Translocation of iris pigment epithelium in patients with exudative age-related macular degeneration: long-term results

Lappas, Alexandra; Foerster, Andreas M H; Weinberger, Andreas; Coburger, Silke; Schrage, Norbert F; Kirchhof, Bernd

How to cite

LAPPAS, Alexandra et al. Translocation of iris pigment epithelium in patients with exudative age-related macular degeneration: long-term results. In: Graefe's Archive for Clinical and Experimental Ophthalmology, 2004, vol. 242, n° 8, p. 638–647. doi: 10.1007/s00417-003-0764-z

This publication URL: https://archive-ouverte.unige.ch/unige:96895
Publication DOI: 10.1007/s00417-003-0764-z

Graefe's Arch Clin Exp Ophthalmol
(2004) 242:638–647

CLINICAL INVESTIGATION

DOI 10.1007/s00417-003-0764-z

Alexandra Lappas
Andreas M. H. Foerster
Andreas W. A. Weinberger
Silke Coburger
Norbert F. Schrage
Bernd Kirchhof

Translocation of iris pigment epithelium in patients with exudative age-related macular degeneration: long-term results

Received: 28 April 2003
Revised: 21 July 2003
Accepted: 11 August 2003
Published online: 6 August 2004

A. Lappas (✉) · A. W. A. Weinberger · N. F. Schrage
Department of Ophthalmology,
University of Aachen,
Pauwelsstrasse 30, 52057 Aachen,
Germany
e-mail: alappas2000@yahoo.com
Tel.: +49-221-4784105
Fax: +49-221-4785922

A. M. H. Foerster · B. Kirchhof
Department of Ophthalmology,
University of Cologne,
Cologne, Germany

S. Coburger
Department of Medical Statistics,
Informatics and Epidemiology,
University of Cologne,
Cologne, Germany

Abstract *Purpose:* To report the practicability and efficacy of autologous iris pigment epithelium (IPE) translocation in exudative age-related macular degeneration (ARMD) over 1 year. *Methods:* The consecutive interventional case series included 56 patients with exudative ARMD. During vitrectomy the submacular neovascular membrane (CNV) was removed and IPE cells, harvested from a peripheral iridectomy, were injected into the submacular space. Included were patients with subfoveal occult CNV (11 eyes), classic CNV (10 eyes), mixed CNV (17 eyes), CNV with a pigment epithelial detachment (13 eyes) or CNV with a hemorrhage (5 eyes). Outcome measures were visual acuity, foveal fixation, size of CNV and rate of recurrence based on fluorescence angiographic imaging. *Results:* All patients underwent successful surgical removal of the CNV with consecutive subretinal IPE injection. Visual acuity was better than 20/100 in 19 patients preoperatively and in 18 patients postoperatively. A visual acuity of 20/100 or less was found in 37 patients preoperatively and in 38 patients postoperatively. Mean preoperative visual acuity (1.0±0.3 logMAR units) did not change significantly after 1 year (1.0±0.3 logMAR units). Ten eyes (18%) developed a recurrence. Fixation within the surgically denuded area could be demonstrated in 25 eyes (45%). *Conclusions:* Autologous IPE translocation for ARMD over one year can preserve foveal function on a low level, but cannot improve visual acuity. IPE translocation is technically feasible with a low rate of complications. Continued research seems justified to improve functional outcome.

Introduction

Age-related macular degeneration (ARMD) is characterized by diseased retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris followed by insufficiency of photoreceptor cells and visual loss. In exudative ARMD neovascular choroidal vessels grow through Bruch's membrane, underneath the RPE and neurosensory retina, accelerating photoreceptor cell loss. Selective removal of classic CNV [7, 17] was found to be more beneficial in young patients with presumed ocular histoplasmosis syndrome (POHS) or myopia [34, 35] than in patients with ARMD [16, 24]. So far, CNV removal in ARMD has been unable to maintain or revive subfoveal RPE. As RPE cells are considered crucial for maintenance and function of photoreceptors, restoration of RPE cell function is under investigation either by translocation of the macula to neighboring intact RPE [8, 9, 20, 40] or by transplantation/translocation of pigmented cells. Autologous translocation of RPE cells has been reported [5, 25]. Homologous RPE transplantation failed due to macular edema, probably as a result of immunologic graft rejection [3, 39]. Recently, IPE cells have been suggested as an RPE substitute [27, 30]. IPE cells can easily be isolated from an iridectomy and be injected subretinally. IPE translocation was performed in patients with ARMD and

followed for 6–8 months [18, 37]. Stable visual acuity was reported for up to 6 months. We now report the follow-up results 1 year after autologous IPE translocation in patients with exudative ARMD.

Methods

A consecutive interventional case series comprised patients with exudative ARMD recruited between 1998 and 2000 in Aachen (Germany). The prospective pilot study was set up on 56 consecutive patients (56 eyes), 38 women and 18 men.

Inclusion criteria were: exudative ARMD, fluorescein angiographic evidence of classic, occult or a mixed subfoveal neovascularization according to the MPS (Macular Photocoagulation Study Group) classification. Classic CNV size needed to be more than 2 disc areas, a size that was found not to be beneficial according to the MPS study [22]. Photodynamic therapy was not yet approved in Germany at the time of the study. Inclusion into the study also required a visual acuity below 20/63 (0.5 logMAR) and above light perception (2.0 logMAR); that the patient had experienced a recent, subjectively relevant visual loss; and willingness to participate in the trial and to attend all follow-up examinations after informed consent. Exclusion criteria were: prior macular laser photocoagulation, radiation therapy or submacular surgery, severe systemic or additional ophthalmic disease, and participation in any other study.

