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Stem Cell Research 2018-First-Year Results of Subretinal Mesenchymal Stem Cell Implantation in Severe Retinitis Pigmentosa- Ayse Oner- Erciyes University

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Introduction

Since their introduction by Thomson et al. human Embryonic Stem Cells (hESCs) have drawn attention to their potential clinical use. Despite their great therapeutic potential, various concerns have risen regarding their limitless ability for selfrenewal and plasticity, including hyperproliferation, tumor, and ectopic tissue formation. Although there have been various clinical trials using Stem Cells (SCs) in retinal diseases, their long term results are still in the process of discovery. Retinitis Pigmentosa (RP) is a potentially blinding disease with severe vision loss by age 40-50 and characterized by the death of retinal cells. It affects over 2 million patients worldwide. Its clinical diagnosis is based on the presence of night blindness, visual field construction, bone spicule pigmentation and a reduction in electroretinograms (ERGs). Although there is no effective therapy for the disease up to date, new treatments including gene therapy and SC implantation to have been under investigation. Finding an effective and safe treatment may reduce the economic burden on the patients and society. There have been four types of stem/progenitor cells; retinal progenitor cells, ESCs, induced pluripotent SCs (iPSCs) and mesenchymal SCs (MSCs), that have been used in retinal diseases all having pros and cons [7]. Developmentally mature organs, such as bone marrow, adipose tissue, umbilical cord or amniotic fluid are the generation sources of MSCs, which have paracrine and immunosuppressive effects while having the disadvantages of low rate of cell migration and differentiation. Compared to bone marrow-derived MSCs (BM-MSCs), adipose tissue-derived MSCs (ADMSCs) can be obtained and expanded easily; and also have a higher immunomodulatory capacity [8]. MSCs can secrete various cytokines, growth factors, and proteins and show anti-apoptotic, anti-inflammatory, immunomodulatory and angiogenic activity which are thought to be the mechanisms of retinal cell survival. Here we aim to report first-year results of patients with severe RP who received subretinal stem cells and to discuss the safety and tolerability of the procedure.

Material and Methods

This single-center, prospective, phase 1 clinical safety study included 14 subjects of RP which are legally blind. The study followed the tenets of the Declaration of Helsinki, it was approved by the Institutional Review Board and the Review Board of Stem Cell Applications within the Ministry of Health according to the regulations in our country. Inclusion criteria of the patients, surgical technique, and postoperative follow-up procedures were described in our published data before. The production protocols of ADMSCs were previously mentioned by our study group [5]. Patients completed 12 months follow up period. Visual acuity results, the incidence, and variety of ocular and systemic side effects associated with ADMSCs treatment were evaluated.

Result

Morphology and phenotype of culture-expanded hADMSC and the demographic and clinical characteristics of the 14 study patients who attended to the study were presented in our previous report [5]. Follow-up BCVA and eye examination All 14 patients completed the one-year period and none of them had systemic side effects. Eight subjects had no ocular adverse effects regarding the SC treatment. Choroidal neovascular membrane (CNM) developed in one subject at the implantation site and treated with

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intravitreal anti-VEGF injection (Patient number 3). The first operated six patients including the patient with CNM, had epiretinal membrane (ERM) on the surface of the retina at the periphery with peripheral tractional retinal detachment, which needed second vitrectomy including total membrane peeling and silicon oil injection in five of them. One of the patients experienced mild band keratopathy six months after the treatment (Patient number 1) and another patient had retrolental fibrous tissue at a 1-year follow-up examination (Patient number 2) who had a normal posterior segment on the ultrasound (Figure 1). The development of these membranes and fibrous tissue is thought to be due to the vitreal reflux and undesirable preretinal proliferation of MSCs. To avoid the occurrence of this complication, the operation technique was modified as described in our previous report group [5]. This modification inhibited membrane formation in the remaining eight patients.

Discussion

Retinitis pigmentosa is a potentially blinding, hereditary progressive neurodegenerative disease with no approved and effective treatment making these patients search to try new treatment modalities. Recent investigations include nutritional supplementation, light reduction and gene therapy; valproic acid and vitamin A supplementation with modest benefits and potential side effects [9]. Surgical interventions other than stem cell-based therapies for the potential treatments for RP include use of retinal prosthetics and intravitreal delivery of encapsulated cells secreting neurotrophic factors [10-13]. Very few studies exist in the literature regarding stem cell-based treatment modalities in RP. Park et al reported the phase 1 clinical trial results of intravitreal autologous bone marrow CD34+ cell injection in various retinal disorders including one patient with RP with the baseline VA of 20/640 [14]. The patient reached 20/250 at 2 weeks as the best follow-up BCVA, declined to 20/400-2 letters at the final examination. The patient also had recovery on visual function evaluated by Goldmann perimetry, which persisted at the final visit. He had flat ERG readings through the follow-up period of the study. Their findings showed that the procedure was effective and safe. In the Reticell-clinical trial, the investigators analyzed the quality of life of 20 subjects with RP who received intravitreal use of autologous, bone marrow-derived, stem cell implantation [9]. All patients had improvement in the quality of life evaluated with National Eye Institute Visual Function Questionnaire-25 (NEIVFQ) 3 months after the injection; unfortunately, the improvement disappeared in the 12th month. The paper did not mention any adverse effects. In a recent phase 1, prospective open-label study conducted in Iran, the investigators studied the safety of single intravitreal implantation of autologous bone marrow-derived MSC in patients with severe RP [15]. All patients in their study group had visual acuity of slight light perception bilaterally. There were no side effects in eyes of 2 out of 3 patients who also described increase in the perception of light after 2 weeks of the injection, which persisted for 3 months.

Conclusion

Subretinal implantation of ADMSCs may have some adverse effects and the patients should be followed up carefully. The result of this study clarifies the complications of the therapy which would be beneficial for future studies. Further studies with larger groups will be necessary to optimize the surgical technique and to determine the effects of this therapy.

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