Transplantation of Autologous Iris Pigment Epithelium After Removal of Choroidal Neovascular Membranes

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Background: Transplantation of autologous iris pigment epithelium (IPE) into the subretinal space has been suggested as one approach for the treatment of age-related macular degeneration, as well as for other conditions in which loss of retinal pigment epithelium (RPE) occurs. Surgical removal of choroidal neovascular membranes is associated with traumatic loss of the RPE cell layer, disruption of the integrity of the photoreceptor-RPE complex, and limited visual outcome.

Objective: To examine whether IPE cells can substitute for RPE cells to be transplanted to the subretinal space of patients with either RPE degenerative disease or traumatic loss of the RPE cell layer after subretinal surgery.

Methods: Autologous IPE cells were transplanted to the subretinal space in 20 consecutive patients undergoing removal of subretinal fibrovascular membranes using pars plana vitrectomy. Autologous IPE cells were harvested by iridectomy, isolated, and transplanted directly to the subretinal spaces. Transplants were evaluated for 6 to 11 months by funduscopy, fluorescein angiography, and scanning laser ophthalmoscopic (SLO) microperimetry.

Results: For the entire follow-up period, no evidence of any immunologic response was observed. Revisional surgery was necessary in 3 patients because of complications (rhegmatogenous retinal detachment [n=1]; proliferative vitreoretinopathy [n=1]; and macular pucker [n=1]); 1 patient did not receive IPE cells. Five of 19 phakic eyes underwent cataract surgery; in 1 case this was combined with the vitrectomy. Five patients showed improved visual acuity of 3 to 4 lines, 13 patients had stable visual acuity (±2 lines), and 2 patients had reduced visual acuity of 6 lines.

Conclusions: In this pilot study, the transplantation of autologous IPE cells was done as an addition to conventional surgical excision of choroidal neovascular membranes. Transplanted cells were well tolerated in the subretinal space and did not adversely affect the function of the photoreceptors, since improvement or stable visual acuity was observed in 18 patients after IPE transplantation. These results suggest that autologous IPE cells may be used as a substitute for autologous RPE cells to transplant to the subretinal space to treat age-related macular degeneration.

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A NUMBER of investigators have postulated that the transplantation of retinal pigment epithelial (RPE) cells may be a useful approach for the treatment of age-related macular degeneration (AMD). However, the transplantation of fetal RPE cells in human subjects has resulted in rejection caused by slow host-graft response.[1,2] To prevent rejection, it would be necessary to transplant autologous RPE cells; however, to obtain autologous RPE cells for transplantation is difficult. On the other hand, autologous iris pigment epithelial cells (IPE), which share the same embryonic origin as RPE, can be readily obtained by rather simple surgical procedures. Previous studies have demonstrated that RPE and IPE have in common a number of important properties, such as pigmentation, cellular morphology, and tight junctions.[3-7] In addition, it has been shown that in vitro human, porcine, and rat IPE cells acquire the ability to phagocytize photoreceptor outer segments (ROS), which is a specific property of RPE cells in situ.[8-10] It has been also shown that in rabbits autologous IPE cells can be transplanted to the subretinal space, where they form a monolayer on top of the original RPE, phagocytize ROS, develop microvilli, establish contact with the photoreceptor outer segments, and show no evidence of rejection during a 20-week follow-up.[11] Recent studies have demonstrated that bovine IPE express messenger RNA for proteins involved in retinol metabolism, namely RPE65, cellular retinoic acid binding protein, and 11-*cis*-dehydrogenase;

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PATIENTS AND METHODS

PATIENTS

Iris pigment epithelial cells were transplanted to the subretinal space of 20 consecutive patients (15 women and 5 men) aged 33 to 85 years who underwent surgery, between June and November 1998 for removal of subretinal neovascular membranes. Informed consent was obtained from each patient, indicating that the procedure was a novel experimental approach and an alternative to conventional membrane extraction surgery, laser photocoagulation, and radiation therapy. Fluorescence angiography in 10 of 17 patients with AMD depicted the classic subfoveal neovascularization, whereas occult neovascularization was observed in the remaining patients (**Figures 1** and **2**). Three younger patients showed well-defined choroidal neovascular membrane (CNV) secondary to dominant drusen or myopia.

