EXPERT REVIEWS

Current surgical treatment of age-related macular degeneration

J Emanuel Ramos de Carvalho[1], Alissa Willig[1], Ronald Chung[1], Enrico Peiretti[1,2] and Marco Mura*[1]

[1]Department of Ophthalmology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[2]Department of Surgical Sciences, Eye Clinic, University of Cagliari, Cagliari, Italy
*Author for correspondence:
Tel.: +31 205 669111
m.mura@amc.nl

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible central vision loss in individuals over 65 years of age throughout much of the developed world. The advent of anti-VEGF therapy has had a great impact in the long-term natural history of this condition, more specifically in patients afflicted with exudative AMD. However, at the end-stages of the disease, therapeutic regimens such as anti-VEGF therapy and/or laser fail to achieve symptom resolution often leading to severe visual impairment and legal blindness. In selected cases, surgery has been advocated as a valid treatment modality in order to preserve vision. This review will evaluate the recent advances in surgical management of AMD, highlighting the different techniques that have been proposed and developed in the last 15 years. In addition, potential therapeutic strategies will be discussed and results obtained in clinical studies will be described.

KEYWORDS: age-related macular degeneration • choroidal neovascularization • geographic atrophy • pars plana vitrectomy • retinal pigment epithelium cells suspension • tissue plasminogen activator

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among the elderly worldwide [1,2]. In the future, and due to increased life expectancy, the number of affected patients is expected to increase exponentially [3,4]. AMD is a neurodegenerative disease of the macula, characterized by dysfunction of the underlying retinal pigment epithelium (RPE) layer [5,6]. The disease can be further classified as *exudative* or *wet* – whenever choroidal neovascularization (CNV) is present, and *non-exudative* or *dry* – characterized by atrophic degeneration of the macula that can eventually lead to geographical large areas of atrophy. Dry or nonexudative AMD is characterized by loss of the RPE, choriocapillaris and overlying photoreceptors. Geographical atrophy usually starts as round or ovoid lobular regions that slowly increase in number and ultimately encircle the fovea. At this stage, both eyes are generally affected, which often leads to legal blindness. For this group of patients, no medical therapy is able to halt progression of the disease or to reinstitute some form of visual function. Progression of dry or nonexudative AMD is irreversible but often slow, whereas exudative or wet AMD usually has a more rapidly deteriorating course.

In the exudative stage, current therapeutic modalities with anti-VEGF agents may control progression of the disease [7–9]. Exudative or wet AMD can eventually lead to dry AMD and likewise, patients affected by dry AMD can develop CNV.

End-stage AMD is characterized by fibrovascular scar tissue covering the macula that grows from the choriocapillaris into the sub-RPE and subretinal space. The advent of anti-VEGF therapy has led to great advances in the care of AMD patients although still no cure has been found for this disease [9,10]. Many retinal specialists advocate surgery as a valid last option in selected cases of end-stage AMD [11]. Moreover, surgery, and specifically pneumatic displacement of the submacular blood, has an important role in the treatment of submacular hemorrhages secondary to CNV or as complications of anti-VEGF therapy [12].

In the following sections, we will discuss four surgical techniques currently being used in the treatment of AMD: intravitreal recombinant tissue plasminogen activator (rTPA) and gas, macular translocation surgery, autologous RPE–choroid patch graft and RPE cell suspension transplantation.

Intravitreal rTPA & gas

Pneumatic displacement of submacular blood was first reported by Heriot et al. [13]. This minimally invasive procedure involves the intravitreal injection of rTPA and gas. The combined effects of the gas bubble and gravity displace the hemorrhage inferiorly and away from the submacular region. Modifications to the original procedure have been reported. These include performing vitrectomy, injecting rTPA subretinally with a small gauge needle and tamponading with air or gas. After displacing the submacular blood, additional anti-VEGF treatment may be added or continued.

Various case series have been published over the years since Heriot et al. first described pneumatic displacement. However, comparing results is difficult since there was no uniformity in reporting the size of submacular hemorrhage, initial visual acuity, time to treatment and treatment protocols.

Hess et al. [14] described the effects of intravitreal injection of rTPA and gas on submacular hemorrhage in 11 eyes with subretinal hemorrhage involving the fovea due to AMD. Subretinal hemorrhage ocurred 12 h to 14 days before treatment. Injection of rTPA (50 or 100 μg) through the pars plana was performed. Different volumes (0.2–0.4 ml) of SF6, C2F6 and C3F8 gas were instilled either immediately after rTPA injection or during the following day. After intravitreal injection of rTPA, subretinal clots were totally or partially liquefied when treatment started up to 3 days after the onset of bleeding. All patients treated with 100 μg of rTPA developed a large exudative retinal detachment of the inferior retina, which reabsorbed spontaneously within 2 weeks. The authors argued that this may have been due to a toxic response and subsequently lowered the dosage to 50 μg. No exudative detachments were observed on this lower dosage. After reattachment of the exudative retinal detachment, hyperpigmentation of the RPE was noted. Postoperative visual acuity increased in five patients (45.5%).

