 6 months after cell therapy. The patient reduced her mycophenolate dose from 1500 mg/day to 500 mg/day and required no steroid therapy during the 15-month follow-up.[85] Stem cells are also considered another treatment approach for RP. Studies in animal models of RP revealed that subretinal injection of BM-MSCs may delay degenerative changes of photoreceptor cells. A single-arm and single-center trial investigated the safety and efficacy of purified adult autologous BM-MSCs through a 48-month follow-up period on RP patients. These cell types have the potential to differentiate into specific functional cell types to regenerate damaged retinal tissue. Clinical-grade purification systems are also available to purify the cell populations in clinically approved methods[86] [Table 2].

Data from several clinical trials have also shown that Ad-MSCs' transplantation in patients is safe and nontoxic.

Table 3: Clinical use of autologous adipose-derived mesenchymal stem cell in eye diseases

Disease	Locations	Years	Phase	Evaluation after cell therapy	NCT number
GN	Russian	2014–2019	I/II	Evaluated types, probability, and severity of treatment-emergent SAEs and SARs. Changes in structures of fundus of the eye assessed by funduscopy: Changes of configuration and size of optic disc, neuroretinal rim thinning, degree of optic disc pallor, hemorrhages on the optic nerve and retina, vascular changes, presence of degenerative changes of retina, optic disc drusen, edema, and retinal detachment	NCT02144103
NAION	Spain	2018–2020	II	Conjunctival hemorrhages, anterior chamber inflammation, changes in IOP, infectious endophthalmitis, vitreous inflammation, retinal detachment, choroidal detachment, corneal opacities, lens opacities, neovascularization, macular edema, or any other adverse event that may appear	NCT03173638
NMO	China	2013–2014	II	Compare EDSS, Annual relapse rate, Lesion load and a RNFL change before and one year after MSC infusion	NCT02249676
CD	Lebanon	2015–2017	I	The BCVA will be measured in each postoperative visit to control any important decrease relative to the surgery. At each postoperative visit a measurement of Anterior surface topography of the transplanted cornea will be carried out to detect any abnormal evolution. At each postoperative visit, the corneal aspect relative to increase in irregular astigmatism will be evaluated by refraction measurement	NCT02932852

MSC=Mesenchymal stem cells; SAEs=Serious adverse events; SARs=Serious adverse reactions; GN=Glaucomatous neurodegeneration; RNFL=Retinal nerve fiber layer; MLD=Minimum linear diameter; NAION=Nonarteritic ischemic optic neuropathy; CD=Corneal diseases; MHs=Refractory macular holes; NMO=Neuromyelitis optica; BCVA=Best-corrected visual acuity; IOP=Intraocular pressure; NCT=National clinical trial number; EDSS=Expanded disability status scale

Table 4: Clinical use of human embryonic stem cell-derived retinal pigmented epithelium in eye diseases

Disease	Locations	Years	Phase	Evaluation after cell therapy	NCT number (clinicaltrials.gov)
ORT	Brazil	2015–2019	I/II	Incidence of surgical-related side effects: Retinal detachment, ocular inflammation, increase in IOP, infection (endophthalmitis), and loss of vision due to surgical-related complications. Incidence of side effects related to the treatment itself (injection and implantation of subretinal stem cell-related RPE). Inflammation/rejection cell migration/differentiation tumor formation proliferative vitreoretinopathy/retinal detachment implant migration	NCT02903576
dry-AMD	China	2017–2019	I/II	The safety and tolerance of transplantation of hESC-derived RPE will be considered safe: No above moderate adverse events or severe adverse events which related to transplantation of retinal pigment epithelial cells; Cells without infectious; No tumorigenicity. Through the clinical signs of subjects and laboratory examination to judge the tolerance, integrity, repellency of RPE cells, and monitoring the presence of local or systemic infection, and presence of metastatic tumor cells	NCT03046407
AMD	China	2016–2018	I/II	Patients with treatment-related adverse events caused by local rejection of implanted cells or systemic immunosuppression treatment. VA is reflected by number of ETDR letters participants can recognize. Retinal electrophysiological function is tested by FERG. Optic nerve function as assessed by FVEP. Local retinal function as assessed by MFERG	NCT02749734
dry-AMD	Korea	2016–2019	I	The transplantation of hESC-RPE cells will be considered safe in the absence of 1: Any grade 2 (NCI CTCAE V4.03) or greater adverse event related to the cell product 2: Any evidence that the cells are contaminated with an infectious agent. 3: Any evidence that the cells show tumorigenic potential. Best-corrected ETDRS VA scores. Structural evidence (OCT imaging, fluorescein angiography, autofluorescence photography, slit-lamp examination with fundus photography) that cells have been implanted in the correct location	NCT03305029
SMD	UK	2011–2017[11]	I/II	Focal areas of subretinal hyperpigmentation developed in all participants in a dose-dependent manner in the recipient retina and persisted after withdrawal of systemic immunosuppression. No evidence of uncontrolled proliferation or inflammatory responses. Improvements in BCVA in 4 participants either were unsustained or were matched by a similar improvement in the untreated contralateral eye. Microperimetry demonstrated no evidence of benefit at 12 months in the 12 participants	NCT01469832
SMD	USA	2011–2015[12]	I/II	There was no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue. Adverse events were associated with vitreoretinal surgery and immunosuppression. BCVA, monitored as part of the safety protocol, improved in ten eyes, improved or remained the same in seven eyes, and decreased by more than ten letters in one eye, whereas the untreated fellow eyes did not show similar improvements in VA. Vision-related quality-of-life measures increased for general and peripheral vision, and near and distance activities, improving by 16–25 points 3–12 months after transplantation in patients with atrophic age-related macular degeneration and 8–20 points in patients with Stargardt's macular dystrophy	NCT01345006
Dry ADM	USA	2011–2016[13,14]	I/II	The hESC-derived RPE cells showed no signs of hyperproliferation, tumorigenicity, ectopic tissue formation, or apparent rejection after 4 months. The future therapeutic goal will be to treat patients earlier in the disease processes, potentially increasing the likelihood of photoreceptor and central visual rescue	NCT01344993
Dry AMD	USA	2015–2018	I/II	No side effect after cell therapy. Comparison of product, procedure, and immunosuppression-related adverse events in the implanted eye to those experienced in the nontreated eye	NCT02590692
Dry AMD	UAS	2014–2018	I/II	Measurement of change in GA lesion area will be performed based on available imaging data by a central reading center. Change in VA will be measured by ETDRS chart	NCT02286089
SMD	Korea	2012–2015	I	Evidence show the successful engraftment of stem cell. The transplantation of hESC-derived RPE cells MA09-hRPE will be considered safe and tolerated in the absence of Any grade 2 (NCI grading system) or greater adverse event related to the cell product, any evidence that the cells are contaminated with an infectious agent, and any evidence that the cells show tumorigenic potential	NCT01625559