Visual acuity, fundus photography, fluorescein and indocyanin green angiography, and macular perimetry were performed preoperatively, 3 weeks, 3 months, and 6 months after surgery, and at the last visit of follow-up. Each patient was also examined by ophthalmoscopy and slitlamp microscopy at all times. Visual acuity was determined using Early Treatment Diabetic Retinopathy Study charts. Macular perimetry and fixation point was evaluated using a scanning laser ophthalmoscope (SLO II; Rodenstock, Munich, Germany).

CELL ISOLATION

A large iridectomy was performed on the eye undergoing vitrectomy over a peripheral corneal incision. The tissue was placed in a glass well with a drop of balanced salt solution (BSS), and the IPE cells were isolated using the procedure of Hu et al,[5,6] but without using trypsin, to avoid possible damage and alteration to the cells. Cells were suspended in a volume of 20 µL of BSS for injection.

SUBRETINAL TRANSPLANTATION

Before surgery, we obtained autologous serum from each patient, which was then transferred to the operating room. In all patients, a 3-port pars plana vitrectomy was performed. A small retinotomy was made superior or temporal to the fovea; the fibrovascular membrane was seized with a forceps and extracted slowly through the retinotomy. If necessary, the bleb retinal detachment was enlarged by injecting a stream of BSS. The IPE cells were injected into the subretinal space using a Hamilton syringe fitted with a glass pipette tip. The syringe, which had been coated with autologous serum before filling it with IPE cells, was introduced and positioned just over the retinotomy. After the transplantation was completed, a fluid-air or a fluid-gas exchange was performed. In one case, cataract surgery before iridectomy and vitrectomy was performed.

HISTOLOGY

The fibrovascular membranes were fixed in 4% formaldehyde stained with hematoxylin-eosin and analyzed by light microscopy.

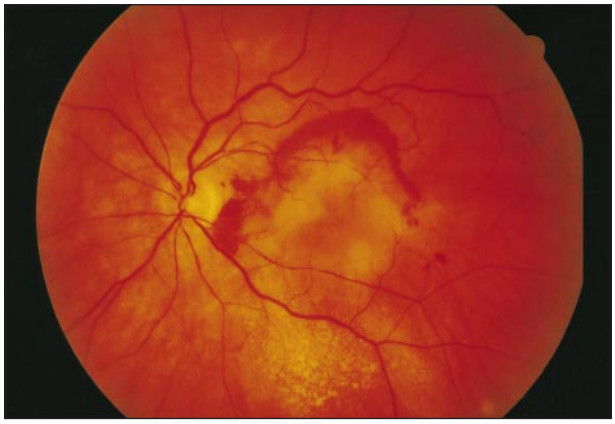

Figure 1. *Fundus photography of a 77-year-old patient with occult choriodal neovascularization before surgery.*

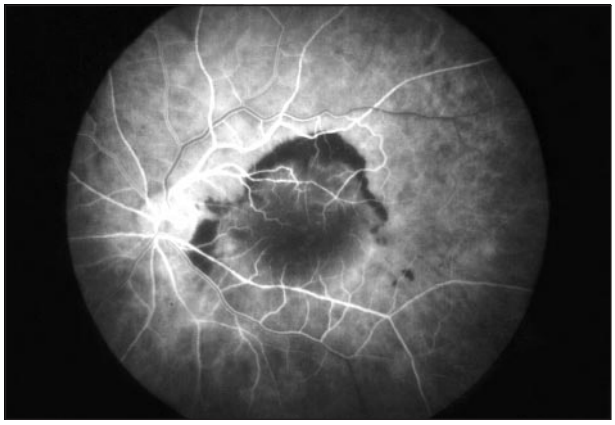

Figure 2. *Fluorescein angiography of the same patient as in Figure 1 before surgery.*

however, immunohistochemistry did not reveal the presence of the protein in IPE cells in situ.[12] Adult RPE and IPE cells retain the ability to transdifferentiate into other cell types, such as lens epithelial cells[13,14] and neural retinal cells.[15-17] Since IPE cells are phenotypically plastic, have in common many properties with RPE cells, and have a common embryonic origin, it is can be assumed that IPE cells transplanted into the subretinal space would transdifferentiate into RPE cells. Therefore, IPE cells seem to be an ideal substitute for RPE cells to be transplanted to the subretinal space of patients that have RPE degenerative diseases, or of patients who suffer traumatic loss of the RPE cell layer after subretinal surgery.

