STEM CELL TREATMENT IN DEGENERATIVE RETINAL AND OPTIC NERVE DISEASES

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Abstract: Use of stem cells in the treatment of retinal diseases is a new and popular topic in ophthalmology. Embryonic and bone marrow derived stem cells can be used for treatment. Age-related macular degeneration, Stargardt’s macular dystrophy and retinitis pigmentosa are common encountered retinal diseases causing progressive vision loss. The researches therefore mostly focus on these diseases which have no curative treatment modality in order to evaluate the efficacy of stem cell therapy. In this review, we aimed to present the results of the phase 1/2 clinical studies about stem cell treatments in eye diseases. Stem cell therapies are the rising trends in treatment of retinal diseases. Further clinical studies are required for standardization of the therapy and obtaining long-term data about the results and complications.

Key words: Optic nerve diseases, retinal diseases, stem cell therapy.

Introduction

Degenerative retinal diseases are among the main causes of irreversible vision loss. Most of these degenerative processes affect the outer retina, which include photoreceptors and retinal pigment epithelium (RPE). Most retinal diseases occur due to apoptosis of retinal neural cells or adjacent supporting tissue. The underlying mechanism of most diseases can be different but retinal degeneration is the end point (Strauss 2005). Although there is no effective treatment for these degenerative diseases, stem cell implantation, following the succesful results of experimental studies in recent years, is now available as a treatment option to restore visual function in these diseases (Lamba et al. 2009).

Type of Stem Cells in Ophthalmology

Stem cell is defined as a pluripotent or multipotent cell, which has the ability of self renewal and differentiation. These cells are capable of differentiating into other cell types of the body. They also have the potential to repair tissue and restore function after injury (Siqueira et al. 2010, Siqueira 2011). Adult stem cells, induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) are non-embryonic stem cells and have been widely used in the treatment of retinal diseases (Zarbin 2016).

Embryonic stem cells (ESCs) are special pluripotent cells derived from internal cell mass of the embryo (blastocyst). These cells have the capability to differentiate into other types of body cells. Although they are valuable in the treatment of transplantation in some diseases, their use is limited for various reasons. The process can lead to destroy or disaggregate embryos so it still continues to cause ethical concerns and is prohibited by law in many countries. However some studies showed that it is possible to obtain these cells without destroying the embryo (Chung et al. 2008).

Mesenchymal stem cells may be derived from many tissues such as bone marrow, fat, skin and cartilage. Bone marrow MSCs (BMMSCs) and adipose-derived MSCs (ADMSCs) are the most common type of stem cells that are used as a source of different retinal cells. These cells
are considered as multipotent cells, which can differentiate into many types of specialized cells in the body (Yu et al. 2007).

Induced pluripotent stem cells are pluripotent like ESCs and they can differentiate into other types of retinal cells. The process of IPSC production for therapy has a high cost and is achieved by application of long protocols (Alonso-Alonso & Srivastava 2015).

Cord blood stem cells are isolated in vitro from cord blood following delivery. Amniotic fluid stem cells are isolated in vitro from cells obtained from amniotic fluid (Zarbin 2016).

In recent years, there have been significant developments about stem cells. MSCs have the advantages of trophic support that allows slowing down of retinal cell degeneration and immunosuppression, but, on the other hand, they have low rates of cell migration and differentiation. Compared to BMSCs, ADMSCs have the advantages of easier harvest from donors, faster expansion, more protein secretion and higher immunomodulatory capacity. MCSs increase support to surrounding cells by secreting growth factors, show anti-apoptotic, anti-inflammatory, immunomodulatory and angiogenic effects. It is thought that various cytokines, growth factors and proteins, which are secreted by stem cells, can cause photoreceptor survival promotion. Thus, it could be useful to treat retinal diseases in their early stage (Jones et al. 2017, Tang et al. 2017, Öner 2018).

