Stem Cell Therapies in AMD

Subjects: Ophthalmology
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Age-related macular degeneration (AMD) is a highly prevalent irreversible impairment in the elderly population worldwide. Stem cell therapies have been considered potentially viable for treating AMD through the direct replacement of degenerated cells or secretion of trophic factors that facilitate the survival of existing cells.

Keywords: regenerative medicine ; retinal pigment epithelium ; iPS cell ; ES cell ; stem cell ; age-related macular degeneration ; clinical trial ; retina ; immune reaction ; transplantation

1. Introduction

Age-related macular degeneration (AMD) is one of the most common causes of blindness worldwide, especially in the elderly population. As the global prevalence is 8.7% and the age of onset varying from 45 to 86 years, it is estimated to affect approximately 288 million individuals in western countries by 2040 [1]. Given the diverse variations among ethnicities, AMD is 10 times more prevalent among Caucasians compared to African-Americans. The early stages of AMD are characterized by the hallmarks, known as drusen and depigmentation of the retinal pigment epithelium (RPE) cells. Its progression from early to intermediate and advanced levels is driven by the increase in the numbers of drusen and degenerated RPE cells, resulting in pigmentary changes and the formation of choroidal neovascularization (CNV). The advanced stages of AMD are categorized into two forms: Non-neovascular (dry, non-exudative, or geographic) and neovascular (wet or exudative). Dry AMD is characterized by geographic atrophy of the RPE, photoreceptor, and choriocapillaris, resulting in gradual retinal cell loss and decreased visual acuity. In the wet-type AMD, CNV causes sub-retinal leakage of blood, lipids, fluids, and the formation of fibrous scars. Currently, AMD patients are recommended to receive routine medical management, including antioxidant supplements and anti-vascular endothelial growth factor (anti-VEGF) agents. The former, including vitamins, lutein, and zeaxanthin, are applied to protect the retinal cells from oxidative stress. Meanwhile, intravitreal injection of anti-VEGF agents, such as ranibizumab, aflibercept, and bevacizumab, which bind to VEGF receptors to block VEGF, is commonly used for treating wet-type AMD. However, current treatments do not target the underlying degeneration inherent in the disease, leading to a high recurrence rate upon the discontinuation of treatment. Furthermore, there are currently no effective methods for treating dry-type AMD. To address these problems, retinal cell therapy has attracted worldwide attention as the new era of treatment for retinal degenerative diseases [2][3][4][5], such as reconstruction and functional recovery of RPE by cell transplantation to maintain or restore visual function.

Currently, there are two types of formulations used for the administration of RPE cell products, namely, cell sheets with or without scaffolds and cell suspensions. In the case of RPE cell sheet transplantation, various dedicated devices have been used in previous publications [2][6][7][8]. Meanwhile, a soft-tip sub-retinal cannula is used for transplanting an RPE cell suspension [2][9][10][11]. Generally, the risk of surgical complications of RPE sheet transplantation is higher than RPE cell suspension due to the greater surgical invasiveness, involving a wider incision site and occasional removal of CNV before RPE sheet transplantation. The safety results of the transplantation of pluripotent stem cell-derived retinal pigment epithelial cells (RPE) in both formulations have been described in previous literature [6][7][8][9][10][11][12][13][14][15].

The conceptual mode of action of pluripotent stem cell-derived RPE cells for wet-type AMD (A) and dry-type AMD (B) in either formulation, RPE cell sheet, or RPE cell suspension were shown, respectively.

2. History of RPE Cell Therapy for Age-Related Macular Degeneration

Research on RPE cell transplantation began attracting attention in the late 1980s. Transplanting human RPE cells into a monkeys' sub-retinal space revealed engraftment on Bruch's membrane [16]. Since then, several reports have been published on the protective effect of RPE cell transplantation on the neural retina in animal models [2], demonstrating the possibility of securing materials for photoreceptor cells and RPE for use in the cell therapy of diseases with impaired retinal outer layer. Additionally, a proof of concept for treatment was obtained for the RPE.

In humans, Peyman first reported RPE transplantation in patients with AMD in 1991 [17]. In the first case, autologous cell transplantation was performed after removing the proliferative tissue under the macula. The nearby RPE was then transplanted into the macula to improve visual acuity. In the second case, the RPE was exfoliated from the donor's eye as a sheet before being transplanted, but no visual acuity improvement was observed. The AMD-related CNV was removed, and a cell sheet obtained by culturing fetal-derived RPE was transplanted [18][19], but immune rejection occurred after the operation. Weisz also attempted injecting the fetal RPE as a cell suspension, but no improvement in the visual acuity was observed. Graft fibrosis was also observed [20]. Meanwhile, Del Priore transplanted a donor RPE sheet after removing the CNV, but the poor engraftment and visual acuity did not improve [21]. Almost all transplants using allografts in the eyes with a damaged blood-retinal barrier due to CNV removal showed rejection and deterioration in visual acuity.

