Evidence of Retinal Function Using Microperimetry following Autologous Retinal Pigment Epithelium-Choroid Graft in Macular Dystrophy

Fred K. Chen, Gurmit S. Uppal, Gary S. Rubin, Andrew R. Webster, Peter J. Coffey, and Lyndon Da Cruz

PURPOSE. To describe the outcomes of autologous retinal pigment epithelium (RPE)-choroid graft in macular dystrophy.

METHODS. In this prospective interventional case series, five patients with macular dystrophy were enrolled to undergo autologous RPE-choroid patch graft between August 2005 and January 2007. All patients received preoperative and postoperative evaluations including visual acuity, contrast sensitivity, reading ability, microperimetry, fluorescein angiography, indocyanine green angiography, fundus autofluorescence (AF) imaging, and optical coherence tomography (OCT).

RESULTS. Patients were followed up for an average of 13.4 (9–23) months. Two patients gained reading acuity but only one regained visual task function after graft. This was maintained for approximately 12 months. Although there is an overall loss of visual acuity, contrast sensitivity, and reading ability, postoperative microperimetry demonstrated retinal sensitivity over the graft in all patients with maximum sensitivity, using a Goldmann size III stimulus of 200-ms duration, ranging from 12 to 20 dB. After surgery, one patient developed retinal detachment and two required cataract extraction at the time of removal of oil. ICG angiography demonstrated perfusion of the graft in four patients. With image registration, homogenous AF pattern in areas of the graft was found to be associated with retinal sensitivity.

CONCLUSIONS. Autologous RPE-choroid graft can be performed in patients with macular dystrophy. Although microperimetry showed evidence of retinal function over a perfused and autofluorescent graft, the overall loss of visual acuity and reading ability raises concerns over the use of this novel surgical technique in these patients. (Invest Ophthalmol Vis Sci. 2008; 49:3143–3150) DOI:10.1167/iovs.07-1648

Macular dystrophy is a heterogeneous group of disorders characterized by bilateral progressive and irreversible central visual loss. The age of onset is variable. Although its presentation can be asymmetrical, with loss of vision in one eye followed by loss in the second eye many months or years later, the ultimate visual acuity tends to be similar between the eyes. The exact pathophysiology of macular dystrophy is unknown. However, in a subset of this condition, linkage to several genes expressed in the photoreceptor cells suggests a possible sequence of events: abnormal outer segments and their interaction with retinal pigment epithelial (RPE) cells leading to RPE cell death with subsequent choriocapillaris atrophy and photoreceptor cell loss. In some of these patients, the macular lesion may resemble geographic atrophy of age-related macular degeneration (AMD), in which photoreceptor cell loss is also thought to result from primary RPE cell death or impaired chorioidal perfusion.

There is no effective treatment for patients with macular dystrophy. RPE cell transplantation is one therapeutic approach that may prevent progressive visual loss in the subset of patients in whom macular RPE atrophy precedes photoreceptor cell loss. The proof of principle for this approach comes from the wealth of information on the anatomic and functional outcomes of RPE transplantation in the Royal College of Surgeons (RCS) rat. In this model of retinal dystrophy, a mutation in the merTK gene prevents phagocytosis of the outer segment of photoreceptor cell by the RPE cell. Subretinal injection of RPE cells in this dystrophy model has been shown to rescue photoreceptor cells and to maintain visual function. Initial attempts in human RPE transplantation were limited to treatment of chronic and acute exudative AMD. Unlike the merTK mutation in the RCS rat, eyes with exudative AMD have RPE-Bruch membrane-choriocapillaris defects limited to the posterior pole and acute visual loss caused by retinal edema or subretinal hemorrhage secondary to choroidal neovascularization. In these patients, autologous patch graft of the RPE and choroid has been shown to become perfused and to support retinal function for up to 4 years. RPE transplantation as a cell suspension or a patch graft has also been performed in atrophic AMD. Similar to exudative AMD, autologous RPE-choroid graft in eyes with geographic atrophy can also become perfused and can support retinal function up to 12 months. Although RPE-choroid graft in macular dystrophy has not been reported, macular translocation, which in principle is a form of RPE reconstitution, has been performed in a patient with adult vitelliform macular dystrophy, with limited improvement in reading ability after surgery.

