

Retinal Pigment Epithelium–Retina Transplantation for Retinal Degenerative Disease

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IN THIS ISSUE OF THE JOURNAL, RADTKE AND ASSOCIATES report on the results of a phase 2 clinical trial of fetal retinal pigment epithelium (RPE)–retina transplantations in patients with retinitis pigmentosa (RP) and age-related macular degeneration (AMD).¹ Visual acuity (VA) improved in seven of 10 study eyes and in three of 10 fellow control eyes. Some issues that merit consideration are: the study design, the basis of the visual improvement, the potential immunogenicity of the transplantation, alternative approaches to retinal transplantation, and current challenges to further progress. Each of these issues is considered below.

Regarding methodology, a strength of the trial is that VA was studied carefully before and after surgery. All patients underwent cataract extraction with intraocular lens placement and posterior capsulotomy before surgery in the study eye. Because fellow eyes did not, as a matter of protocol, undergo this procedure, there is a potential source of bias in the study design. Among the fellow eyes, seven underwent cataract surgery before the transplantation; two subsequently underwent cataract surgery; and one did not have cataract surgery (Radtke N, personal communication). Thus, the visual loss in the fellow eyes probably was the result of progressive retinal degeneration. The use of experimental visual stimulation videos may be a confounding variable. Patients were instructed to cover the nontransplanted eye, but compliance was a concern (Radtke N, personal communication). If these videos have an effect, it may be masked by the way in which the stimulation was applied. Some of the diagnostic testing (e.g., optical coherence tomography, MP1, scanning laser ophthalmoscopy [SLO], and multifocal electroretinography) was not standardized. This limitation does not detract from the fundamental findings of the study. Some of these tests probably do not have the resolution needed to identify the portion of host retina that is revitalized by the graft. Evidence from Stargardt disease patients indicates that one can lose approximately 90% of the cones in the fovea and still retain 20/30 to 20/100 vision.² Thus, the number of functioning photoreceptors mediating improved VA in the study patients may be so small that they cannot be visualized currently, even with high-resolution tech-

niques such as adaptive optics.³ SLO and MP1 testing, however, are valuable, as they permit identification of the preferred fixation locus(i) with respect to the graft.

It is possible that visual improvement in the study eyes is not entirely the result of the transplanted cells. In one animal model of RP, lensectomy and vitrectomy alone improved retinal survival.⁴ Retinal detachment (RD) seemed to have a neuroprotective effect on cones and rods in another animal model of RP.⁵ Furthermore, as the authors note, inserting a needle into the subretinal space without injecting cells can result in improved vision in animal models of retinal degeneration. The authors posit that the effect of surgery alone (vs the transplantation) is unlikely to account for the sustained improvement in vision based on the duration of the sham surgery effect in preclinical models. Nonetheless, because there is evidence that lensectomy, vitrectomy, and RD can improve photoreceptor survival in preclinical models and because the existence (and duration) of this effect in humans with RP, AMD, or both is unknown, there may be limitations in using unoperated fellow eyes as controls. Ideally, a fellow eye with a similar degree of disease severity at the start of the study that undergoes the same surgery as the study eye except for the receipt of the retinal graft is the best control for the sight-restoring effect of the transplanted cells. This approach poses ethical dilemmas, but they may not be insurmountable.

If visual improvement was the result of the transplantation, it seems likely to have been largely via a so-called rescue (vs a so-called replacement) mechanism,⁶ which is consistent with the MP1 findings in Patient 1 showing increased sensitivity in an area adjacent to but not overlying the graft. Whether visual recovery mediated by a retinal transplantation is better, the same, or worse than that achieved by administration of specific neurotrophic factors is unknown. In principle, RPE–retina transplantations can produce more than one neurotrophic substance, which may be an advantage of this approach. The degree of visual improvement in the eyes receiving transplantations was quite modest. Perhaps visual recovery would have been better if patients had undergone surgery earlier in the course of their disease. At this time, it may not be wise, based on the results of this study, to place fetal RPE–retina grafts under the fovea in patients with vision of 20/20 to 20/100. However, visual stabilization is highly desirable for patients with inexorably progressive disease. Assuming that the main benefit of the grafts is photore-

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TABLE. Some Potential Sources of Cells for Photoreceptor Replacement*

Cell Type	Developmental Capacity
Totipotent stem cell	Can form all lineages of the organism (including the placenta)
Pluripotent stem cell	Can form all lineages of the body (e.g., embryonic stem cell)
Multipotent stem cell	Can form multiple cell types of one lineage (e.g., retinal progenitor cell)
Reprogrammed cell	Nuclear transfer, cell fusion, or genetic manipulation to create a pluripotent cell
Immature postmitotic rod precursor	Can form rod photoreceptors
Fetal retina–retinal pigment epithelium sheets	Includes rods, cones, and other differentiated retinal neurons as well as Müller cells

*Modified from Jaenisch and Young.¹⁵

ceptor rescue, one may consider placing the tissue adjacent to the fovea in patients with relatively good VA.

Radtke and associates assessed immune surveillance of the transplantations carefully. As they note, the HLA antibody studies do not rule out the possibility that the donor tissue was recognized. The absence of inflammation on fluorescein angiography is encouraging in this regard, but recent results in AMD indicate that chronic inflammation can occur at the level of RPE–Bruch membrane with no signs of inflammation on angiography. The loss of RPE pigmentation in eight of 10 patients may be innocuous. In some cases, it may signify RPE death, which would be consistent with the progressive choriocapillaris atrophy seen in patient 7.⁷

It seems unlikely that, if effective, fetal RPE–retina transplantations can be provided on a large scale. Different approaches merit consideration, depending on whether one is attempting rescue vs replacement. RPE cells and photoreceptors can produce substances that have a rescue effect on host photoreceptors.^{8,9} Thus, one may be able to transplant adult RPE–photoreceptor sheets to stabilize vision. (It is possible that fetal tissue is less likely to undergo immune rejection.) In some cases, gene therapy probably will be more effective for photoreceptor rescue than cell-based therapy.^{10,11} Different types of cells may be

used to achieve photoreceptor replacement (Table). Multipotent retinal progenitor cells,¹² immature postmitotic rod precursors,¹³ and fetal RPE–retina sheets¹⁴ all have been transplanted in preclinical retinal degeneration models and have shown evidence of synapse formation with host retina and some improvement in visual behavior. At this time, however, the process is extremely inefficient. In one study, less than 0.5% of transplanted cells integrated with the host retina.¹³

Significant challenges for foveal reconstruction by replacement therapy include: efficient tissue delivery,¹⁶ integration of the transplantation with the host and reestablishment of functional synaptic circuitry,¹⁷ maintenance of an appropriate state of differentiation by the transplanted tissue,¹⁵ and immune surveillance.¹⁸ Solutions to these challenges may depend on the specific retinal degenerative disease in question, the duration of the disease, and the type of cell one is transplanting. Restoration of precision vision for patients with advanced disease seems more likely to be achieved by a replacement strategy than by rescue, so these obstacles are worth addressing. The work of Radtke and associates and many other investigators is bringing us closer to the resolution of these issues and the establishment of sight-restoring therapy for retinal degenerative disease.

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