RESULTS

SUBRETINAL TRANSPLANTATION

Autologous IPE cells were transplanted in 19 of 20 patients. In 1 patient, the retinal bleb could not be enlarged sufficiently to inject the cell suspension; this patient underwent revision vitrectomy and pucker peeling 5 months after the initial surgery. Two of the 19 patients successfully injected with IPE cells experienced significant complications, namely retinal detachment and proliferative vitreoretinopathy, during the first 2 months

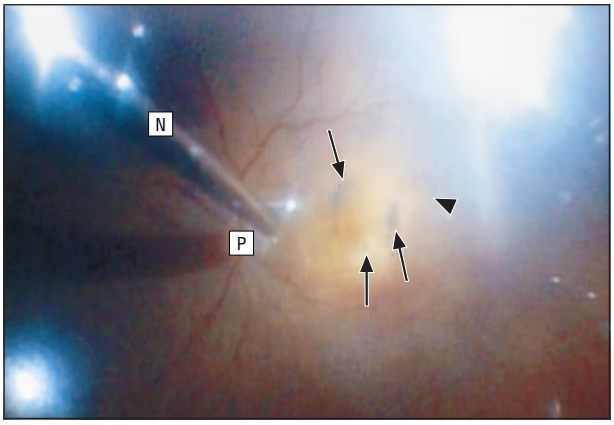

Figure 3. *Intraoperative setting of subretinal iris pigment epithelial transplantation of the same patient as in Figure 1. The transplanted cells can be identified as patches of heavy pigmentation at the site of transplantation (arrows); the arrowhead indicates the retinotomy site; N, the fluid needle; and P, the optic nerve head.*

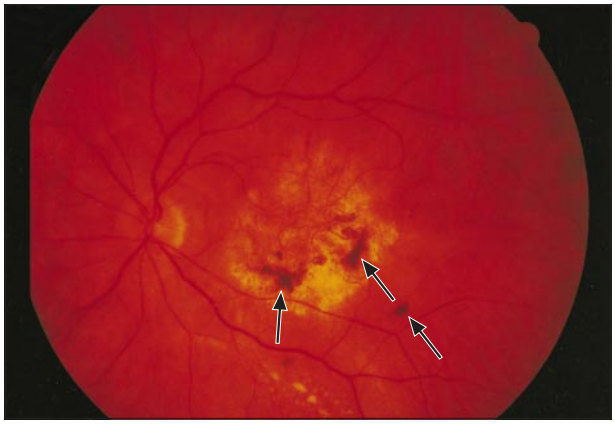

Figure 4. *Fundus photograph of the same patient as in Figure 1, 6 weeks after subretinal membrane extraction and iris pigment epithelial transplantation. The transplanted cells can still be identified as patches of heavy pigmentation at the site of transplantation (arrows), although they moved in the subretinal space because of gravity.*

postoperatively and at 3 months after the transplantation. These patients underwent revision vitrectomy with silicone oil endotamponade. The patient with the proliferative vitreoretinopathy had to undergo a second revisional vitrectomy with silicone oil endotamponade, combined with cataract surgery, because of the growth of new membranes. Five of 19 phakic eyes underwent cataract surgery; in 1 case, this was combined with the initial vitrectomy and transplantation.

In fundus photographs, transplanted cells appeared as a darker zone in the area of the transplant (**Figures 3** and **4**), which seemed to remain stable in size and shape throughout the observation period. Throughout the 6- to 11-month follow-up period, the retina seemed healthy and no evidence of immunologic rejection (eg, edema) was observed in any patient.