We performed a pilot study examining feasibility, safety, and outcomes—specifically the presence of retinal function—using microperimetry after autologous RPE-choroid graft in patients with macular dystrophy. We selected the eye with progressive visual loss for surgery and used the contralateral eye, which already had severe visual loss, as the internal control. This is the first report of the anatomic and functional outcomes of this novel surgical procedure in a cohort of patients with this condition.
MATERIALS AND METHODS

Patients

Five patients with macular dystrophy were enrolled between August 2005 and January 2007. These patients satisfied the following inclusion criteria: age 25 years or older, visual acuity of 6/36 or worse in the fellow eye, a clinical diagnosis of macular dystrophy, a recent (6 months) decline in visual function such as reading, no clinical or electrophysiological evidence of severe generalized retinal dysfunction, and the ability to consent to participate in the study. We chose patients with poor vision in one eye and deteriorating vision in the second, better-seeing eye so that we could capture this window of opportunity to reconstruct the submacular RPE before photoreceptor cells are permanently damaged or lost. Because patients are not aware of the loss of their central island of vision when this occurs in the first eye, we relied on awareness of this decline when it occurred in the second, better-seeing eye to guide the timing for RPE graft. Since the outcome of this type of surgery is unknown, we ensured that all study participants understood that the central island of vision could be damaged by the surgery and that other blinding complications could develop. Therefore, patients were excluded if they were unable to give informed consent, had ocular comorbidities that could impair vitreoretinal surgery and increase surgical risk, were unfit to receive general anesthetic, or were unable to complete the follow-up program.

The local research ethics committee approved this study on July 26, 2005 (05/Q0504/29). In addition to a detailed participant information sheet, each eligible patient received extensive explanation and counseling regarding the experimental nature and the potential risks of this treatment and the voluntary nature of their participation in this study. Written consent was obtained from each patient before enrollment. The tenets of the Declaration of Helsinki were followed.

Surgery

All surgical procedures were performed by one surgeon (LDC) at one center. The surgical technique was similar to that described previously.16,21 In these cases, however, removal of a subretinal neovascular membrane was not required. After a minimum of 2 months, patients underwent removal of silicone oil. Phacoemulsification cataract surgery was also performed only if there was visually significant lenticular opacity.

Visual Acuity, Contrast Sensitivity, and Reading Ability

Standardized refraction and best-corrected distance visual acuity (VA) were measured in all patients on the back-illuminated ETDRS charts (Lighthouse Low Vision Products, Long Island City, NY) at 4 m. Patients were instructed to read from the top of the chart and stopped only if an entire line could not be read. If fewer than 15 letters were read at 4 m, the patient was moved to 1 m from the chart reading with an add of +0.75 D. Letter score was converted to logarithm minimal angle of resolution (logMAR), as described by Holladay.22 Contrast sensitivity (CS) was measured at 1 m using a wall-mounted Pelli-Robson contrast sensitivity chart (Clément Clarke Inc., Harlow, Essex, UK). Scoring and stopping rules used are described by Pelli et al.23 Reading ability was assessed with the MNRead acuity charts (Lighthouse Low Vision Products). The chart contains 19 sentences of incremental print sizes ranging from −0.2 to 1.5 logMAR when the chart is read at 25 cm. Two different charts were used for different eyes. Patients held the chart 40 or 25 cm away from the eye (measured with a ruler) with the sentences covered initially. While wearing a +2.50 or +4.00 D add (for 40 or 25 cm, respectively) over the optimally refracted distance correction, the patient was instructed to read the sentence aloud as each sentence was revealed. A stopwatch was used to record the time taken to read each sentence. Reading acuity was calculated as recommended by the manufacturers. Maximum reading speed was calculated by taking the average of the speed at the plateau of the highest reading rates. If there was no plateau, the single highest reading speed was used. The ETDRS, MNRead, and Pelli-Robson charts were read under standard background luminance of 100 cd/m2 (±15%).