There are a number of advantages of stem cell applications in the eye. The amount of required stem cells is low which reduces the cost. The surgical technical is easy and the transplanted cells can be seen with the imaging methods used in clinical practice. The non-operated eye can be used as a control to evaluate the effect of the therapy. The eye is known as immun priviliged and long-term immunosuppressive treatment is not required after the implantation. The application of healthy stem cells in the place of degenerated retinal cells has promoted cell regeneration, creation of new intercellular connections, and improvement of visual function. Stem cells have the potential to differentiate into many cells in their environment, including the retinal neural cells and photoreceptors. Earlier experimental studies have shown that stem cells are very compatible with the retina and are able to adapt to Müller, amacrine, bipolar, horizontal and glial cells, and photoreceptors (Tucker et al. 2014, Whiting et al. 2015).

Retinal degeneration occurs in several forms, such as age-related macular degeneration (AMD), Stargardt’s macular dystrophy (SMD) and retinitis pigmentosa (RP).

**Studies on Retinitis Pigmentosa**

Retinitis pigmentosa is the most common form of inherited progressive retinal dystrophy. It mainly affects rod photoreceptors and gives rise to progressive loss of rod and cone photoreceptors than RPE cells. This initially manifests as nyctalopia or difficulty with night vision which is the initial manifestation of impairment of the photopigment retinol function and cycling. Night blindness and progressive visual field loss, often leading to complete blindness can be seen in different stages of the disease, and no curative treatment has been described yet (Rivolta et al. 2002, Hims et al. 2003, Ramsden et al. 2013).

A clinical study was performed with 20 RP patients by using intravitreal bone-marrow-derived stem cells and the quality of life was determined with National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ) 3 months after the injection. The results showed that the quality of life of the patients improved significantly 3 months after the treatment, but by the 12th month there was no significant difference from baseline (Siqueira et al. 2015). It was reported that functional visual score, functional field score, and functional visual acuity of the American Medical Association guidelines were equally correlated to the questionnaire in the same RP patients. No adverse effects were reported (Seo et al. 2009).

Parks et al. (2015) reported the findings of a phase 1 clinical trial of intravitreal autologous bone marrow CD34+ cell injection. Various ischemic and degenerative retinal disorders were included in the study. Intraocular inflammation or hyperproliferation were not observed during the study. Their findings showed that the treatment was safe and a patient with RP was noted to have improvement on visual function on Goldmann perimetry which appeared sustained at the 6-month follow-up visit.

In a recent study, the safety of a single intravitreal injection of autologous BMMSCs in patients with advanced RP was studied (Satarian et al. 2017). Stem cells were also injected into the mouse vitreous cavity for further evaluation. No adverse events were observed in eyes of 2 out of 3 patients who reported improvement in light perception which lasted for 3 months. The third patient experienced extensive pre-retinal and vitreal fibrosis starting at the second week of the therapy and further ciliary injection, cyclitic membrane, shallow anterior chamber, ocular hypotony and nearly total tractional retinal detachment at the 3 month follow-up. Ocular examination revealed vision of no light perception, mature cataract, iris neovascularization, ocular hypotony and shallow anterior chamber at 1 year follow-up.

In a phase 1 clinical safety study, subretinal ADMSC implantation was performed to advanced stage RP patients. There was no statistically significant difference in visual acuity from baseline. Four patients experienced visual acuity improvement during the 6 month follow-up. Although there were no systemic complications, 5 of the 11 patients experienced various ocular complications. One patient had choroidal neovascularization (CNV) at the site of the implantation which was treated with one injection of intravitreal anti-VEGF. Five patients had ERM around the transplantation site and at the periphery causing localized peripheral tractional retinal detachment at the periphery (Öner et al. 2016).
Recently, seventeen patients with bilateral visual loss due to RP included Stem Cell Ophthalmology Treatment Study (SCOTS and SCOTS 2) and followed-up at least 6 months. Affected eyes were treated with autologous BMMSCs. Patients were treated either retrobulbar, subtenon and intravenous SCs or retrobulbar, subtenon, intravitreal and intravenous. In 33 treated eyes, 15 eyes (45.5%) improved an average of 7.9 lines of Snellen acuity, 15 eyes (45.5%) remained stable, and 3 eyes (9%) worsened by an average of 1.7 lines of Snellen acuity. No surgical complications were reported. The study also reported that duration of the disease did not appear to affect the ability of the eyes to respond (Weiss & Levy 2018).