VISUAL ACUITY

Functional results measured with the Early Treatment of Diabetic Retinopathy Study charts are summarized in the **Table**. Five patients showed improved visual acuity of 3 to 4 lines, 13 patients retained stable visual acuity (±2 lines), and 2 patients showed reduced visual acuity of 6 lines. Of the 2 patients who showed decreased visual acuity, one was the patient who had experienced proliferative vitreoretinopathy and underwent 2 revisional interventions; the other suffered from progressive maculopathy (dominant drusen) accompanied by choroidal neovascularization with subfoveal extension. The fellow eye of this patient showed a poor spontaneous course of the disease.

ANGIOGRAPHY

Preoperative angiography revealed classic subfoveal neovascularization in 10 eyes and occult neovascularization in 7 eyes (Figure 2). The eyes of 3 younger patients showed either dominant drusen or CNV associated with myopia. We did not observe any recurrence of CNV at any point in any patient in the postoperative angiograms. The pigment epithelium defect in the area of membrane extraction was well demarcated, and no evidence of edema was present at any time (**Figure 5**). In most cases, the transplanted IPE cells could be identified as dark spots or islands (Figure 5).

MACULAR PERIMETRY (SLO)

Preoperative perimetry showed reproducible results in 9 patients; 4 eyes fixated centrally, 2 above the fovea, 1 nasally, 1 temporally, and 1 below the fovea. Two patients with central fixation retained their fixation point throughout the follow-up period. Seven patients fixated above the fovea after surgery, 10 nasally, and 1 temporally to the fovea. In the postoperative follow-up, SLO fixation results remained stable throughout the follow-up period in all patients.

Two patients (**Figure 6**) showed responses over the transplanted areas at 6 weeks; however, these responses were no longer detectable at 3 and 6 months postoperatively.

COMMENT

Surgical extraction of choroidal neovascular membranes has been associated with limited visual outcome, especially in cases with ill-defined AMD.[18-21] Most studies have concluded that visual acuity in the best cases can be stabilized or slightly improved after membrane extraction, and that to improve postoperative visual acuity, membrane extraction should be accompanied by the restoration of the Bruch membrane–RPE complex.[18,20] The development of neovascularization leads to irreversible damage to the RPE and photoreceptors, and removal of the membranes is associated with the traumatic loss of the RPE cell layer.[22,23] Gouras et al[24] postulated that RPE cell transplantation to the area of RPE loss would reestablish functional and morphological integrity of the retina-photoreceptor complex and thus improve or restore vision. Algvere and coworkers[1,2] transplanted human fetal RPE cells in patients with nonexudative and exudative AMD; however, the cells were rejected, especially in patients with neovascu-

Patient Data*

Patient No.†/Diagnosis	Visual Acuity						Difference in VA Steps (ETDRS)	Follow-up, mo
	Before	3 Weeks Later	3 Months Later	6 Months Later	Final	Final/Before		
1/AMD (o)	20/400	20/250	20/250	20/200	20/200	Improved	+3	7
2‡/AMD (c)	20/1000	20/400	20/640	20/400	20/400	Improved	+4	11
3/AMD (c)	20/400	20/320	20/250	20/125	20/160	Improved	+4	6
4/drusen	20/500	20/200	20/200	20/200	20/200	Improved	+4	9
5/AMD (c)	20/1000	20/400	20/400	20/400	20/500	Improved	+3	6
6‡/AMD (o)	20/200	20/200	20/200	20/125	20/125	Stable	+2	8
7/myopia	20/125	20/125	20/100	20/80	20/80	Stable	+2	9
8/AMD (c)	20/200	20/400§	20/200	20/125	20/125	Stable	+2	7
9/AMD (c)	20/250	20/200	20/160	20/160	20/200	Stable	+1	6
10‡/AMD (c)	20/800	20/800	20/400	20/400	20/500	Stable	+2	6
11/AMD (o)	20/250	20/200	20/200	20/200	20/200	Stable	+1	7
12‖¶/AMD (c)	20/640	20/640	20/500	20/320	20/400	Stable	+2	6
13/AMD (c)	20/125	20/125	20/100	20/100	20/100	Stable	+1	6
14#/AMD (c)	20/400	20/500	20/320	20/500	20/400	Stable	0	9
15#/AMD (o)	20/160	20/250	20/200	20/160	20/160	Stable	0	9
16#**††/AMD (o)	20/500	20/500	20/400	20/400	20/800	Stable	–2	9
17/AMD (o)	20/125	20/250§	20/320§	20/200	20/200	Stable	–2	9
18‡/AMD (o)	20/250	20/250	20/250	20/250	20/320	Stable	–1	9
19‡‡§§/AMD (c)	20/200	20/320	20/500§	20/640§	20/800§	Worse	–6	11
20/dominant drusen	20/200	20/500§	20/640§	20/800§	20/800§	Worse	–6	7
Mean VA	20/320	20/320	20/250	20/250	20/250	. . .		
VA≥0.1, No. of patients	. . .	6	7	0	. . .	. . .		

