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Case Report Open Access

Use of Human Embryonic Stem Cells in the Treatment of Age-Related Macular Degeneration

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Abstract

Introduction: Age-related macular degeneration (AMD), a progressive neurodegenerative condition, primarily affects the retinal pigmented epithelium resulting in degeneration of photoreceptors. The previously available anti-vascular endothelial growth factor and retinal translocation do not appear to be valuable in restoring the lost vision. Now-a-days, cell-based therapy has gained a momentum in the treatment of AMD.

Case Report: We report a case of 73-yr old female with AMD who was treated with human embryonic stem cells (hESCs). hESC therapy consisted of different treatment phases (T1, T2, T3) with gap phases in-between. In T1 phase (8-Week to 12-Week), hESCs were administered via intramuscular route twice daily (0.25 ml), intravenous route every 10 days (1 ml) and supplemental routes every 7 days (1-5 ml). Following the treatment, the patient showed improvement in the focus, was able to see an image through right (Rt) eye and with left (Lt) eye occluded and could identify color through Lt eye with Rt eye occluded. No other study attempted the use of direct injection of hESCs in the patient with AMD.

Conclusion: Although, the use of hESC therapy in our patient showed favorable outcomes, but are not enough to confirm the efficacy of hESC in the treatment of patients with AMD. So, future clinical trials with large number of patients assessing the efficacy and safety of hESCs in the patients with AMD are required to be conducted.

Introduction

As per the World Health Organization, age-related macular degeneration (AMD) is the third most common pathological condition leading to visual impairment, succeeding cataract and glaucoma [1]. AMD, a progressive neurodegenerative condition primarily affects the retinal pigmented epithelium (RPE), secondarily resulting in degeneration of photoreceptors in people ≥ 50 years [2].

Factors that may increase the risk for occurrence of AMD includes a gene defect, age, smoking and nutritional factors [3]. The disease progress in two different ways; exudative or wet AMD (rapidly progressing) and geographic atrophic or dry AMD (slowly progressing), both finally leading to the loss of vision. Exudative form is accountable for AMD-related visual impairment in 80 percent of the cases and is associated with choroidal neovascularization in the subretinal macular region that result in a sudden fibrous scarring of the macula [4]. Dry form, a less prevalent form of AMD-related visual impairment is characterized by accumulation of drusen (a deposit of lipids and proteins) between the RPE and Bruch's membrane [5].

Cell-based therapy has gained a momentum in the treatment of AMD. As the underlying cause for AMD is impaired functioning of RPE and their death that leads to the degeneration of photoreceptors. Thus, replacing damaged RPE with cell-based therapy can help rescue photoreceptors. Stem cells withability to self-renew and differentiate into any cell type has been the promising source for AMD treatment. Stem cells that have been explored in animal models for the treatment of AMD include embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) [2,6]. In our previous studies we have shown the improvement in the patient's condition suffering from cerebral palsy, cortical visual impairment (CVI), Lyme's disease, spinocerebellar ataxia, Friedreich's ataxia and spinal cord injury after human embryonic stem cells (hESCs) therapy [7-12].

In our study, we report the use of hESCs in the treatment of patient with AMD who was affected with both the forms of AMD i.e. the dry of the left (Lt) eye and the wet of the right (Rt) eye.

Methodology

hESCs are cultured and maintained as per our proprietary in-house patented technology in a Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP) and Good Tissue Practices (GTP) certified laboratory at Nutech Mediworld (Patent-WO 2007/141657A PCT/1B 2007 Published 13 Dec 2007). The evidence for the use of hESCs at Nutech Mediworld has also been submitted in written and accepted at House of Lords, Regenerative Medicine, Science and Technology Committee [13]. The cell lines are free of animal product and are chromosomally stable. We have also established the safety of hESCs in patients with terminal conditions [14].

The treatment approach was divided into phases with gap phases in between. The first phase T1 (8-Week to 12-Week) administered 0.25 ml (<4 million cells) hESCs through intramascular (i.m) route, twice daily to "prime" the body and allow for the recipient immune system not to reject the stem cells, 1 ml hESCs (<16 million cells) were administered through intravenous (i.v) route every 10 days to "home in" to the required area and 1 to 5 ml hESCs were administered every 7

days by any of the supplemental routes (retrobulbar) to introduce the stem cells as near the affected site as possible (local action). Subsequent phases; T2 (4 to 6 weeks), T3 (4 to 6 weeks) also followed the same dosage regimen. The gap phase of 4-8 months between treatment phases was included to enable injected cells to grow, mature and regenerate the affected region. The time period for gap phase was decided based on the time required for development of complete organs in human fetus (14-16 weeks) [15].

A written informed consent was provided by the patient prior to start of the treatment. The patient was video graphed before, during and after the treatment periods. The trained physicians and nurses observed the patients for antigenic or anaphylactic responses.