Fixation and Microperimetry

Fundus-controlled microperimetry was performed at two or more time points in five patients using the Nidek microperimeter, software version 1.6.0 (MP 1; Nidek Technologies, Padova, Italy). This was performed before slit lamp examination and fundus imaging. Pupils were dilated with tropicamide 1% and phenylephrine 2.5%. With a +4.00 D (ash) background illumination, a white cross fixation target (set at 100 asb) was used for recording fixation pattern during a 30-second period. The size of the cross was chosen so that the patient could see the center of the cross. Fixation stability and eccentricity were classified according to those proposed by Fujii et al.24 Microperimetry, using a Goldmann III stimulus of 200-ms duration and a 4 × 2 staircase thresholding strategy, was performed initially with a customized Cartesian grid pattern and repeated with an identical grid after surgery. Because of the retinal distortion after RPE-choroid graft in some patients, it was not possible to precisely register the preoperative and postoperative retinal images to ensure identical test loci at subsequent examinations. Therefore, new boundaries of the test grid were chosen to cover the graft and a rim of surrounding retina for follow-up microperimetry. The brightness of test stimulus ranges from 4 to 400 asb (20 – 0 dB). Starting stimulus brightness was set at 0 dB. During examination, the automated tracking system provided by the microperimeter compensated for any eye movement by monitoring a preselected reference landmark through the infrared camera and adjusting the test location every 40 ms. Microperimetric maps were overlaid on fundus color photographs and fundus autofluorescence (AF) images taken within 1 month of the microperimetry to enable analysis of any correlation between retinal sensitivity and graft AF pattern. Normal average macula sensitivity is between 16 and 18 dB for patients 40 to 70 years of age.35

Structural Assessment

All patients underwent preoperative and postoperative slit lamp examination, including grading of cataract according to the Lens Opacities Classification System (LOCS) III.26 Digital color photography with fluorescein angiography (1 g/5 mL) and indocyanine green (ICG) angiography (25 mg/5 mL) was performed (TRC-50 IA/IMAGEnet H1024 system; Topcon, Tokyo, Japan) before and after surgery. ICG angiography was examined specifically for an intrinsic vascular pattern within the graft, and fluorescein angiography was reviewed specifically for leaking neovascular tissues. Optical coherence tomography (OCT) with StratusOCT software version 4.0 (Carl Zeiss Meditec, Inc., Dublin, CA) or SOCT Copernicus software version 1.35 (Optopol Technology Sp. Z o.o., Rogów, Poland) was performed. For StratusOCT, six radial-line B scans (85 A scans/mm) through the fovea were obtained. For SOCT Copernicus, 50 or more raster-line B scans (88 A scans/mm) centered on the fovea and six radial-line B scans (353 A scans/mm) through the fovea were performed. We specifically examined for any evidence of the reflective layer within the outer retina that corresponds to the outer plexiform layer and for any signs of epiretinal membrane, intraretinal edema, and subretinal fluid. Fundus AF was obtained in all five patients by using a scanning laser ophthalmoscope (Heidelberg Retina Angiograph II [HRA II]; Heidelberg Engineering GmbH, Dossenheim, Germany). A series of five to nine images over a 30° field was acquired and then aligned and averaged with the image analysis software provided with HRA II (Heidelberg Eye Explorer; Heidelberg Engineering GmbH). Fundus AF images were analyzed qualitatively for changes in the intensity, distribution, and pattern of AF over and surrounding the graft during the follow-up period.

RESULTS

Patient Characteristics

Tables 1 and 2 summarize the demographic and baseline data of the five patients. These patients, between 41 and 66 years of age.
TABLE 1. Patient Summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Study Eye</th>
<th>Fellow Eye VA (logMAR)</th>
<th>Specific Clinical Features</th>
<th>PERG</th>
<th>FERG</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>R</td>
<td>1.10</td>
<td>AFD</td>
<td>Undetectable</td>
<td>Borderline normal cone function</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>L</td>
<td>1.00</td>
<td>PPA</td>
<td>Undetectable</td>
<td>Abnormal cone function</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>M</td>
<td>L</td>
<td>0.80</td>
<td>None</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>M</td>
<td>R</td>
<td>0.80</td>
<td>BEM</td>
<td>Undetectable</td>
<td>Borderline normal cone and rod function</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>F</td>
<td>L</td>
<td>1.00</td>
<td>AFD</td>
<td>Reduce</td>
<td>Borderline normal cone function</td>
</tr>
</tbody>
</table>

AFD, autofluorescent drusen; BEM, bull’s eye maculopathy; FERG, full-field electroretinography; L, left; PERG, pattern electroretinography; PPA, peripapillary atrophy; R, right.