*VA indicates visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; AMD, age-related macular degeneration; o, occult choroidal neovascularization; c, classic choroidal neovascularization; ellipses, not applicable.

†All patients underwent parts plana vitrectomy with subretinal removal or choroidal neovascularization and transplantation of autologous iris pigment epithelium cells unless otherwise indicated.

‡Also underwent cataract surgery.

§Visual acuities below 2 lines of the initial VA.

‖Received subretinal surgery without iris pigment epithelium transplantation.

¶Patient underwent revisional vitrectomy and pucker peeling.

#Rhegmatogenous retinal detachment treated by revision vitrectomy with silicone oil endotamponade.

**Removal of silicone oil combined with cataract surgery.

††Iris capture was treated by anterior segment revision, followed by retrolental bleeding.

‡‡Proliferative vitreoretinopathy retinal detachment was treated by revisional vitrectomy and silicone oil endotamponade.

§§Proliferative vitreoretinopathy was treated by revisional vitrectomy and silicone oil endotamponade combined with cataract surgery.

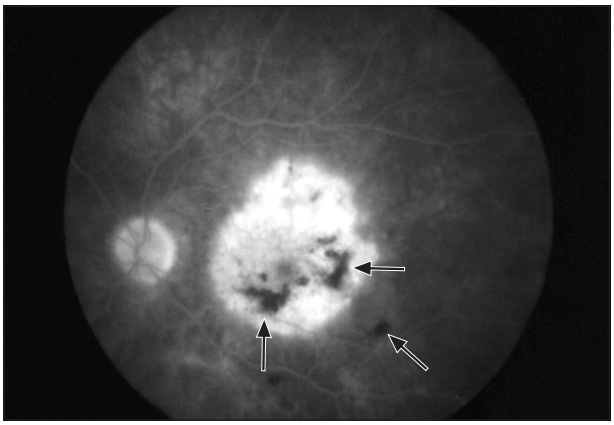

Figure 5. *Fluorescein angiography of the same patient as in Figure 1, 6 weeks after surgery. The pigment epithelium defect is clearly demarcated and the transplanted iris pigment epithelial cells are visible as dark spots (arrows).*

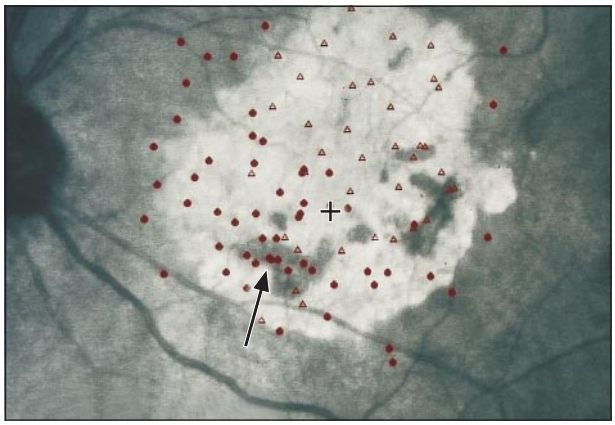

Figure 6. *Microperimetry of the same patient as in Figure 1, 6 weeks after surgery. Responses over the transplanted iris pigment epithelial cells (arrow). Dots indicate a positive response, in which stimulus was detected; deltas indicate a negative response, in which stimulus was not detected; and the plus sign represents the main fixation point.*

lar AMD. These studies demonstrated that transplantation of human RPE cells to the subretinal space is feasible and that in patients with an intact blood-retinal barrier, namely patients with dry AMD, these RPE cells survive for up to 12 months without adversely affecting the photoreceptors.[1,2] When the fetal RPE cells were transplanted to the subretinal space after the removal of subfoveal membranes, macular edema accompanied by reduction of visual acuity developed over 1 to 6 months, suggesting host-graft rejection.[1,2]

