AMD & STEM CELLS: FACT SHEET

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss and blindness. Among those aged 40 years and older, 1.5 million Americans suffer from late-stage AMD, out of approximately 18 million affected individuals[1]. As increasing age is the most significant risk factor for AMD, the rapid growth of the aging population will make AMD an increasing burden, with estimates suggesting that the global prevalence of AMD will reach 288 million people by 2040[2]. AMD impairs patients' central vision. The early and intermediate stages of AMD are characterized by a varying extent (size and area) of lipoprotein-rich deposits called drusen below the retinal pigment epithelial (RPE), a monolayer that provides nourishment and functional support to the overlying photoreceptors. Drusen progression is associated with RPE mottling and thickening of Bruchs membrane.

TYPES OF AMD

Advanced stages of AMD are categorized into two major types: “dry” (non-exudative) AMD and “wet” (exudative or neovascular) AMD.

1. Dry AMD accounts for approximately 90% of all cases. Dry AMD can progress to a late stage, known as advanced dry AMD or geographic atrophy (GA), which is associated with functional atrophy of the retina due to damage and death of the RPE and the overlying photosensitive-photoreceptor cells. Recently, the first FDA-approved therapeutics for dry AMD, which inhibit components of the complement pathway, have come to market for individuals with GA[3]. However, those taking this drug will not experience vision improvement, and its ability to reduce GA progression is modest[3].
2. Wet AMD is thought to primarily occur because of vascular endothelial growth factor (VEGF)-driven neovascular ingrowth into the RPE that can lead to exudation of fluid and/or blood. The use of anti-VEGF intravitreal therapies for wet AMD has seen explosive growth and has been shown to stabilize and improve vision[4,5]. However, a significant proportion of wet AMD patients do not respond to anti-VEGF therapies, suggesting that other non-VEGF-driven pathogenic pathways are involved in this disease[6]. While more recent therapies, such as intravitreal, high dose bi-specific antibodies that simultaneously target Tie2 and VEGF, have been recently FDA-approved for wet AMD, non-responders persist[7].

“High risk” variants within genes that encode components in the complement pathway, DNA repair, and lipid metabolism are linked to both forms of AMD[8,9]. Ultimately, advanced AMD threatens an individual's ability to read, drive, recognize loved ones, and maintain independence. The exponential growth of the aging population combined with the presence and persistence of non-responders to existing anti-VEGF therapies and the limitations of new anti-complement therapies underscores a profound and growing unmet medical need in AMD treatment.

RATIONALE FOR USING CELL-BASED THERAPIES FOR AMD

The death of RPE and photoreceptors, along with the presence of intact inner retinal cells, provides a potential rationale for cell replacement therapy for the outer retina and the RPE, which are the primary sites of damage and degeneration in AMD. Several approaches have been explored to replace macular RPE cells. The first approach involved grafting autologous RPE/choroid sheets from the peripheral retina to the macula, which yielded mixed results. Some patients demonstrated improved visual acuity up to 7 years post-procedure[10]. More recently, submacular injection of RPE cell suspensions have been employed using RPE derived from aspirated autologous peripheral RPE, cultured primary RPE, RPE progenitor-like cells derived from allograft donors, or RPE differentiated from either autologous induced pluripotent stem cells (iPSCs) or allogenic human embryonic stem cells (hESCs)[11].

ADDITIONAL RESOURCES

About Stem Cells
aboutstemcells.org

National Eye Institute (US)
nei.nih.gov

Macular Degeneration Foundation
eyesight.org/

Prevent Blindness
preventblindness.org/

Macular Society (UK)
macularsociety.org/

Each source has its own caveats: allogeneic sources require immunosuppression, derivation of RPE from autologous iPSCs may induce alterations in oncogenes and tumor suppressors, injected cell suspensions may not settle into a monolayer, and scaffolds involve more intensive vitreoretinal surgery with increased risks for hemorrhage and scarring. Early submacular injections of autologous peripheral RPE showed promise, with the majority of patients improving by 2 lines or more at a median follow-up of 17 months[12]. However, RPE cells are not the only source for cell therapy. There have also been efforts to develop scaffolds containing photoreceptor cells, in addition to RPE, for transplantation[13].

Ophthalmology is one of the few fields that has quantified patient perception of risk in cell therapies. A study conducted at an academic eye center surveyed 178 patients to assess their risk tolerance regarding potential visual improvement from stem cell-derived treatments compared to the risk of malignancy. Results showed that patients were willing to accept a risk of malignancy that exceeded actual risk levels for the prospect of visual improvement. Furthermore, older patients and those with intermediate visual function loss were found to be more tolerant of risk[14]. This tolerance of risk can lead some patients outside of regulated clinical trials, which in some cases has contributed to poor outcomes and reduced visual acuity due to the intraocular injection of adipose-derived autologous cells at "stem cell clinics"[15].

CLINICAL STATUS OF CELL-BASED THERAPIES AND CLINICAL TRIALS FOR AMD

Several clinical trials are currently underway to evaluate the safety and efficacy of submacular RPE cell injections from a variety of sources, including:

- Safety and Tolerability of RPE Stem Cell-derived RPE(RPESC-RPE) Transplantation in Patients With Dry Age-related Macular Degeneration (AMD) (NCT04627428): This trial is assessing the safety and efficacy of submacular injection of progenitor-like RPE derived from cultured cadaveric RPE[16].
- Autologous Transplantation of Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium for Geographic Atrophy Associated With Age-Related Macular Degeneration (NCT04339764): This trial is assessing the safety and efficacy of submacular transplantaton of RPE sheets derived from patient iPSCs[17].
- Study of Subretinal Implantation of Human Embryonic Stem Cell-Derived RPE Cells in Advanced Dry AMD (NCT02590692): This trial is assessing the safety and efficacy of hESC-derived RPE injection. Follow-up at one year was underpowered to assess efficacy but demonstrated tolerance[18].
- A Study of Implantation of Retinal Pigment Epithelium on Subjects With Acute Wet Age Related Macular Degeneration (NCT01691261): Phase 1 trial is assessing the safety and efficacy of RPE patch transplantation to treat exudative AMD. Five-year follow-up of two patients noted improved best-corrected visual acuity between 2 and 5 years; however, associated adverse events included suture-related scleral erosion, peripheral retinal detachment, hyperglycemia secondary to corticosteroids, and a transient ischemic attack (TIA)[19,20].

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- Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form Age-Related Macular Degeneration (NCT02286089): This Phase I/IIa trial is evaluating the safety, tolerability, and initial efficacy of hESC-derived RPE suspension delivery in GA stage of dry-AMD. Injections have been well tolerated, and visual acuity improvement was maintained in all of the most recent cohort of patients for 4.5 to over 15 months[21].
- Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration (Dry AMD) (NCT01344993): This Phase I/II trial is evaluating the safety, tolerability, and initial efficacy of hESC-derived RPE suspension to treat AMD. At a median 22 months follow-up, allografts as part of this trial and another hESC-derived RPE transplantation trial for Stargardt's macular dystrophy demonstrated safety, survival, and improved visual acuity in 10 out of 18 individuals (with 7 remaining the same and 1 worsening)[22].
- Safety and Efficacy of Autologous Transplantation of iPSC-RPE in the Treatment of Macular Degeneration (NCT05445063): This trial is assessing the safety and efficacy of subretinal autologous iPSC-derived RPE injection to treat late stage of AMD.

A comprehensive review of clinical trials that were ongoing or completed as of 2024 was conducted by Klymenko et. al[23].

CENTERS WORKING ON THE CLINICAL APLICATION OF STEM CELLS FOR AMD

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