Intervention

IPE translocation was done as reported in a previous study [18] with minor modifications. Briefly, isolation of IPE cells from two peripheral iridectomies was followed by a complete pars plana vitrectomy including a delamination of the posterior vitreous. According to the fluorescein angiographic images, the edges of the neovascular membrane were evaluated and the retinotomy site determined. Usually, the retinotomy was positioned temporal to the fovea at the margin of the membrane. A retinal bleb was created by a slow subretinal injection of BSS with a 20-μl glass micropipette that was connected by a flexible tube to a 2.0-ml syringe. An angled subretinal pick was used to free the CNV from the surrounding tissue. Then the membrane was grasped and removed with horizontally opening subretinal forceps (Dutch Ophthalmic Research Center, Int., b.v., Netherlands) through the same retinotomy. If necessary, additional BSS was injected into the retinal bleb to achieve a tight wall. A fluid/air exchange was performed, and any remaining fluid was removed from the posterior pole via flute needle. The isolated fresh IPE cells were injected with the glass micropipette through the peak of the retinal bleb into the subretinal space. An average of 36,000 (±17,920) cells were isolated and injected as determined in previous experimental studies [18]. Patients were postured supine at the day of surgery to support adhesion of the injected cells until the subretinal bleb was absorbed. All treatments were given in accordance with the guidelines of national legislation and the declaration of Helsinki.

Main outcome measures

The size of the CNV was expressed in correlation to disc areas. The area of the CNV and the optic disc were measured using Heidelberg Eye Explorer software (Heidelberg, Germany). The size of classic CNVs was determined during the early phase of fluorescein angiography, including the area of hyperfluorescence and the surrounding hypofluorescent rim. The borders of occult CNVs were estimated by early leakage during the late phase of fluorescein angiography. The area of pigment epithelial detachments was assessed by early leakage in fluorescein angiography. The size of occult CNVs associated with submacular hemorrhage was estimated with fluorescein and indocyanine angiography including the dimensions of the CNV (late hyperfluorescence) and blocked fluorescence due to subretinal blood. Submacular bleeding was classified as hemorrhage when it covered an area greater than 6 disc areas.

Follow-up examinations were performed 6 weeks, 3 months, 6 months and 1 year postoperatively. The size of the postoperative surgically denuded area was determined on the basis of the early hyperfluorescent area in fluorescence angiography. Pre- and postoperative examinations included best-corrected visual acuity based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. ETDRS acuity was tested at 4, 2 or 1 m. The last fully identified line was considered as visual acuity. Means were calculated with logMAR values. Hand movements were set to 2.0 logMAR units. Slit-lamp examination, color fundus photography, and fluorescein and indocyanine angiography were performed at each follow-up examination.

Macular fixation was determined using the Rodenstock scanning laser ophthalmoscope (SLO; Rodenstock, Germany) with refined software for microperimetry (Software Aachen) [38]. The size of the fixation cross was 10×10 to 20×20 pixels. Each fixation test involved an adaptation of the retinal image to the presented fixation cross with a retinal landmark. The microperimetrically determined fixation site was transferred to the fundus photographs and to the angiograms to relate it to the estimated fovea and the postsurgical RPE defect.

Evaluation of risk factors

As potential predictors for a significant change in visual acuity, pre-, intra- and postoperative observations were considered. As preoperative factors, age, gender, diagnosis, visual acuity, and the size of the CNV were examined. As an intraoperative factor, choroidal hemorrhage was included. As postoperative observations, size of the surgically denuded area, change of fixation, and recurrences and complications were taken into consideration. The influence of cataract surgery was also examined.

Patients were subdivided into groups within each factor and their *P*-values were compared to determine a significant decrease in visual acuity using chi-squared test or Fisher's exact test. The decision between chi-squared test and Fisher's exact test was made on the basis of expected cell frequencies. Logistic regression was used to evaluate the relationship between a significant decrease in visual acuity and the variables showing a distinct interdependency with the decrease of visual acuity of at least 3 lines.

Results

Of the 56 patients with subfoveal CNV, 11 eyes (20%) showed an occult type, 10 eyes (18%) showed a classic type and 17 eyes (30%) showed a mixed type of CNV, 13 eyes (23%) had a pigment epithelial detachment (PED) and 5 eyes (9%) presented with submacular hemorrhage. Mean preoperative visual acuity was 20/200 (1.0±0.3 logMAR). The average time between IPE-translocation and drop of visual acuity was 17.4 (±12.9) weeks. One year after surgery mean visual acuity was 20/200 (1.0±0.3 logMAR). Pre- and postoperative visual acuities are shown in Table 1.

Table 1 Pre- and postoperative visual acuity

Visual acuity	Number of patients (%), preoperatively	Number of patients (%), postoperatively
	n=56	*n*=56
>20/100	7 (13%)	4 (7%)
20/100–20/160	12 (21%)	14 (25%)
20/200–20/320	26 (46%)	30 (54%)
<20/320	11 (20%)	8 (14%)

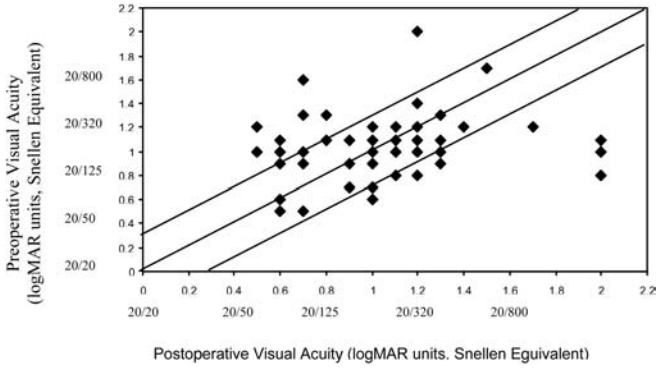

Fig. 1 Pre- and postoperative visual acuity 1 year after IPE translocation. The area outside the lines represents a significant change of at least 3 lines of visual acuity. In most patients, visual acuity did not change significantly. Improvement could be observed in patients with low preoperative visual acuity

A significant change in visual acuity was defined as a change of at least 3 ETDRS lines. Visual acuity improved significantly in 13 cases (23%), decreased in 13 cases (23%) and remained unchanged in 30 cases (54%) (Fig. 1).

With respect to preoperative visual acuity, a significant improvement in visual acuity was observed in 9 (82%) out of 11 patients with a preoperative visual acuity lower than 20/320. A significant decrease was found in 5 (71%) out of 7 patients with a preoperative visual acuity better than 20/100. Most patients had a preoperative visual acuity between 20/100 and 20/320 (38 cases, 68%), only 21% (8 patients) of those developed a significant decrease in visual acuity. No patient with low visual acuity (<20/320) showed a significant decrease in visual acuity.