Buhl et al. [15] reported a series of 53 eyes treated with intravitreal injection of rTPA and sulfahexafluoride gas (SF6) for submacular hemorrhage. Unlike in the series reported by Hess et al., all patients uniformly received intravitreal 50 μg of rTPA in 0.1 ml (BSS) and 0.5 ml SF6. The patient was in prone position for 24 h. In 23 patients with CNV, visual acuity improved by two lines and more, whereas in 12 patients visual acuity remained unchanged. In 12 patients visual acuity deteriorated. Postoperative complications included four cases of vitreous hemorrhage and one case of endophthalmitis. No cases of exudative detachment were reported. This reconfirms the safety of 50 μg dosage for intravitreal rTPA. The study shows that some patients may gain visual acuity after intravitreal rTPA and gas injection although more refined selection criteria may be needed in order to identify patients likely to benefit from this procedure.

Schulze et al. [16] described patient characteristics that may be likely associated with better postoperative outcomes. In his retrospective study, patients with better preoperative visual acuity and smaller diameter of subretinal hemorrhages had better visual outcomes postoperatively. Age, duration of hemorrhage and thickness of hemorrhage were found to have no prognostic value. The best visual outcome was described in patients with visual acuity of less than 0.1 caused by a small subretinal hemorrhage. Patients with subretinal hemorrhages with a diameter of more than 5 mm were unlikely to obtain a visual improvement postoperatively. Vitreous hemorrhage was a significant postoperative complication. The size of the submacular hemorrhage (>10 disc diameters of subretinal hemorrhage) appears to be a risk factor for such complication. However, vitreous hemorrhage was found not to affect final visual acuity outcome in one study [17].

Along with the significant development of 23- and 25-gauge vitrectomy techniques and the availability of anti-VEGF therapy, pneumatic displacement of submacular hemorrhage also underwent modifications. The ability to inject fluid in the subretinal space with an automated 41-gauge needle helps to directly deliver rTPA to subretinal blood. This technique was thought to allow better dissolution of subretinal blood and thus provide better visual acuity postoperatively.

Hillenkamp et al. [18] reported a comparative study between patients who underwent pars plana vitrectomy with intravitreal injection of rTPA and gas versus pars plana vitrectomy with subretinal injection of rTPA and intravitreal injection of gas. The group that received subretinal rTPA had a better rate of hemorrhage displacement than the group receiving intravitreal rTPA group (55 vs 22%). The final visual acuity was, however, not different between the two groups. Pneumatic displacement of submacular hemorrhage did improve visual acuity for some patients postoperatively. However, in the long term, visual function tended to decline. This may have been related to the progression of the underlying exudative AMD. With the availability of anti-VEGF therapy, a combination treatment regime may help to provide better, prolonged visual outcome after pneumatic displacement. Treumer et al. [19] reported outcomes of patients managed with such a regime. The results indicated a short-term improvement (3 months) in all patients. Nevertheless, long-term follow-up showed that 50% of patients suffered some visual loss despite additional intravitreal anti-VEGF injections, titrated with changes in visual acuity. According to these results, it appears that patients undergoing pneumatic displacement of submacular hemorrhage secondary to AMD may need to receive more frequent anti-VEGF treatment in order to protect vision gained postoperatively.

In summary, this technique has been shown to improve prognosis in patients. Application of new developments in vitreoretinal surgical techniques with intravitreal anti-VEGF may yield the best results. Specific management protocols still have not been determined, and further randomized controlled trials are needed to optimize this technique.

Macular translocation surgery

As mentioned previously, end-stage forms of AMD may not respond to treatment with anti-VEGF therapy, and surgery has been advocated as a valid attempt to improve visual function

for a selected group of patients [6,10,11]. In 1993, Machemer and Steinhorst described a surgical technique appropriately named macular translocation. The theoretical principle of this technique is that by moving the macula with underlying diseased RPE to a new location where the function of the RPE–choriocapillaris complex is normal, one could stabilize or improve the function of the macula [20,21]. The technique was first attempted in small animals [20] and later extrapolated to human subjects [21]. It involved a complete lensectomy and vitrectomy with subsequent deliberate total retinal detachment by infusion of fluid into the subretinal space by transscleral infusion of fluid beneath the retina. A 360° peripheral retinotomy was then performed with the vitrector, allowing mobilization of the retina. Reflection of the retina allows identification and removal of subretinal blood and membranes. Afterward, the retina was rotated to a new position within the retina. Intraoperative injection of rTPA is possible whenever a clot is present. A soft-tipped cannula was used for rotation of the retina, and perfluorocarbon was injected to unfold the retina. Gentle suction at the periphery was used to grasp the retina and rotate. A 30–80° rotation is carried out to ensure that the retina is repositioned to an area of normally functioning RPE–choriocapillaris complex. The retina was then reattached by photocoagulation of the peripheral retina and silicone oil tamponade. Machemer and Steinhorst performed this procedure on three patients: 5 months postoperatively one patient, although with resulting excyclotorsion of images, had improvement in visual acuity from 1/200 to 20/80, whereas the other two developed proliferative vitreoretinopathy [21]. Driven by the potential good visual outcome of this procedure and the rationale behind it, others began attempting macular translocation on patients afflicted with AMD. Since then, variations in the surgical technique have been proposed.