Case Presentation

A 73-yr old female from Germany was admitted to our facility on 23 October 2013 with complaints of progressive blurring of vision and color blindness of left (Lt) eye.

Patient was apparently well till 2006 when she first started noticing progressive decrease in vision (R>L) and color blindness in the Lt eye. Patient was unable to read due to decreased vision, was not able to drive well due to color blindness and was unable to recognize familiar faces occasionally. Patient was diagnosed with AMD (dry type) of Rt eye and AMD (wet type) of Lt eye. Her history revealed that she had hypertension and was on regular treatment for it. She also had a family history for AMD.

On examination, the patient had difficulty in focusing from Rt eye, difficulty in forming image from Lt eye, difficulty in identifying color from Lt eye, difficulty in understanding people when they talk, had central vision affected and peripheral vision spared. Vision test showed left sided colour blindness. Visual evoked potential (VEP) testing showed slight delay in P100 wave. In ERh testing of the eye, seotopic response showed the normal 'a' wave with minimal delay in the 'b' wave and phototopic response showed the normal 'a+b' wave and the amplitude.

Patient was treated with hESC therapy along with occupational therapy. During the treatment, patient was also given propranolol-CT (40 mg OD) and amlodipin (5 mg OD). Following the treatment, the patient reported significant improvement in ability to focus, could see image through Rt eye and with Lt eye occluded and could identify color through Lt eye with Rt eye occluded. The patient has been followed up in December 2014 and reported that deterioration of visus has stopped since November 2013. The patient also reported slight improvement in the shortsightedness. She has developed scars below the retina with Lucentis-Injections.

Discussion

Our study used in-house cultured hESCs for the treatment of patient with AMD. We directly injected hESCs via i.m, i.v and supplemental routes (such as retrobulbar) to the patient. Following the therapy, patients showed significant improvement in the vision and the ability to identify colors. Although several treatment options are available for AMD but none has been beneficial in curing the disease. Excessive amount of vascular endothelial growth factor (VEGF) has been demonstrated as an underlying cause of increased neovasularization (immature and abnormal growth of blood vessels) in choroid layer and these abnormal vessels are susceptible to hemorrhage, causing macular damage [16]. Anti-VEGF therapies including bevacizumab and ranibizumab are available to obstruct abnormal neovascularization [17], but are known to result in side effects such as macular hemorrhages [18]. Surgical treatment involves translocation of macula towards the undamaged RPE. The surgical intervention showed improved vision in certain number of patient, but the surgery has several complications associated with it; such as fibrosis and diplopia [6].

The above discussed treatment options; anti-VEGFs and surgery, do not have capability to restore the vision completely. Presently, researchers are focusing on the use of cell-based therapies for the treatment of AMD. The options may include replacement of damaged RPE with the healthy RPE from the donors or using stem cells therapy for replacing the abnormal or dysfunctioning cells [6].

An in vitro study examined the potential of retinal progenitor cells (RPCs) and MSCs in retinal transplantation. The study demonstrated that RPCs and MSCS could differentiate into retinal neurons in the presence of growth factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and basic fibroblast growth factor (bFGF). However, rhodopsins like cells were only observed in the differentiated RPCs and not in the differentiated MSCs, indicating that MSCs do not appear to have applicability in the retinal transplantation [19].

Other studies assessed the likelihood of using ESCs in RPE replacement in animal models. Haruta et al injected monkey embryonic stem (ES) cell-derived pigment epithelial cells (ESPEs) into subretinal space of rats. The grafted ESPEs were found to promote the survival of photoreceptors [20]. Another study by Lu and colleagues assessed the safety and functioning of hESCs-derived RPE in rats. This study also supported the findings of the study by Haruta et al reporting the long-term safety of grafted hESCs-derived RPEs, as no teratoma/tumor formation was observed [21].

Recently, Schwartz et al conducted a clinical trial using hESC-derived cells in human patients with dry AMD. Patients showed improved vision and no concerns were reported regarding the safety of the grafted cells. No signs of tumorigenicity, hyperproliferation, ectopic tissue formation, or apparent rejection were observed [22].

All these above discussed studies injected in-vitro derived RPEs into animals and humans. However, our study is the first to attempt the direct injection of hESCs in humans. We have previously reported improvement in vision in our patients with CVI who were treated with hESC therapy (8). Our hESCs are very small is size (0.5-2 μm) and are thus easily able to penetrate the blood brain barrier, reach the injured tissue and aid in regeneration. Thus, hESCs in our patient might have resulted in regeneration via the same mechanism. Contrast to the fear about using hESC therapy, we did not observe teratoma formation and any other adverse events. However, we assessed the efficacy and safety of hESC in a single patient with AMD; further clinical studies with large sample size are needed to be further strengthen the findings.

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Conflict of Interest

The author declares that there is no conflict of interests regarding the publication of this paper.

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