Contd...

Table 4: Contd...

Disease	Locations	Years	Phase	Evaluation after cell therapy	NCT number (clinicaltrials.gov)
SMD	USA	2012–2018[12]	I	This study provides the first evidence of the medium-term to long-term safety, graft survival, and possible biological activity of pluripotent stem cell progeny in individuals with any disease. results suggest that hESC-derived cells could provide a potentially safe new source of cells for the treatment of various unmet medical disorders requiring tissue repair or replacement	NCT02445612
AMD	USA	2012–2019	I	Safety assessed by AEs of special interest in regard to the investigational product. Evidence of unanticipated and persistent or increasing noninfectious ocular inflammation (e.g., vasculitis, retinitis, choroiditis, vitritis, pars planitis, anterior segment inflammation/uveitis)	NCT02463344
AMD	UK	2015–2019	I	Change in baseline in ETDRS BCVA - proportion of subjects with an improvement of 15 letters or more at week 24. No side effect after cell therapy	NCT01691261

VA=Visual acuity; AMD=Age-related macular degeneration; BCVA=Best-corrected VA; SMD=Stargardt's macular dystrophy; ETDRS=Early treatment diabetic retinopathy study; ORT=Outer retinal degeneration; hESC-RPE=Human embryonic stem cell-derived retinal pigmented epithelium; AEs=Adverse events; IOP=Intraocular pressure; GA=Geographic atrophy; FERG=Flash electroretinogram; FVEP=Flash visual evoked potential; MFERG=Multifocal electroretinogram; NCT=National Clinical Trial number; NCI CTCAE= National cancer institute common terminology criteria for adverse events

[2,87] Recent clinical trials have shown the therapeutic effect of BM-MSCs' transplantation in different eye diseases [Table 3]. A previous single-arm study used Ad-MSCs' transplantation for the treatment of glaucomatous neurodegeneration disease. Autologous adipose-derived regenerative cells (ADRCs) were extracted by Celution 800/CRS System from a portion of the fat harvested from the patient's front abdominal wall. ADRCs were administered one time into the subtenon space of the patient's eyeball.

Some clinical trials have evaluated the therapeutic effect of human embryonic stem cell-derived retinal pigmented epithelium (hESC-RPE) in eye diseases [Figure 1 and Table 4]. RP is a group of inherited retinal disorders characterized by progressive loss of photoreceptors, eventually leading to retina degeneration and atrophy. A recent nonrandomized clinical trial study has investigated the therapeutic effect of hESC-RPE transplantation in 12 patients with Stargardt's macular dystrophy. The patients were transplanted with sequential doses of hESC-RPE cells, starting at a dose of 50,000 cells transplanted and increasing to a maximum dose of 200,000 cells transplanted. Patients will be evaluated at 18, 24, 36, 48, and 60 months posttransplant. The follow-up will include obtaining information about ophthalmological findings and events of special interest as defined in the primary outcome. At the last visit of this follow-up study, whether at 60 months posttransplant or at early discontinuation, patients will be invited to participate in a life-long annual health survey under a separate protocol to monitor long-term safety further.[88]

Recent studies have also recommended MSC-derived exosomes (MSC-Exos) for treating eye diseases.[89] They have garnered a growing interest as novel therapeutic products in treating eye diseases. Similar to MSCs, they have strong immunomodulatory and anti-inflammatory properties. A growing number of studies have focused on the potential role of MSC-Exos in treating eye diseases such as glaucoma, retinal injury, optic neuropathy, diabetic retinopathy, and autoimmune uveitis. MSC-Exos have been recommended to treat other eye diseases, such as large and refractory macular holes (MHs).[90] For example, a clinical trial study revealed that MSC-Exos therapy is a useful and safe method for improving postsurgical visual outcomes in patients with MH.[90]

CONCLUSION

Findings from current and past clinical trials indicate that stem cell therapy is a promising and safe method to restore visual function in different eye diseases. Serious ocular side effects such as tumor formation and uncontrolled proliferation have not been observed. The reported improvements in visual function are encouraging and promising. However, larger future studies with longer follow-up periods are needed to determine where this treatment is applied.

Acknowledgments

The authors of this manuscript wish to express their thanks and appreciation to the Department of Ophthalmology at Qiqihar Medical University, China. This is a review article and there is no ethics number for this review.

Financial support and sponsorship

Science and technology plan Heilongjiang Provincial Health Commission (20230707020510) and Basic Scientific Research Projects of Colleges and Universities in Heilongjiang Province (2024-KYYWF-0893).

Conflicts of interest

There are no conflicts of interest.

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