There was no significant change in visual acuity with respect to the type of CNV (Table 2). Preoperative fixation was foveal in 43 patients (77%) and extrafoveal in 13 patients (23%). Postoperatively, fixation crosses were related to the surgically denuded area that was left after removal of the CNV and could be identified with SLO perimetry as a bright area. In 25 patients (45%), fixation occurred within the surgically denuded area (Figs. 2, 3). In 18 patients (32%), fixation occurred outside the surgically denuded area. These patients lost foveal fixation after surgery. In 13 eyes (23%) preoperatively, extrafoveal fixation was retained after surgery at an extrafoveal location at the margin or outside the surgically denuded area.

Preservation of fixation within the RPE defect was not related to size of the RPE defect. Preoperative foveal fixations were found in small as well as in large CNVs (71%–90% of patients with foveal fixation; Fig. 4) and could be found within small to large surgically denuded areas (40–56% of patients with fixation within the surgically denuded area; Fig. 4). Moreover, postoperative fixation within the RPE defect was not related to the type of CNV. Fixation within the RPE defect could be found in 36% of occult CNVs (four cases), 46% of PEDs (six cases), 47% of mixed CNVs (eight cases), 40%of classic CNVs (four cases) , and in 60% of patients with a submacular hemorrhage (three cases).

However, mean preoperative visual acuity was significantly lower in patients with preoperative extrafoveal fixation (20/400, 1.3±0.3 logMAR) than in those with foveal fixation (20/200, 1.0±0.3 logMAR). Postoperatively, mean visual acuity did not differ significantly in patients with fixation within the surgically denuded area (20/200, 1.0±0.3 logMAR) compared with patients who lost foveal fixation or maintained extrafoveal fixation (20/

Table 2 Visual acuity with respect to type of choroidal neovascular membrane (*CNV*) *PED* Vascularized pigment epithelial detachment, *SMH* submacular hemorrhage, *HM* hand movements

Diagnosis (type of CNV)	No. of patients (%)	Preoperative visual acuity, range	Preoperative visual acuity, mean (logMAR)	Postoperative visual acuity, range	Postoperative visual acuity, mean (logMAR)
Occult	11 (19.6%)	20/125–HM	20/320 (1.2±–0.4)	20/125–20/400	20/250 (1.1±0.2)
PED	13 (23.2%)	20/63–20/630	20/200 (1.0±0.4)	20/100–20/500	20/250 (1.1±0.2)
SMH	5 (8.9%)	20/100–HM	20/250 (1.1±0.5)	20/63 - HM	20/250 (1.1±0.6)
Mixed	17 (30.4%)	20/63–20/630	20/160 (0.9±0.3)	20/63–20/1000	20/200 (1.0±0.3)
Classic	10 (17.9%)	20/100–20/400	20/250 (1.1±0.2)	20/100–20/320	20/320 (1.0±0.2)

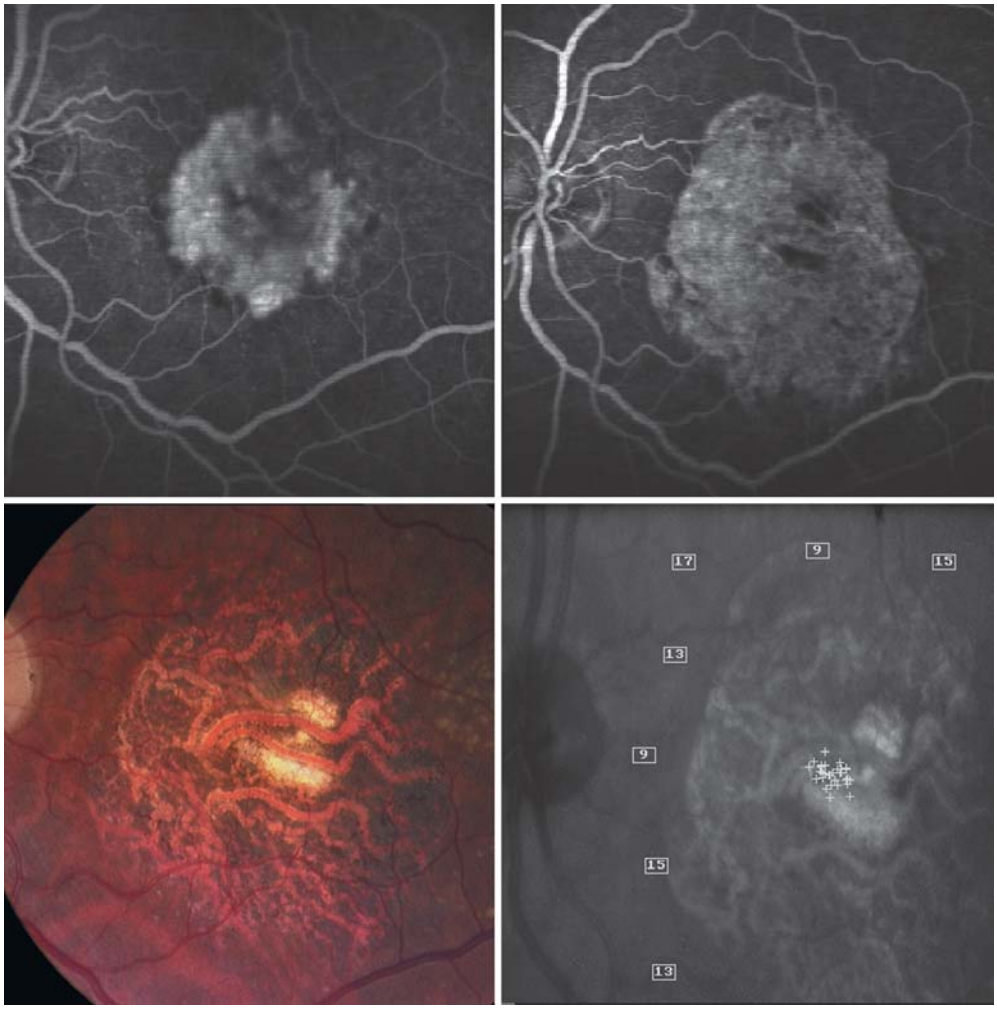

Fig. 2 *Upper left:* Fluorescence angiogram of a 72-year-old female patient with a classic CNV and a visual acuity of 20/400. *Upper right:* The postoperative fluorescence angiogram displays a surgically denuded area, visual acuity improved to 20/250. *Lower left:* Postoperative fundus photograph showing some pigmented material at the posterior pole. *Lower right:* Postoperative SLO microperimetric image demonstrating fixation within the surgically denuded area

200, 1.0±0.3 logMAR). Among the 43 patients (77%) with preoperative foveal fixation, only 13 (30%) experienced a significant decrease in visual acuity, and none of those with preoperative extrafoveal fixation experienced such a decrease.