Autologous transplantation is ideal for avoiding rejection. For some time, the RPE used for transplant was frequently collected from the peripheral area [22][23][24]. Although some patients had improved visual acuity, it was difficult to collect a sufficient number of autologous RPE cells with stable quality, and serious adverse events frequently occurred due to surgical invasion. In addition, among patients transplanted with peripheral RPE patches with the choroid, some resulted in improved visual acuity, but the surgical procedure had a higher risk of lacerating the patches. Furthermore, the choroid acted as a fibrous tissue if it was not connected to the host choroidal vessels.

As a countermeasure to these problems, the transplanted cell source was reviewed, and we reported RPE cells derived from pluripotent stem cells (ES cells, iPS cells) as candidate graft cells [25][26][27]. RPE cells derived from ES and iPS cells have the same functions as those derived from living organisms, and these cells form cell sheets through the collection of elegant hexagonal cells with tight junctions. Due to their easier preparation compared to primary cultured RPE cells, these have made dramatic developments in the cell therapy for AMD. Furthermore, RPE cell transplantation advanced first among the pluripotent stem cells due to the following characteristics of ES/iPS cell-derived RPE cells, making them more suitable for clinical application: (1) They have the required functions (quality), (2) the retina requires a small number of cells so that enough can be manufactured for transplantation (amount), (3) cells with certified quality for clinical use can always be obtained (reproducibility), and (4) the standard of purity was satisfied because of the color (purity). Furthermore, sub-retinal surgeries, such as CNV removal, have already been performed in the past. Thus, as described above, the field of ophthalmology has contributed greatly to the clinical application of pluripotent stem cells.

3. Cell Therapy for Age-Related Macular Degeneration Using Pluripotent Stem Cell-Derived RPE Cells

This section describes the implementation status of clinical studies on pluripotent stem cells in terms of the raw materials and the dosage form of the final product. The mode of action of cell therapy using pluripotent stem cell-derived RPE cells is shown in Figure 1, and a summary of clinical trials using pluripotent stem cell-derived RPE cells, with an updated status as of 31 December 2020 is presented in Table 1.

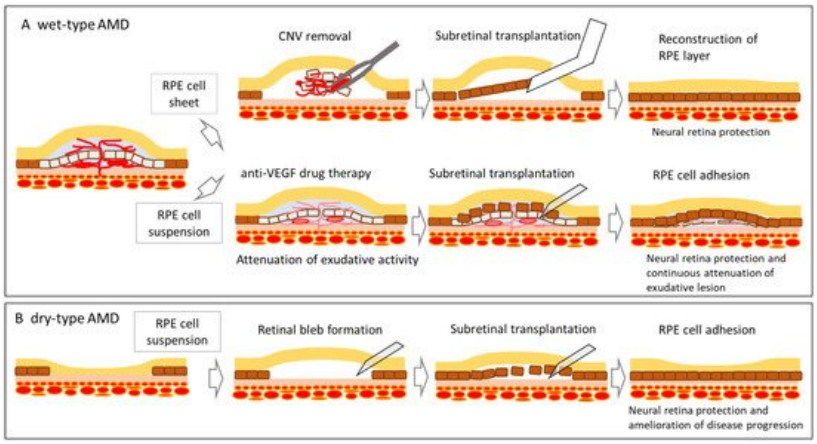

Figure 1. A conceptual mode of action of cell therapy using pluripotent stem cell-derived RPE cell products.

Table 1. Stem cell therapies for AMD with pluripotent stem cell derived-RPE.

No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion Date	Status	Study ID
1	A Study of transplantation of autologous induced pluripotent stem cell (iPSC) derived retinal pigment epithelium (RPE) cell sheet in subjects with exudative age-related macular degeneration	the Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology	autologous hiPSC derived RPE cell sheet	50 years and older	P1	1	October 2013 /September 2018	completed	UMIN000011929
2	Autologous Transplantation of Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium for Geographic Atrophy Associated With Age-Related Macular Degeneration	National Institutes of Health Clinical Center, Bethesda, Maryland, U.S.	Combination Product: hiPSC-derived RPE/PLGA scaffold	55 years and older	P1	20	July 2020 /March 2029	Recruiting	NCT04339764
3	A Study Of Implantation Of Retinal Pigment Epithelium In Subjects With Acute Wet Age Related Macular Degeneration	Moorfields Eye Hospital NHS Foundation Trust, London, U.K.	PF-05206388: RPE living tissue equivalent for intraocular use in the form of a monolayer of RPE cells immobilized on a polyester membrane.	60 years and older	P1	2	July 2020 /March 2029	Recruiting	NCT04339764