age at enrollment, were followed up for 9 to 23 (mean, 13.4) months after graft. Baseline VA of the operated eyes ranged between 44 and 69 ETDRS letters (0.32–0.82 logMAR). Visual acuities in the fellow eye ranged from 30 to 45 letters (0.80–1.10 logMAR), and they had been stable at these levels for several years. Two patients were unable to read the largest print size at 25 cm (1.5 logMAR) on the MNRead chart before surgery. All patients were phakic before surgery and had LOCS III cataract grading scores of 2 or less for nuclear color and opalescence. None had any cortical or posterior subcapsular opacity. In two patients (patients 3 and 4), RPE atrophy already involved the center of fovea in the study eye with the patient eccentrically fixating. The remaining three patients (patients 1, 2, and 5) had variable amounts of RPE atrophy sparing enough fovea to allow foveal fixation before surgery. Patient 2 had a family history suggestive of autosomal dominant inheritance. He had an R172W mutation in the peripherin/RDS gene associated with normal implicit time but reduced cone amplitude, similar to that described previously.27 He also had the characteristic peripapillary atrophy and increased, speckled, autofluorescence pattern surrounding the area of atrophy.27 Patients 1 and 5 had features of autofluorescent basal laminar drusen. They had no history of renal disease, and renal functions were normal. None of the patients had the yellow subretinal flecks typically seen in Stargardt disease and fundus flavimaculatus or the yellow submacular deposit characteristic of Best disease and adult vitelliform macular dystrophy.

Surgical Outcome

All five grafts were successfully transplanted under the fovea (Fig. 1). Although grafts were harvested as a round patch, when delivered through a small retinotomy, the graft has a tendency to wrap around the spatula and form an elongated shape with folded edges when released in the submacular space (Fig. 1). Two patients had intraoperative retinal breaks requiring additional retinopexy. One patient had macula-on retinal detachment 2 months after graft, requiring revision and delaying the removal of oil to 5 months after surgery. One patient required two operations for oil removal because of the significant residual oil after the initial surgery. Cataracts developed in two patients (patients 1 and 5) and were removed at the time of oil removal. The macular retinotomy was open in one patient with no adjacent epiretinal membrane or retinal detachment (Fig. 1). All patients had some degree of epiretinal membrane, but one had significant epiretinal membrane causing focal retinal thickening inferotemporal and superotemporal (patient 4) to the graft, not affecting the retinotomies (Fig. 1). Patient 2 developed a stable intraretinal neovascularization on the nasal border of the graft that was not associated with subretinal fluid, exudates, or hemorrhage during the 11 months of follow-up (Fig. 1).

Functional Outcome

The median VA declined from 0.60 to 1.10 and 1.08 logMAR at the 6-month and the final visit, respectively. Loss of VA ranged from two to nine lines at the final visit. The median CS also declined from 1.25 to 0.90 and 1.05 logCS at the 6-month and the final visit, respectively. The change in CS ranged from a gain of two to a loss of three lines at the final visit. Two patients gained reading acuity after surgery, but only one of these felt his near vision was functionally better (>0.3 logMAR improvement in both patients at the 6-month follow-up). Reading

### Table 2. Visual Outcome and Surgical Complication Summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>Visual Acuity (logMAR)</th>
<th>Contrast Sensitivity (logCS)</th>
<th>Reading Acuity (logMAR) (MRS, words per minute, CPS, logMAR)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6-Month</td>
<td>Final</td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>0.76</td>
<td>1.10</td>
<td>0.96</td>
<td>1.20</td>
</tr>
<tr>
<td>2</td>
<td>0.44</td>
<td>1.40</td>
<td>1.32</td>
<td>0.60</td>
</tr>
<tr>
<td>3</td>
<td>0.32</td>
<td>1.34</td>
<td>1.08</td>
<td>1.65</td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>1.00</td>
<td>1.06</td>
<td>1.50</td>
</tr>
<tr>
<td>5</td>
<td>0.60</td>
<td>1.10</td>
<td>1.12</td>
<td>1.25</td>
</tr>
</tbody>
</table>

CPS, critical print size; logCS, logarithm of contrast sensitivity; MRS, maximum reading speed; NA, not available; RD, retinal detachment; ROSO, removal of oil
acuity was unchanged for one patient and declined in two patients (>0.8 logMAR loss) at 6 months (Table 2). Of the three patients with foveal fixation before surgery, one remained fixating at the fovea after surgery. His improved near acuity was maintained until approximately 12 months after surgery. When he was tested again with microperimetry at 16 months, two preferred retinal loci were present with the new locus fixating at the fovea after surgery. His improved near acuity was unchanged until approximately 12 months after surgery.