Postoperative fluorescein angiography revealed hyperfluorescence in the surgically denuded area without late leakage in most cases, indicating that the choroidal neovascular membrane was removed successfully and did not recur. (Fig. 5). The mean preoperative size of the choroidal neovascular membranes was 6.5±6.0 disc areas (range 2–35 disc areas). Postoperatively, the mean size of the surgically denuded area was 9.5±6.8 disc areas (range 2–45 disc areas). Mean visual acuity did not differ significantly, either pre-or postoperatively, between small and large membranes (Fig. 4).

In 10 patients (18%), we observed a recurrence or persistence of the CNV. Seven patients (13%) showed late hyperfluorescence as early as 6 weeks after surgery developing into a recurrence during the later follow-up. In 3 cases (5%), late hyperfluorescence was found 3 months postoperatively. This suggests that in most cases a persistence could be the reason for a recurrent CNV. In 3 cases (5%), the recurrence was treated by argon laser photocoagulation as it showed well demarcated borders and was located extrafoveally.

Further postoperative complications were retinal detachment with PVR that was treated by pars plana vitrectomy and injection of silicone oil (1 eye). One patient developed a macular pucker and another patient showed subretinal bleeding and vitreous hemorrhage. Both underwent pars plana revitrectomy. Postoperative complications resulted in a decrease in visual acuity (mean preoperative visual acuity 1.0±0.2 logMAR units, mean postoperative visual acuity 1.4±0.5 logMAR units), whereas mean visual acuity in patients without complications remained unchanged (mean preoperative visual acuity 1.1±0.4 logMAR units, mean postoperative visual acuity 1.0±0.3 logMAR units).

Intraoperative bleeding during removal of the subfoveal membrane was observed in five cases (9%). Subretinal injections with balanced salt solution were per-

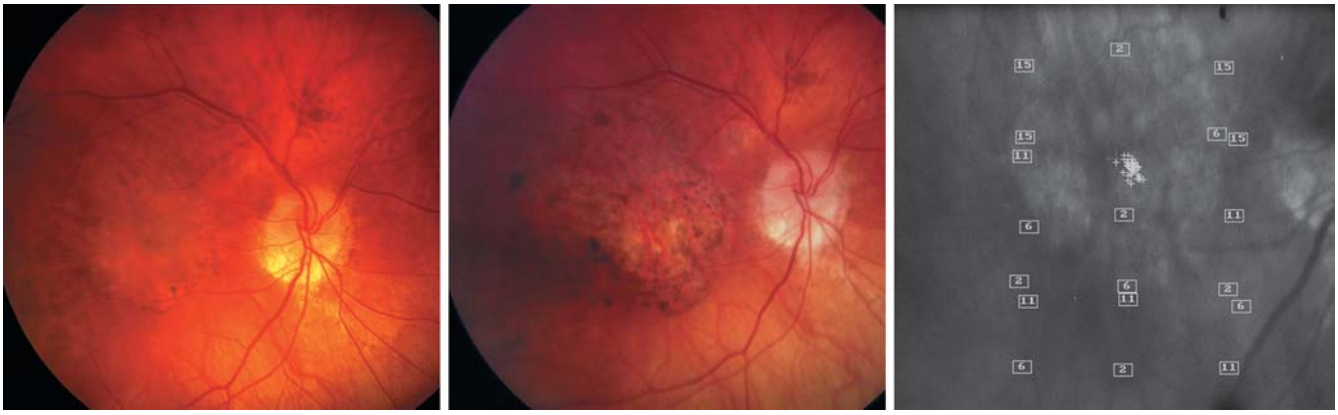

Fig. 3 *Left:* Preoperative photograph of a 67-year-old, male patient with an occult CNV and a visual acuity of 20/1000. *Center:* The postoperative fundus photograph shows a surgically denuded area with pigmented material. Visual acuity improved significantly to 20/320. *Right:* SLO microperimetric image demonstrating fixation within the surgically denuded area

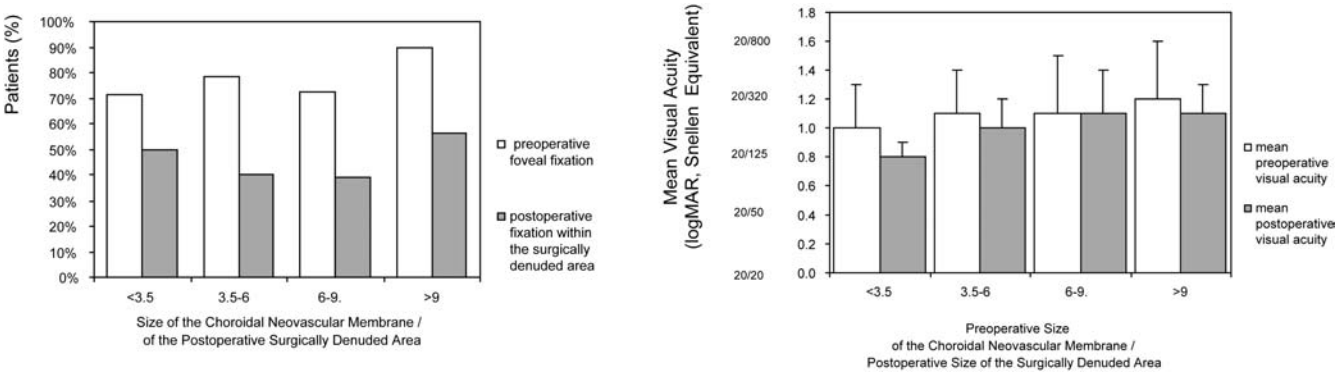

Fig. 4 The pre- and postoperative size of the CNV or the RPE defect were not related to fixation (*left*) and visual acuity (*right*)

formed to remove the hemorrhage until no further blood was left. Intraoperative bleeding resulted in a significant decrease in visual acuity in four out of five cases (80%; mean preoperative visual acuity 0.9±0.2 logMAR units, mean postoperative visual acuity 1.4±0.4 logMAR units).