**Studies on Aged-related Macular Degeneration and Stargardts’ Macular Dystrophy**

Age-related macular degeneration is one of the causes of vision loss in developed countries. It affects elderly patients with progressive and irreversible deterioration of central vision. The disease prevalence is expected to increase in the near future (Wong et al. 2014). In contrast to AMD, SMD affects mainly young people, often starting in late teens or early 20s. It is the most common inherited macular dystrophy in both adults and children. Similar to AMD, central visual loss is seen. These patients have also dyschomatopsia and central scotoma with characteristic macular atrophy and yellow white flecks at the level of the RPE (Fujinami et al. 2013, 2015).

Schwartz et al. (2012) studied with human ESCs (hESCs) for the first time in AMD and SMD. The results of subretinal transplantation of hESC-derived RPE in patients with SMD and the dry type AMD revealed no hyperproliferation, abnormal growth or immune mediated transplant rejection during the first 4-month period. hESC-derived cells were well tolerated for up to 37 months without serious adverse effect. Visual acuity improved in ten eyes, improved or remained the same in 7 eyes and decreased by more than ten letters in one eye, whereas the untreated fellow eyes of the patients did not show similar improvements. The results of this study provided the first evidence of the medium-term to long-term safety, graft survival and possible biological activity of pluripotent stem cells in individuals with retinal disease (Schwartz et al. 2015).

Another study about the safety and tolerability of subretinal transplantation of hESC-derived RPE was published by Song et al. (2015). The study consisted of 4 patients, 2 with AMD and 2 with SMD. Improvement of 9-19 letters in visual acuity in 3 patients was identified after 1-year follow-up. The other patient with AMD remained stable. One patient with AMD developed an epiretinal membrane (ERM) persisting at 1-year follow-up with retinal puckering and choroidal neovascularization (CNV) and was treated with intravitreal anti-VEGF. The other patient with AMD also developed ERM’s, intraretinal cysts and dye pooling on fluorescein angiography persisting throughout the period of the study. Song et al. (2015) concluded that the long-term safety and efficacy of hESC-derived RPE required further studies.

In the study of Limoli et al. (2014), the patients received a cell graft between choroid and sclera. The researchers used ADMSCs in 12 eyes of 12 patients with AMD. In addition to these stem cells, platelet-rich plasma (PRP) was also used. Electrophysiological evaluation of all eyes enrolled in the study revealed a significant increase especially in the electoretinogram (ERG) values recorded by scotopic rod-ERG after cellular autograft. No adverse effects were reported in any of the patients.

Limoli et al. (2016) used the same technique in another study with a larger group of patients. 36 eyes of 25 patients with AMD received implantation of ADMSCs and platelets from PRP in the suprachoroidal space. After 6 months, the treatment improved visual performance and the increase was better if retinal thickness recorded by OCT (optic coherence tomography) was higher. They assumed that a greater number of residual cells lead to greater interaction between growth factors and chorioretinal cellular membrane receptors, more intense cellular activity and, ultimately, improvement of visual quality.

In a recent case report, subretinal transplantation of autologous iPSC-derived retinal cells generated from skin fibroblasts in a patient with neovascular AMD was described (Mandai et al. 2017). The removal of the neovascular membrane was performed at the surgery. After 1-year-follow up, the patient remained stable in terms of visual acuity still having cystoid macular edema. There was no sign of graft rejection or recurrence of the neovascular membrane. IPS-based autologous transplantation was reported to be safe and feasible in the treatment of the patient (Mandai et al. 2017).

Kuriyan et al. (2017) reported 3 patients with AMD with the development of bilateral severe visual loss after receiving intravitreal injections of autologous ADMSCs at stem-cell clinics associated with ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined tractional and rhegmatogenous retinal detachment or lens dislocation.