Preoperative microperimetry was available for comparison in four patients. A common feature was the presence of dense central scotoma surrounded by a rim of reduced sensitivity. In patient 1, after surgery, retinal sensitivity was present over the inferotemporal portion of the graft (Fig. 2A) and at the fovea (located adjacent to the inferior edge of the graft; Fig. 2B). The sensitivity over the inferotemporal region of the graft and at the fovea declined during reexamination at 16 months (Fig. 2C). Patients 2, 3, and 4 had some retinal sensitivity over the edge and the center (patient 4) of the graft within 6 months that deteriorated further at approximately 1 year (Figs. 2D-R). Patient 5 had retinal sensitivity over the superior half of the graft at 9 months (Figs. 2U-X). Table 3 summarizes the findings of microperimetry.

**Anatomic Outcome**

Postoperative angiography in four patients demonstrated an intrinsic vascular pattern in the area of RPE-choroid graft suggesting perfusion of the transplanted choroid patch at 6 months (Fig. 1). Although AF was present over all five grafts to a varying degree, patient 4 had the least intensity, with only a faint AF signal at the superior pole of the graft. Small portions of the graft exhibited a homogenous pattern of AF in the other four patients: temporally (patient 1), superiorly (patients 2–5), and inferiorly (patient 3; Fig. 2). These areas of the graft with focal retinal traction outside the graft were observed at 8 months with horizontal slices (Fig. 2). Increased AF corresponded to the edge of RPE atrophy at the area of intraretinal neovascularization (arrow) away from the graft. Fundus photograph of patient 3 at baseline (I) and at 12 months (J) showing pigment hyperplasia at the side of the retinotomy. ICG was unavailable during follow-up, but AF imaging showed the presence of AF at the site of pigment hyperplasia and increased AF temporal to the graft (K). Spectral OCT at 12 months with horizontal slices (L) showed foveal depression with irregular graft surface (upper) and intact outer retinal structures (asterisk) over inferior portions of the graft (lower). Typical bull’s-eye appearance in patient 4 before surgery (M) and the graft at 10 months (N) showing focal tractional elevation of the retina (asterisk). ICG angiography showed an intrinsic choroidal vascular pattern within the superior part of the graft (O). Spectral OCT (P) showed foveal depression over the graft (upper) and an area of focal retinal traction outside the graft (lower).
FIGURE 2. Patient 1 had a visual acuity of 1.10 logMAR and a reading speed of 57 words per minute (0.80 logMAR text) at the 6-month follow-up, and microperimetry with 70 test loci showed a maximum retinal sensitivity of 20 dB over the temporal part of the graft (A) and in the foveal region near fixation (B). The temporal region of the graft was tested at 16 months (C) using 41 test loci. A maximum sensitivity of 11 dB over the graft with eccentric and relatively unstable fixation temporal to the graft was found. At this time, visual acuity was 0.96 logMAR, and the patient was unable to read the 1.50 logMAR text. Sensitivity is seen over a small area of the graft with homogenous autofluorescence pattern (D). Patient 2 had a large central scotoma on preoperative microperimetry (E). He had a maximum light incremental sensitivity of 14 dB over the graft (F) with unstable and eccentric fixation outside the graft (G) at 6 months. By 11 months, maximum sensitivity dropped to 10 dB at the edge of the graft (H, I). Patient 3 had a small central scotoma on preoperative microperimetry (J). Retinal sensitivity (maximum, 14) was present over the inferior and inferotemporal aspects of the graft (K), with unstable eccentric fixation (L) at 3 months after surgery. By 12 months, the maximum sensitivity had reduced to only 6 dB inferiorly (M, N). Patient 4 had a small ring scotoma but used the small central island for fixation (O). The maximum sensitivity was 14 dB (P) at 6 months, with eccentric fixation outside the graft (Q). By 12 months, only a small area of retina over the graft superiorly, corresponding to faint autofluorescence on the graft (R, S), was functioning. Patient 5 had a small central scotoma at baseline (T). Her microperimetry at 9 months showed retinal sensitivity over the superior half of the graft and eccentric and relatively unstable fixation temporal to the graft (U–W). The superior half of the graft had the more homogenous pattern of autofluorescence (X).
and the opening of the macular retinotomy (Fig. 2). OCT showed prominent and acute elevation of the highly reflective band that was likely to represent the graft RPE layer. In parts of the graft, the undulation of the highly reflective band suggested folds on the surface of the graft. Over some portions of the graft, the retina retained the reflective layer derived from the outer plexiform layer (Fig. 1).28 Areas with intact outer retinal structures corresponded to areas with retinal sensitivity on microperimetry. There was no evidence of retinal edema or subretinal fluid except for the small area of epiretinal membrane traction outside the graft, causing retinal thickening (Fig. 1).