Further surgical procedures included implantation of an intraocular lens in 11 cases (20%). Twenty-eight patients (50%) were pseudophakic preoperatively or an intraocular lens was implanted at the time of IPE translocation (6 cases, 10%). The remaining 11 patients (20%) were still phakic at the end of the follow-up.

Evaluation of risk factors

As potential predictors for a significant change in visual acuity after surgery, age, gender, cataract surgery, preoperative visual acuity, size of the CNV, intraoperative choroidal hemorrhage, postoperative size of the surgically denuded area, preoperative foveal fixation, and recurrences were taken into consideration (Table 3). Promising indicators for visual prognosis were: preoperative visual acuity (P<0.0001), preoperative fixation (P=0.026) and intraoperative hemorrhage (P=0.008).

In relation to patients with a preoperative visual acuity better than 20/100, patients with a visual acuity of 20/100–20/160 [P=0.041; odds ratio=0.122; 95% confidence interval (CI) 0.016–0.913], 20/200–20/320 (P=0.0074; odds ratio=0.017; 95% CI 0.001–0.337) had a lower risk of experiencing a significant decrease in visual acuity as shown by logistic regression. Patients without intraoperative hemorrhaging are at a lower risk for experiencing a decrease in visual acuity than patients with an intraoperative hemorrhage (P=0.021; odds ratio=0.043; 95% CI 0.003–0.626). No patient with a preoperative visual acuity lower than 20/320 and no patient with extrafoveal fixation showed a significant decrease in visual acuity.

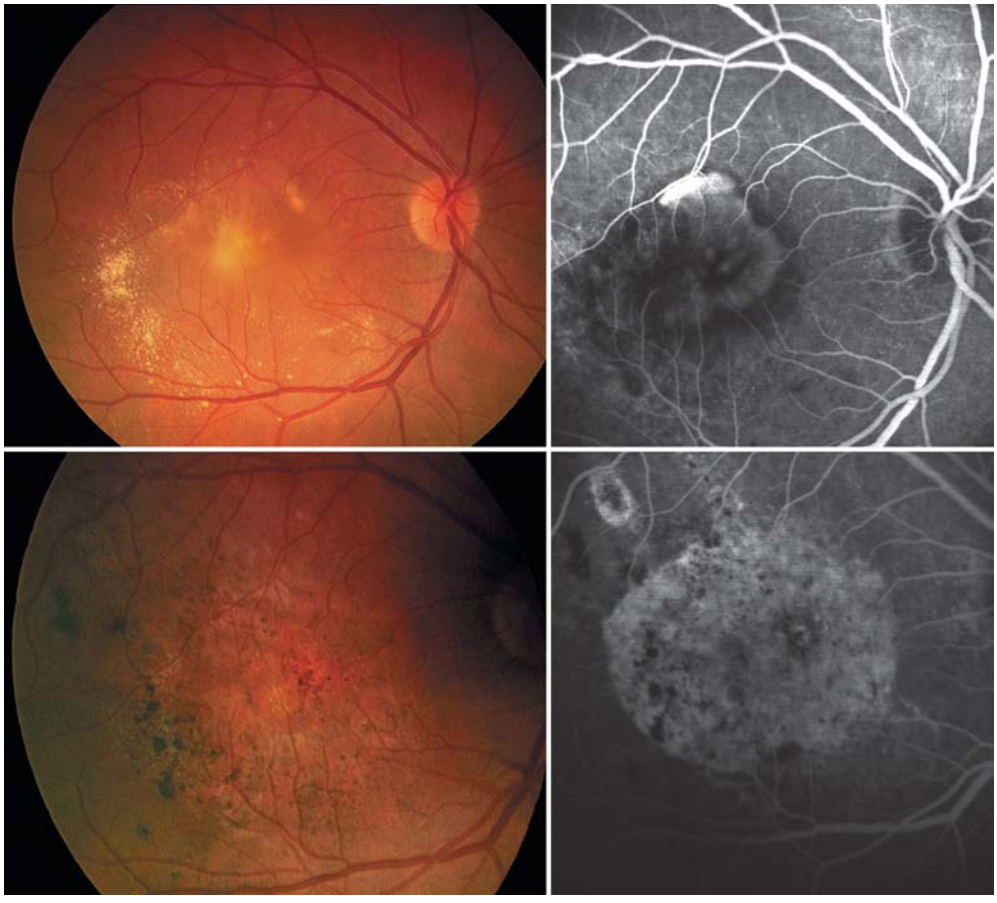

Fig. 5 Preoperative photograph (*upper left*) and fluorescence angiogram (*upper right*) of a female patient, 65 years old, with a vascularized pigment epithelial detachment. Visual acuity was 20/200. In the postoperative fundus photograph (*lower left*) some pigmented material is located within the surgically denuded area. Visual acuity was 20/200. In the fluorescence angiogram (*lower right*) no late leakage was detectable

Discussion

This study shows that 12 months after removal of choroidal neovascular membranes and IPE translocation in patients with advanced exudative ARMD mean visual acuity did not change significantly. In contrast to allogenic transplantation of fetal RPE, no morphologic sign of rejection of the translocated cells could be found [13].

Visual acuity

A significant decrease in visual acuity was experienced in 13 patients (23%). According to the MPS, all patients with subfoveal classic membranes with a size of 2–3.5 disc areas showed a mean decrease of 3 lines after 1 year [22]. In our study, mean visual acuity in classic CNVs (CNV size from 2–35 disc areas, mean 6.6) remained unchanged.

In the Photodynamic Study Group (TAP) report, 58% of patients with mixed CNV were reported to lose at least 15 letters (3 lines) without treatment, whereas only 40% of patients lost at least 3 lines with treatment [26]. After IPE translocation, a decrease of at least 3 lines was found in only 29% of patients with mixed CNV. However, in the PDT study 20/200 was the lower limit for visual acuity, the CNV size was not larger than 5400 μm (approximately 3.5 disc areas) and at least 50% of the CNV had to be classic.