No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion Date	Status	Study ID
4	Study of Subretinal Implantation of Human Embryonic Stem Cell-Derived RPE Cells in Advanced Dry AMD	Retinal Arizona LTD, Phoenix, Arizona, U.S./Retina-Vitreous Associates Medical Group, Beverly Hills, California, U.S. and others	CPCB-RPE1 (Human Embryonic Stem Cell-Derived RPE Cells Seeded on a Polymeric Substrate)	55 years to 85 years	P1/2a	16	July 2019 /June 2023	Active, not recruiting	NCT02590692
5	A Study of transplantation of allogenic induced pluripotent stem cell (iPSC) derived retinal pigment epithelium (RPE) cell suspension in subjects with neovascular age related macular degeneration	the Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology, Kobe, Japan/ Kobe City Medical Center General Hosital, Kobe, Japan	Subretinal transplantation of allogenic hiPSC derived RPE cells	50 years to 85 years	P1	5	February 2017 /October 2021	Active, not recruiting	UMIN000026003
6	Stem Cell Therapy for Outer Retinal Degenerations	Federal University of Sao Paulo, Sao Paulo, Brazil	injection of hESC derived RPE in suspension/Procedure: injection hESC derived RPE seeded in a substrate	18 years to 90 years	P1/2	15	September 2016 /July 2020	Completed	NCT02903576
7	Subretinal Transplantation of Retinal Pigment Epitheliums in Treatment of Age-related Macular Degeneration Diseases	Chinese Academy of Sciences/Beijing Tongren Hospital, China	hESC derived RPE	55 years and older	P1/2	10	January 2018 /December 2020	Recruiting	NCT02755428

No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion Date	Status	Study ID
8	Safety and Efficacy of Subretinal Transplantation of Clinical Human Embryonic Stem Cell Derived Retinal Pigment Epitheliums in Treatment of Retinitis Pigmentosa	Qi Zhou, Chinese Academy of Sciences	hESC derived RPE	18 years and older	P1	10	May 2020 /December 2021	Recruiting	NCT03944239
9	Treatment of Dry Age Related Macular Degeneration Disease With Retinal Pigment Epithelium Derived From Human Embryonic Stem Cells	Chinese Academy of Sciences/ The First Affiliated Hospital of Zhengzhou University, China	hESC derived RPE	55 years and older	P1/2	15	September 2017 /December 2020	Recruiting	NCT03046407
10	Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older	P1/2	15	November 2011 /September 2015	completed	NCT01469832

No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion Date	Status	Study ID
11	A Follow up Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older		12	January 2013 /October 2019	completed	NCT02941991
12	Sub-retinal Transplantation of hESC Derived RPE(MA09-hRPE) Cells in Patients With Stargardt's Macular Dystrophy	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older	P1/2	13	April 2011 /August 2015	completed	NCT01345006
13	Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	55 years and older	P1/2	13	April 2011 /August 2015	completed	NCT01344993

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No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion	Status	Study ID
14	Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Patients With Stargardt Macular Dystrophy	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older	P1	13	July 2012 /June 2019	completed	NCT02445612
15	Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Patients With AMD	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older	P1/2	11	February 2013 /August 2019	completed	NCT02463344
16	A Phase I/IIa Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human ES Cell Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age-related Macular Degeneration (AMD)	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	55 years and older	P1/2a	12	September 2013 /June 2020	Active, not recruiting	NCT01674829

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No.	Study Title	Sponsor/Collaborators	Intervention	Age	Phases	No. of Subjects	Start/Completion Date	Status	Study ID
17	A Safety Surveillance Study in Subjects With Macular Degenerative Disease Treated With Human Embryonic Stem Cell-derived Retinal Pigment Epithelial Cell Therapy	Astellas Institute for Regenerative Medicine/Astellas Pharma Inc., U.S.	hESC derived RPE (MA09-hRPE)	18 years and older	P1/2	36	January 2018 /December 2029	Enrolling by invitation	NCT03167203
18	Retinal Pigment Epithelium Safety Study For Patients In B4711001	Moorfields Eye Hospital NHS Foundation Trust, U.K.	hESC derived RPE	60 years and older		2	September 2016 /October 2020	Active, not recruiting	NCT03102138
19	Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form Age-Related Macular Degeneration	Lineage Cell Therapeutics, Inc./CellCure Neurosciences Ltd., Israel	OpRegen	50 years and older	P1/2	24	August 2015 /December 2024	Recruiting	NCT02286089

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