**DISCUSSION**

In this pilot study, we have shown that autologous RPE-choroid graft can be performed in patients with advanced stages of macular dystrophy. However, some patients had significant intraoperative and postoperative complications accompanied by an overall loss of visual acuity and reading ability. Even patients who did not have operative complications had declines in vision. Despite the poor outcome, microperimetry demonstrated retinal sensitivity over all five grafts and showed that the maximum sensitivity over the graft can be within the normal limit (20 dB, patient 1).

The use of a microperimeter, first described by Midena,25,29 has been reported in studies of autologous RPE-choroid graft in patients with exudative AMD.17,21,30 We used this technique to study the ability of the grafted RPE-choroid patch to support and maintain retinal function. In some patients, the area of highest sensitivity was near the edge of the graft. It is possible that in these patients, retina not over the graft was also stimulated by an overall loss of visual acuity and reading ability. Even patients who did not have operative complications had declines in vision. Despite the poor outcome, microperimetry demonstrated retinal sensitivity over all five grafts and showed that the maximum sensitivity over the graft can be within the normal limit (20 dB, patient 1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline* (min, max, number of test loci), dB</th>
<th>Within 6 Months (min, max, number of test loci), dB</th>
<th>At Final Follow-up† (min, max, number of test loci), dB</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>2.4 (0, 20, n = 25)</td>
<td>1.5 (0, 11, n = 17)†</td>
</tr>
<tr>
<td>2</td>
<td>1.0 (0, 10, n = 57)</td>
<td>1.3 (0, 14, n = 20)</td>
<td>0.7 (0, 10, n = 20)</td>
</tr>
<tr>
<td>3</td>
<td>11.0 (0, 20, n = 27)</td>
<td>1.6 (0, 14, n = 27)</td>
<td>1.0 (0, 6, n = 27)</td>
</tr>
<tr>
<td>4</td>
<td>4.5 (0, 20, n = 22)</td>
<td>1.2 (0, 14, n = 22)</td>
<td>0.5 (0, 10, n = 22)</td>
</tr>
<tr>
<td>5</td>
<td>6.5 (0, 18, n = 24)</td>
<td>NA</td>
<td>3.4 (0, 12, n = 31)</td>
</tr>
</tbody>
</table>

Max. maximum; min, minimum; NA, not available.
* Preoperative mean light incremental sensitivity was determined by averaging the responses over the area of retina that subsequently received autologous RPE-choroid graft. Preoperative images were registered with postoperative images to ensure the equivalent area of retina was selected for analysis.
† Follow-up microperimetry did not cover the nasal aspect of the graft.