In patients with occult CNV, a moderate to severe loss of vision of at least 3 lines can be expected without treatment in 66% of eyes after 12 months [6]. In this study, we observed a significant decrease (a decrease of at least 3 ETDRS lines) in 9% of patients with occult CNV and in 31% of patients with PED. In patients with subretinal hemorrhage and lesion sizes larger than 6 disc areas, a final visual acuity less than 20/200 can be expected in 71% of all cases [4].

In the Submacular Surgery Trial (SST), CNV removal was performed in patients with recurrent CNV after laser treatment of juxta- or extrafoveal lesions [31]. A decrease of at least 2 lines was observed in 45% of all cases, compared to a decrease of 23% of at least 3 lines in this study. Again, comparability is limited as the size of the CNV was limited to 9 disc areas including the laser scar in the SST study. Considering that the subfoveal portion was a recurrence of juxta- or extrafoveal CNV the final shortest distance of the recurrent CNV between its outer margin to the fovea might have been smaller than with

Table 3 Visual prognosis in relation to different subgroups (*PED* vascularized pigment epithelial detachment, *SMH* submacular hemorrhage, *VA* visual acuity, *SMC* submacular surgery)

Subgroup	Subgroup	Patients (%), *n*=56	Patients (%) with a decrease in visual acuity of at least 3 lines	*P*-value (a) chi-square test, (b) Fisher's exact test
Age	>=74	29 (51.8%)	7 (24.1%)	0.87 (a)
	<74	27 (48.2%)	6 (22.2%)	
Gender	Women	38 (67.9%)	10 (26.3%)	0.514 (b)
	Men	18 (32.1%)	3 (16.7%)	
Diagnosis	Occult	11 (19.6%)	1 (9.1%)	0.433 (b)
	Mixed	17 (30.4%)	5 (29.4%)	
	PED	13 (23.2%)	4 (30.8%)	
	Classic	10 (17.9%)	1 (10.0%)	
	SMH	5 (8.9%)	2 (40.0%)	
Preoperative VA	>20/100	7 (12.5%)	5 (71.4%)	<0.0001 (b)
	20/100–20/160	12 (21.4%)	7 (58.3%)	
	20/200–20/320	26 (46.4%)	1 (4.8%)	
	<20/320	11 (19.6%)	0 (0%)	
Preoperative foveal fixation	foveal	43 (76.8%)	13 (30.2%)	0.026 (b)
	extrafoveal	13 (23.2%)	0 (0%)	
Size of the preoperative CNV	<3.5 disc areas	21 (37.5%)	5 (23.8%)	0.944 (b)
	3.5–6 disc areas	14 (25.0%)	3 (21.4%)	
	6–9 disc areas	11 (19.6%)	2 (18.2%)	
	>9 disc areas	10 (17.9%)	3 (30%)	
Size of the surgically denuded area	<3.5 disc areas	2 (4.0%)	0 (0%)	0.262 (b)
	3.5–6 disc areas	15 (27.0%)	6 (40.0%)	
	6–9 disc areas	23 (41.0%)	3 (66.7%)	
	>9 disc areas	16 (28.0%)	4 (25.0%)	
Intraoperative hemorrhage	Yes	5 (9.0%)	4 (80.0%)	0.008 (b)
	No	51 (91.0%)	9 (17.6%)	
Recurrence	Yes	10 (18.0%)	2 (20.0%)	1.0 (b)
	No	46 (82.0%)	11 (23.9%)	
Cataract surgery	Prior to SMC	28 (50.0%)	6 (21.4%)	0.841 (b)
	During SMC	6 (10.7%)	2 (33.3%)	
	After SMC	11 (19.6%)	2 (18.2%)	
	None	11 (19.6%)	3 (27.3%)	

IPE translocation suggesting a better visual prognosis [14, 23, 29].

Subgroup analysis revealed that after IPE translocation significant changes in visual acuity could be found in patients with either good or low visual acuity. No patient with a low initial visual acuity (<20/320) experienced a further significant decrease after one year. Although the mean level of initial visual acuity in this category was low (20/800, 1.6±0.3 logMAR units), even those patients showed a significant increase (20/250, 1.1±0.2 logMAR mean postoperative visual acuity). Visual prognosis was not significantly correlated to CNV type or to the size of the CNV. Part of the retinal function compromised by the CNV might have been restored after removal of the CNV together with subretinal exudations that may have formed a barrier to the transport of nutrients from the choriocapillaris. Visual restoration has been also reported after CNV removal and subretinal injection of tissue plasminogen activator in patients with large CNV (>2 disc areas) and low visual acuity ($\leq$20/200) due to ARMD [23].

Five out of seven patients (71%) with a good initial visual acuity (>20/100) experienced a significant decrease in visual acuity following IPE translocation. Other studies have likewise shown that decreases in visual function are more likely in patients with exudative ARMD and good initial visual acuity [22, 23]. Obviously, the removal of the CNV and IPE translocation was not able to preserve retinal function on an elevated functional level. On the other hand, some patients (four cases, 7%) reached good final functional levels (>20/100) after IPE translocation. Consequently, reasons other than the surgical trauma might contribute to the low levels of postoperative visual acuity. Histopathologic studies of choroidal neovascular membranes have shown the photoreceptor cells and the choriocapillaris as part of the fibrovascular tissue [10]. Removal of such still functioning structures cannot be ruled out with any surgical membrane extraction and might result in a non-supportive environment for the translocated IPE cells.

Fixation

Fixation was the second factor found to correlate with visual prognosis after IPE translocation. SLO perimetry revealed an area denuded of RPE at the posterior pole. In

25 patients (45%) postoperatively, fixation could be localized within the RPE defect. It is well accepted that patients with geographic atrophy usually develop central scotomas from the RPE defect, accompanied by extrafoveal fixation at the margin of the atrophic area and only occasionally show fixation within the zone of atrophy [32, 33]. Similar observations are reported after removal of submacular CNV [13, 19].