BMMSCs were used intravitreally in the treatment of 60 advanced dry AMD patients in another study (Kumar et al. 2017). The effect of stem cell therapy was evaluated in terms of visual acuity, amplitude and implicit time in multifocal-ERG (mf-ERG) and the size of geographic atrophy. Although no statistically significant improvement in the best corrected visual acuity (BCVA) after 6 month follow-up occurred, mf-ERG showed significant improvement in amplitude and implicit time in the treated group. Adverse events were not seen in any of the patients. The researchers concluded that the electrophysiological and anatomical improvement in the treatment group may indicate the therapeutic role of BMMSCs in patients with dry AMD (Kumar et al. 2017).
The safety and efficacy of intravitreal injections of bone marrow mononuclear fraction (BMMF) containing CD34+ cells in 10 patients with atrophic AMD were studied (Cotrim et al. 2017). Patients were evaluated with the tests including microperimetry, infrared imaging, fundus fluorescein angiography (FFA) and OCT. During the 12-month follow-up, mean BCVA and mean sensitivity threshold improved significantly. Patients who have smallest areas of atrophy had better results. Choroidal new vessels or tumor growth were not identified according to FFA tests. The authors emphasized that the paracrine effect of CD34+ cells may explain the functional improvement observed in their study (Cotrim et al. 2017).

Another prospective clinical case series aimed to investigate the safety and efficacy of suprachoroidal ADMSC implantation in 4 patients with Dry AMD and 4 patients with SMD. All of the patients experienced visual acuity, visual field and mf-ERG recording improvement during the 6 month follow-up whereas the untreated fellow eyes of the patients did not show similar improvements. No systemic or ocular complications were found during the 6 month follow-up. Stem cell treatment with suprachoroidal implantation of ADMSCs seems to be safe and effective in the treatment of dry type AMD and SMD (Onet et al. 2018).

Studies on Optic Neuropathies

In the study of Weiss et al. (2017), 10 patients with bilateral visual loss due to sequential non-arteritic ischemic optic neuropathy (NAION) underwent autologous BMMS therapy within the Stem Cell Ophthalmology Treatment Study (SCOTS). Affected eyes were treated with either retrobulbar, subtenon and intravenous stem cells or following vitrectomy, intra-optic nerve, subtenon and intravenous stem cell applications. Following the therapy in SCOTS, 80% of the patients experienced improvement in Snellen binocular vision (P=0.029) with 20% remaining stable, and 73.6% of the eyes treated gained vision (P=0.019) and 15.9% remained stable in the post-operative period. Improvements typically manifested no later than 6 months post procedure. Duration of the visual loss did not appear to affect the ability of the eyes to respond to the treatment. Statistically significant improvements in the visual acuity of individual eyes and of binocular vision in this condition have been shown (Weiss et al. 2017).

In a case report, a relapsing auto-immune optic neuropathy caused progressive bilateral visual loss, and the patient underwent vitrectomy with intra-optic nerve injection of BMMSCs in the right eye and retrobulbar, subtenon and intravitreal injection of BMMSCs in the left eye. Both eyes continued to have visual field improvements 1 year after SCOTS treatment. 3 and 6 months after SCOTS treatment, both macular thickness maps and fast retinal nerve fiber layer thickness improved (Weiss et al. 2015).

In 5 Leber’s hereditary optic neuropathy patients who underwent SCOTS treatment, improvements in visual acuity and peripheral vision were found. Several of the eyes experienced dramatic, persistent increases in visual acuity attributable to the BMMSC treatment in SCOTS including finger count to 20/100 and hand motion to 20/200. Visual field improvements were noted. Macular thickness and optic nerve head thickness varied and did not appear to be correlated with vision improvements. No adverse or serious adverse events were observed. These improvements could be a result of revitalization of existing mitochondria in existing neurons and glial cells, as well as transdifferentiation of the BMMSCs and incorporation of newly developed cells in the existing ganglion and optic nerve cell layers. Further exploration of stem cell treatment in mitochondrial disease appears warranted (Weiss et al. 2016).

Conclusion

Stem cell treatment modalities are the rising trends in retinal disease. The common diseases causing vision loss including AMD, SMD and RP have some promising results when treated with ESC or MSCs. Also, there are continuing studies, many ongoing clinical trials aimed to evaluate the stem cell treatment in retina and optic nerve diseases. Today, there is no standardization for this therapy. Long-term safety and efficacy of stem cell application should be followed. More clinical trials should evaluate the methods, timing of the applications and follow-up results. In the near future, the regenerative stem cell therapy may be a standard treatment modality in many degenerative eye disorders.

References