**TABLE 3. Mean Retinal Light Incremental Sensitivity over Graft**

Although two patients regained reading ability at 6 months, all five patients lost distance visual acuity after graft. In one of these two patients, fixation was over the graft in a small island of vision. This improvement in reading acuity may be explained by the restoration of retinal function by the RPE-choroid patch graft. Previous studies of macular translocation have also found greater improvement in near visual function than distance VA, which was attributed to reduction of scotoma size.53-55 The reason for improved reading ability but diminished distance VA in patient 5 can be explained by the improvement in visual span as fixation shifted from the small foveal central island to the edge of the central scotoma.56 The unexpected poor reading performance before surgery might have resulted from factors related to perceptual span, eye movement, or motivation.57-58 The overall loss of vision and retinal sensitivity over and around the graft in all patients after autologous RPE-choroid graft is a major concern. It might have been related to delayed graft perfusion, intrinsic dysfunction of the transplanted RPE cells, surgical trauma, or genetically determined primary photoreceptor cell loss as part of the natural history. Given the possibility of reduced photoreceptor cell reserve in these patients with advanced macular dystrophy, the outer retina may be more prone to mechanical or photic injury during submacular surgery or ischemic injury while the graft was not yet vascularized. Although four of the five patients had no definite abnormalities of the preoperative full-field ERG, the borderline normal cone or rod responses might have indicated that mild dysfunction of midperipheral RPE cells was present and thus might have limited their ability to rescue macular photoreceptors. One patient with a peripherin/RDS R172W mutation also had a poor outcome. This mutation has been associated with varied full-field and pattern ERG responses ranging from isolated unrecordable macular responses to severe generalized cone and rod dysfunction.27,39-42 This is not surprising because the peripherin/RDS gene is expressed in cone and rod photoreceptors. More recently, Roorda et al.43 reported photoreceptor cell loss preceding RPE cell death in two patients with cone-rod dystrophy using adaptive optics imaging. Keeping these in mind, we can hypothesize that the poor outcome of autologous RPE-choroid graft in this patient with peripherin/RDS mutation might have been related to the primary loss of photoreceptor cells and to the greater susceptibility of foveal cones to submacular surgery. In other words, the presence of the peripherin/RDS mutation may predict poor outcome following RPE graft. It is hoped that further understanding of the genetic defects and pathophysiology of macular dystrophy may be helpful in case selection for RPE transplantation.
The complications seen after RPE-choroid graft in this group of patients are similar to those described previously in patients with AMD. Intraoperative and continued postoperative release of RPE cells from the midperipheral RPE donor site into the vitreous cavity contributed to the epiretinal membrane and consequent retinal distortion and opening of the macular retinotomy. Given the absence of metamorphopsia, removal of these membranes was not indicated. Similar to what was observed in patients with geographic atrophy, autologous RPE-choroid graft in macular dystrophy can become perfused despite the lack of inner choroidal vasculature in the area directly underneath the graft. Intentional and unintentional surgical trauma to the Bruch membrane during insertion of the graft may have a role in promoting graft perfusion. Damage to the Bruch membrane may incite an inflammatory response that aids the proliferation of endothelial cells at the interface, between the choriocapillaris at the recipient site and the large choroidal vessels of the undersurface of the patch graft. Experiments in a large animal model have demonstrated bridging vessels between the recipient choroidal bed and the choroid graft as early as 1 week, even if the Bruch membrane was not intentionally damaged and when the graft was placed upside down. The main limitation of this study was the small sample size. However, we reported outcomes in only five patients for several reasons. This pilot study was designed with strict inclusion criteria, such as recent visual decline, so that RPE-choroid graft could be performed at the optimal time before the complete loss of central vision. Furthermore, we had to assess feasibility and safety outcomes early to determine whether the trial should continue or whether modification to the study design was required. Another limitation was the inclusion of patients with advanced disease and borderline or mildly abnormal generalized retinal dysfunction on ERG. These factors are likely to confound the assessment of whether midperipheral RPE can support retinal function in macular dystrophy. Given the unknown risks and benefits of this novel surgical technique for a new indication, it was not considered appropriate to include patients with only mild visual loss.

**CONCLUSIONS**

This study showed that it is possible for retinal function to be maintained over the autologous RPE-choroid graft for a prolonged time in patients with macular dystrophy. However, the high operative complication rate and the poor visual outcomes raise major concerns regarding safety in the use of autologous RPE-choroid graft for this group of patients. Based on these early findings, we postulated that the poor visual outcomes might have been attributed to the choice of patients with advanced disease, preexisting retinal or RPE dysfunction, and genetically determined primary photoreceptor cell loss. Although advanced disease may limit the outcome, it is also inappropriate to operate on patients with early-stage disease given the high complication rate of the current surgical technique in this group of patients. As such, we cannot recommend autologous RPE-choroid graft as a therapeutic approach for patients with macular dystrophy. To take cell-based therapy in macular and retinal dystrophies to the next stage, more work is needed to refine the subtretinal surgical techniques to safely operate at an earlier stage of the disease. We feel that the surgical procedure can be safer if a precreated patch with RPE cells, possibly of stem cell origin, is used during standard pars plana vitrectomy and subtretinal placement of the patch graft.

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**References**