TRANSFORMATION OF IPE CELLS IN THE SUBRETINAL SPACE AND LACK OF REJECTION

To prevent rejection, it would be necessary to transplant autologous RPE cells. Since autologous RPE cells are difficult to obtain, it may be possible to transplant autologous IPE cells, which hypothetically could acquire RPE functions in the subretinal space. The hypothesis that IPE cells may acquire RPE functions in the subretinal space is supported by experiments in which IPE cells were transplanted as a suspension to the subretinal space of rabbits and of Royal College of Surgeons rats. In a 20-week study, IPE cells transplanted to the subretinal space of rabbits survived without the aid of immunosuppressor agents, formed a single layer of cells between the RPE and the photoreceptor cells layer, developed microvilli, attached to the retina and the RPE layer, and demonstrated phagocytosis of ROS without disturbing the morphology of the photoreceptor layer.[11] In the Royal College of Surgeons rat, which is a model of AMD, transplanted IPE cells demonstrated the same characteristics and rescued the photoreceptors.[25-27]

FUNCTIONAL RESULTS IN PATIENTS

In the study presented here, in which 20 patients underwent surgical extraction of subfoveal neovascular membranes followed by autologous IPE transplantation, 18 demonstrated improvement or stabilization of visual acuity. These results, which show a visual outcome at least as good as that reported after membrane extraction alone,[18-21] indicate that no adverse effects accompany IPE cell transplantation. Since visual loss after membrane extraction is in part caused by the destruction of photoreceptors, visual recovery after IPE transplantation can be expected only in areas in which the retina is intact. Since our patients had advanced neovascularization with a profusion of membranes, damage to the RPE was likely to be extensive. Thus, good visual recovery was not expected. It is important, therefore, to develop techniques of membrane extraction that are less damaging and/or to transplant IPE in patients who have dry AMD or who have less advanced neovascularization. Although in rabbits[11] IPE transplanted as a suspension seemed to assume proper morphology, in humans, proper morphology, and thus acquisition of functionality, of the transplanted cells may require that IPE cells be transplanted as a sheet of cells, with apical and basal domains already established.

Better visual outcome has been observed in patients who underwent macular translocation; however, macular translocation surgery is characterized by a high rate of complications,[28-32] whereas IPE cell transplantation has a very low risk of complications, since it is a minor additional procedure in conjunction with conventional surgery for membrane extraction.

LACK OF RECURRENCE OF MEMBRANE FORMATION

One interesting observation in our study was that there was no recurrence of neovascular membranes in any patient. This lack of recurrence is particularly interesting in the light of the high rate of recurrence observed in other therapeutic interventions, such as subfoveal surgery without transplantation.[18-21] If this observation can be replicated in future experiments, it may suggest that the IPE cells produce a substance(s) that inhibits the formation of new vessels, an interesting finding that will necessitate both clinical and basic research.

These results also suggest that IPE transplantation after surgical excision of CNV membranes in humans with early AMD may influence the progress of the retinal dystrophy by producing supporting factors[25] or by providing a substitute for degenerating RPE cells. The observations that transplanted autologous IPE cells were not rejected during an 11-month follow-up and that there was no recurrence of neovascularization in any patient are important and suggest that, with additional research, a suitable therapeutic modality for the treatment of AMD may be developed.

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From the Archives of the ARCHIVES

A look at the past . . .

After falling from a wagon, a laborer, aged twenty-one, was found by Franke to have a left pulsating exophthalmus. Digital compression of the common carotid was employed without any result, so ligation of the left common carotid was done, and, the result of this not being satisfactory, the other carotid was ligated, after which the exophthalmus gradually disappeared.

Reference: *Arch Ophthalmol*. 1898;27:231.