ADVANCES IN HUMAN EMBRYONIC DERIVED STEM CELL THERAPIES FOR RETINAL DEGENERATION

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INTRODUCTION

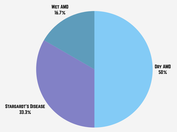
Retinal Pigment Epithelium (RPE) degeneration is the key problem in retinal diseases such as Age Related Macular Degeneration (AMD) and Stargardt's Macular Dystrophy (SMD). In the United Kingdom, there are 663 new cases of AMD per million per year.
Human Embryonic Stem Cell (hESC) derived RPEs are an emerging regenerative treatment modality for these conditions. However, the safety and efficacy of this treatment option remains under researched. This review discusses findings from 5 clinical studies that present the various outcomes associated with the treatment of retinal degeneration using hESC-RPE.

OBJECTIVE

To evaluate the safety, patient response, efficacy, side effects and clinical outcomes of hESC-RPE therapies for degenerative disorders of the retina, in order to highlight areas of improvement, limitations and scope for further research.

METHOD

A systematic search PubMed and Cochrane, was conducted to select studies assessing the clinical findings post treatment with hESC-RPE based interventions. **Inclusion Criteria**: Peer reviewed clinical studies using hESC-RPE based interventions with clear methods
of delivery, conducted within the last 10 years. **Exclusion Criteria**: Publications conducted solely on animal models or in-vitro settings. Non-English articles. Studies using non-hESC interventions.



RESULTS

Paper 1: Song et al. (2015) treated 4 patients, 2 with Stargardt's and 2 with Dry AMD with sub-retinal hESC-RPE **suspension injections**. The vision was improved for 3 patients by **9-19 letters.** No tumorigenicity or ectopic growths were noted.

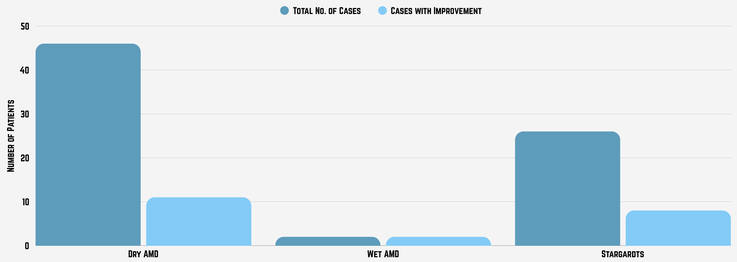
Paper 2: da Cruz et al. (2018) treated 2 patients with severe wet AMD with the use of a hESC-RPE **patch transplanted onto a synthetic membrane** by a custom delivery tool. Both patients required **only local immunosuppression**, **gaining 21 and 29 letters** respectively after a year's follow up, demonstrating a dramatic functional improvement and enhanced feasibility.

Paper 3: Mehat et al (2018) delivered about 200,000 hESC-RPE cells **as a suspension** in 12 patients with Stargardt's disease. While cell survival was noted, there were **no substantial improvements** in vision observed, and **one case of localised harm** was recorded. The study highlights the limited benefit of RPE therapy in late stage retinal degeneration.

Paper 4: Kashani et al. (2021) treated 16 patients with dry AMD with a hESC-RPE based **implant** developed by the California Project to Cure Blindness. After a year long follow up, it was noted that **27% of treated eyes gained >5 letters** vs. 7% of untreated eyes, with improved surgical technique reducing early adverse events. The paper supports **scaffold based RPE-therapy as safe and promising**.

Paper 5: Li et al. (2021) injected 1×10^5 hESC-RPE cells into 7 early-stage Stargardt patients and followed them for a period of 5 years. **5 eyes displayed stability or improvement,** while **2 showed decline**. No systemic or immunologic complications occurred. The study confirmed long term safety but patient outcomes showed a great deal of variability influenced by differences in characteristics.

Paper 6: Kashani et al. (2022), a 2 year long follow up on Paper 4 providing extended data on histopathological and immunological assessments. Donor cells **survived 2 years without long term immunosuppression**, with no signs of immune rejection or intraocular inflammation. The study supports the long term safety and cellular integration of the **scaffolded implant therapy**.



CONCLUSION

Post the review of these 6 studies, it is understood that hESC-derived RPE transplantation was found to be safe uniformly, as there were no reported outcomes of tumorigenicity or severe immune rejections, across multiple methods of delivery.
Functional visual improvement varied considerably across studies, with patch-based and scaffolded therapies yielding more promising results.
It was also seen that the stage of the disease plays a crucial role in determining outcomes, with early stage disease showing more potential for gaining stability and late stage degeneration limited functional rescue.

LIMITATIONS

The studies in this review showed remarkable variation in terms of the diseases studied (dry AMD, wet AMD and Stargardt's), sample size and method of delivery, which made generalisation difficult.
The sample size for all included studies was relatively small, which limits statistical reliability and detecting differences in outcomes for various subgroups.
It is important to note that although BCVA was widely used, studies also considered different functional endpoints such as quality of life, contrast sensitivity etc. Some results also reflected improvements in the form of contralateral eye gains, placebo effects or learning curves.

FUTURE RECOMMENDATIONS

Stratifying patients by disease stage and retinal phenotype could optimize treatment strategies, and therefore visual outcomes.
Larger, multi-center trials are needed to establish the efficacy of hESC-RPE based treatments,
Direct comparison between methods of delivery can help identify the most effective modality.
Long term follow-up periods are necessary to establish durability and study long term adverse effects.

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