Assuming that fixation within the RPE defect might reflect preserved photoreceptor function by translocated IPE cells, we would expect an improvement in visual acuity. Visual acuity, however, did not correlate with postoperative fixation, implying that fixation within the surgically denuded area might be a more sensitive functional parameter than visual acuity in very low levels of visual acuity. Ophthalmoscopy and SLO perimetry revealed pigment clumps in some eyes within the field of RPE defect. As reported earlier, it is impossible to reveal its origin from RPE or from translocated IPE [18]. The injected IPE suspension consisted of cell clumps as well as of single cells. Single cells cannot be detected by ophthalmoscopy. Consequently, translocated IPE single cells cannot be documented. Resident retinal pigment epithelial cells repopulate RPE defects insufficiently after surgical CNV removal in ARMD [12]. Consequently, the RPE defect may not have been covered by resident RPE cells or by translocated IPE cells in some cases, resulting in a low postoperative visual acuity or extrafoveal fixation. In some eyes, fixation was found on hyperpigmented spots within the area of RPE defect. This observation was confirmed by dynamic testing with the SLO fixation cross, when light perception was given in proximity to the pigmented material.

Fixation within the RPE defect was independent from the size of the defect. This observation rules out the possibility that fixation is affected by RPE from the margin of the defect. Patients with subfoveal RPE defects prefer to fixate extrafoveally, namely at the margin of the defect, as documented for 31 eyes (55%) in our series. Similarly, patients with geographic atrophy fixate extrafoveally, at the margin of the atrophy zone, independent from its size [33]. Therefore, fixation in the area of RPE atrophy after IPE translocation in this study may signal a protective effect of IPE on retinal photoreceptors over 1 year. IPE cells have been shown to synthesize similar growth factors as RPE cells in vitro [15] and to be capable of phagocytosis of photoreceptor rod outer segments to some extent [28, 36]. The supportive effect of translocated IPE cells within the RPE defect may be so weak that it does not result in a measurable improvement of visual acuity.

Interestingly, patients with preoperative extrafoveal fixation showed a significant increase in mean postoperative visual acuity despite persistent extrafoveal fixation. In those patients, recovery of foveal fixation might have been hampered by irreversible preoperative damage of foveal photoreceptors. The surgical procedure of CNV removal and IPE translocation stabilized vision significantly at the low mean level of 20/200.

Recurrences and complications

In our series the rate of CNV recurrence and persistence was 18% (10 cases) after 1 year. A similar rate of recurrence (24%) was reported after removal of predominantly classic CNV [23]. Other studies reported a recurrence rate of 46% after removal of classic subfoveal membranes [35]. In the SST, "late hyperfluorescence" was found in more than 50% of all surgically treated eyes at the 12-month examination [31]. This reflects the higher risk for patients with recurrent CNV, after laser treatment, of developing a recurrence after removal of a submacular membrane [21, 22, 31].

In our study, 70% of patients with a recurrence or persistence showed a mixed CNV preoperatively. Histopathologic studies have demonstrated that the classic part of the CNV in fluorescence angiography correlates with choroidal neovascularization above the RPE cell layer, whereas, occult CNV grows beneath the RPE [11]. It might be possible that parts of the mixed CNV show different consistency and adherence to neighboring RPE cells, leading to increased risk of persistence after CNV removal. Recurrences in this study did not result in a significant decrease in visual acuity after 1 year, possibly due to their location outside the fovea and at the surgical margin of the RPE defect.

The rate of intra- and postoperative complications following IPE translocation was 14% (eight cases). Postoperative complications requiring additional repeat pars plana vitrectomy comprised three cases (5%)—which is considerably low. One of those patients (2%) was retreated by silicone oil for PVR. The SST study reported that 9% of patients received additional intraocular treatment due to retinal detachment and 9% due to submacular complications. The rate of intraoperative complications in this study was 9% (five cases), resulting from subretinal bleeding after CNV removal before injection of IPE cells.

Despite the obvious stabilization of visual acuity in many patients in this study after one year, the effect of IPE translocation to date is difficult to interpret. Since IPE cell as well as photoreceptor cell viability and survival cannot directly be tested, a prospective randomized trial could give more insight into significant results of this technique. The low rate of complications and the brevity of the surgical procedure encourage future efforts to investigate IPE translocation, e.g., to improve functional outcome by optimizing IPE cell attachment in the wounded area after CNV removal.

References

1. Algvere PV, Berglin L, Gouras P, Sheng Y (1994) Transplantation of fetal retinal pigment epithelium in age-related macular degeneration with subfoveal neovascularization. Graefes Arch Clin Exp Ophthalmol 232:707–716
2. Algvere PV, Berglin L, Gouras P, Sheng Y, Kopp ED (1997) Transplantation of RPE in age-related macular degeneration: observations in disciform lesions and dry RPE atrophy. Graefes Arch Clin Exp Ophthalmol 235:149–158
3. Algvere PV, Gouras P, Dafgard Kopp E (1999) Long-term outcome of RPE allografts in non-immunosuppressed patients with AMD. Eur J Ophthalmol 9:217–230
4. Avery RL, Fekrat S, Hawkins BS, Bressler NM (1996) Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina 16:183–189
5. Binder S, Stolba U, Krebs I, Kellner L, Jahn C, Feichtinger H, Povelka M, Frohner U, Kruger A, Hilgers RD, Krugluger W (2002) Transplantation of autologous retinal pigment epithelium in eyes with foveal neovascularization resulting from age-related macular degeneration: a pilot study. Am J Ophthalmol 133:215–225
6. Bressler NM, Frost LA, Bressler SB, Murphy RP, Fine SL (1988) Natural course of poorly defined choroidal neovascularization associated with macular degeneration. Arch Ophthalmol 106:1537–1542
7. De Juan E Jr, Machemer R (1988) Vitreous surgery for hemorrhagic and fibrous complications of age- related macular degeneration. Am J Ophthalmol 105:25–29
8. De Juan E Jr, Loewenstein A, Bressler NM, Alexander J (1998) Translocation of the retina for management of subfoveal choroidal neovascularization II: a preliminary report in humans. Am J Ophthalmol 125:635–646
9. Eckardt C, Eckardt U, Conrad HG (1999) Macular rotation with and without counter-rotation of the globe in patients with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 237:313–325
10. Green WR, Enger C (1993) Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 100:1519–1535
11. Grossniklaus HE, Hutchinson AK, Capone A Jr, Woolfson J, Lambert HM (1994) Clinicopathologic features of surgically excised choroidal neovascular membranes. Ophthalmology 101:1099–1111
12. Hsu JK, Thomas MA, Ibanez H, Green WR (1995) Clinicopathologic studies of an eye after submacular membranectomy for choroidal neovascularization. Retina 15:43–52
13. Hudson HL, Frambach DA, Lopez PF (1995) Relation of the functional and structural fundus changes after submacular surgery for neovascular age-related macular degeneration. Br J Ophthalmol 79:417–423
14. Kamei M, Tano Y, Maeno T, Ikuno Y, Mitsuda H, Yuasa T (1996) Surgical removal of submacular hemorrhage using tissue plasminogen activator and perfluorocarbon liquid. Am J Ophthalmol 121:267–275
15. Kociok N, Heppekausen H, Schraermeyer U, Esser P, Thumann G, Grisanti S, Heimann K (1998) The mRNA expression of cytokines and their receptors in cultured iris pigment epithelial cells: a comparison with retinal pigment epithelial cells. Exp Eye Res 67:237–250
16. Lambert HM, Lopez PF (1993) Surgical excision of subfoveal choroidal neovascular membranes. Curr Opin Ophthalmol 4:19–24
17. Lambert HM, Capone A, Jr., Aaberg TM, Sternberg P, Jr., Mandell BA, Lopez PF (1992) Surgical excision of subfoveal neovascular membranes in age-related macular degeneration. Am J Ophthalmol 113:257–262
18. Lappas A, Weinberger AW, Foerster AM, Kube T, Rezai KA, Kirchhof B (2000) Iris pigment epithelial cell translocation in exudative age-related macular degeneration. A pilot study in patients. Graefes Arch Clin Exp Ophthalmol 238:631–641
19. Loewenstein A, Sunness JS, Bressler NM, Marsh MJ, de Juan E Jr (1998) Scanning laser ophthalmoscope fundus perimetry after surgery for choroidal neovascularization. Am J Ophthalmol 125:657–665
20. Machemer R (1998) Macular translocation. Am J Ophthalmol 125:698–700
21. Macular Photocoagulation Study Group (1986) Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. Macular Photocoagulation Study Group. Arch Ophthalmol 104:503–512
22. Macular Photocoagulation Study Group (1991) Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the macular photocoagulation study. Macular Photocoagulation Study Group. Arch Ophthalmol 109:1242–1257
23. Merrill PT, LoRusso FJ, Lomeo MD, Saxe SJ, Khan MM, Lambert HM (1999) Surgical removal of subfoveal choroidal neovascularization in age-related macular degeneration. Ophthalmology 106:782–789
24. Ormerod LD, Puklin JE, Frank RN (1994) Long-term outcomes after the surgical removal of advanced subfoveal neovascular membranes in age-related macular degeneration. Ophthalmology 101:1201–1210
25. Peyman GA, Blinder KJ, Paris CL, Alturki W, Nelson NC Jr, Desai U (1991) A technique for retinal pigment epithelium transplantation for age- related macular degeneration secondary to extensive subfoveal scarring. Ophthalmic Surg 22:102–108
26. Photodynamic Therapy (TAP) Study Group (1999) Photodynamic therapy of subfoveal choroidal neovascularization in age- related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Arch Ophthalmol 117:1329–1345
27. Rezai KA, Kohen L, Wiedemann P, Heimann K (1997) Iris pigment epithelium transplantation. Graefes Arch Clin Exp Ophthalmol 235:558–562
28. Rezai KA, Lappas A, Farrokh-siar L, Kohen L, Wiedemann P, Heimann K (1997) Iris pigment epithelial cells of Long-Evans rats demonstrate phagocytic activity. Exp Eye Res 65:23–29
29. Scheider A, Gundisch O, Kampik A (1999) Surgical extraction of subfoveal choroidal new vessels and submacular haemorrhage in age-related macular degeneration: results of a prospective study. Graefes Arch Clin Exp Ophthalmol 237:10–15
30. Schraermeyer U, Kociok N, Heimann K (1999) Rescue effects of IPE transplants in RCS rats: short-term results. Invest Ophthalmol Vis Sci 40:1545–1556
31. Submacular Surgery Trials I (2000) Submacular surgery trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: I. Ophthalmic outcomes submacular surgery trials pilot study report number 1. Am J Ophthalmol 130:387–407
32. Sunness JS, Bressler NM, Maguire MG (1995) Scanning laser ophthalmoscopic analysis of the pattern of visual loss in age-related geographic atrophy of the macula. Am J Ophthalmol 119:143–151

33. Sunness JS, Applegate CA, Gonzalez-Baron J (2000) Improvement of visual acuity over time in patients with bilateral geographic atrophy from age-related macular degeneration. Retina 20:162–169
34. Thomas MA, Kaplan HJ (1991) Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome. Am J Ophthalmol 111:1–7
35. Thomas MA, Dickinson JD, Melberg NS, Ibanez HE, Dhaliwal RS (1994) Visual results after surgical removal of subfoveal choroidal neovascular membranes. Ophthalmology 101:1384–1396
36. Thumann G, Bartz-Schmidt KU, Heimann K, Schraermeyer U (1998) Phagocytosis of rod outer segments by human iris pigment epithelial cells in vitro. Graefes Arch Clin Exp Ophthalmol 236:753–757
37. Thumann G, Aisenbrey S, Schraermeyer U, Lafaut B, Esser P, Walter P, Bartz-Schmidt KU (2000) Transplantation of autologous iris pigment epithelium after removal of choroidal neovascular membranes. Arch Ophthalmol 118:1350–1355
38. Toonen F, Remky A, Janssen V, Wolf S, Reim M (1995) Microperimetry in patients with central serous retinopathy. Ger J Ophthalmol 4:311–314
39. Weisz JM, Humayun MS, de Juan E, Jr., del Cerro M, Sunness JS, Dagnelie G, Soylu M, Rizzo L, Nussenblatt RB (1999) Allogenic fetal retinal pigment epithelial cell transplant in a patient with geographic atrophy. Retina 19:540–545
40. Wolf S, Lappas A, Weinberger AW, Kirchhof B (1999) Macular translocation for surgical management of subfoveal choroidal neovascularizations in patients with AMD: first results. Graefes Arch Clin Exp Ophthalmol 237:51–57