Ninomiya et al. [22] suggested a technique involving detachment of the temporal retina with subsequent 180° peripheral retinotomy. The fovea would then be moved inferiorly or superiorly after a superior or inferior radial incision. In this technique, smaller degrees of rotation were achieved, 10–20° compared with the 30–80° rotations of the original technique. A smaller retinotomy was expected to lead to a lower incidence of complications. This technique was dismissed after reports of high rates of postoperative vitreoretinal proliferation [22,23].

In order to limit the possible adverse consequences of extended peripheral retinotomy, a 'limited' macular translocation was proposed in 1998 by de Juan et al. [24] as opposed to the original technique referred to 'full' macular translocation. In this technique, a crescent-shaped limbus parallel shortening of the choroid and sclera was performed near the equator at either the superotemporal or the inferotemporal quadrant. A near-total retinal detachment was then created by means of an internal retinotomy. Subsequently, the edges of the resected sclera were sutured hereby creating a shortening of the sclera. Reattachment of the retina results in translocation of the macula to a new location of intact RPE without a 360° retinotomy. Photocoagulation of the CNV complex is performed upon

fovea translocation, which avoids damage to the fovea from surgical manipulation. Three patients were operated using this technique. At 4–6 months follow-up, mean visual acuity had improved in all patients from 20/162 to 20/57. No serious complications were reported in two patients; the third patient eventually suffered two retinal detachments, one thought to be due to an iatrogenic peripheral retinal tear and the second due to a leaking retinotomy. Both retinal detachments were repaired and proliferative vitreoretinopathy did not develop. In 2000, the same group reported on a larger series of patients who had undergone the modified procedure, with a final count of 102 eyes [25]. Eighty-six eyes completed the 1-year follow-up with 40.7% of eyes achieving visual acuity of 20/100 or better, while 39.5% eyes experienced two or more Snellen lines of visual improvement. Photocoagulation of the CNV complex was performed in 52 eyes and 1 year after 34.6% of this group of patients experienced recurrence of CNV growth [26]. Follow-up of the first series of patients revealed that diplopia and tilted image were common side effects experienced by patients. Eckardt et al. described a series of patients in which muscle surgery was performed simultaneously or after macular translocation in order to minimize postoperative diplopia and cyclotropia, a common disorientating complaint among patients. The authors concluded that muscle surgery is a suitable option to control diplopia and tilted image [27].

Macular translocation remains a complex surgical procedure, but Toth et al. showed that increased surgeon's experience and improved surgical techniques led to better visual outcomes and decrease in the rate of postoperative complications [28]. Patients operated after implementation of surgical advancements fare better than patients operated before such advancements were introduced. These include change in instrumentation to induce retinal detachment, improved illumination and translocation of the retina, use of a more advanced wide field viewing system and stabilization of the retina with perfluorocarbon liquid. Surgical time is significantly decreased with these technical adjustments and so does the number of postoperative retinal detachments. This eventually led to better visual outcomes reported in the group of patients operated after introduction of the above-named advancements, with gain of three letters after 1-year follow-up. The same authors later published a prospective consecutive case series of 61 patients. Visual acuity significantly improved from 20/125 to 20/80 after 1 year [29]. Also mean near acuity improved significantly from 20/100 to 20/55, and this led to an improvement in reading speed from 71 words per minute to 105 at 1 year. In this series, five retinal detachments were reported. In another study, Toth et al. reported significantly improved near visual function (near acuity, reading speed and contrast sensitivity) in patients who had undergone surgery [30].

An alternative treatment for subfoveal neovascular AMD is photodynamic therapy with verteporfin. In a randomized prospective controlled pilot clinical trial by Gelisken et al. [31,32], 1 and 2-year follow-up results of patients treated with both treatment modalities were reported. Twenty-five patients with

predominantly classic subfoveal CNV due to AMD were randomized to each modality; patients with prior treatment for exudative AMD were excluded from the study. At 24 months, 15 patients out of 25 from the macular translocation group gained three or more ETDRS lines compared with 4 patients out of 25 from the photodynamic therapy group. Macular translocation patients gained seven letters in near vision compared with an average loss of 10 (9.6) letters of patients from the photodynamic therapy group. During the first year, 14 patients (56%) of macular translocation patients experienced recurrence of CNV compared with nine patients (36%) in the photodynamic therapy group. Other common complications during the first year follow-up in the macular translocation group included 6 retinal detachments (24%) and 13 patients with complaints of diplopia and/or tilted image. At 24 months follow-up, five patients (20%) from the macular translocation group and three patients (12%) from the photodynamic therapy group experienced recurrent CNV. No retinal detachments were reported at 2 years follow-up, and only two patients complained of diplopia. The small number of included patients led to some inconsistent reported results – a statistically significant difference was found in favor of full macular translocation for mean visual acuity and vision improvement but not for vision worsening [33].

Microperimetry is often used as a clinical parameter to assess retinal sensitivity and function before and after macular translocation surgery in neovascular AMD. This examination technique also allows the evaluation of patients with eccentric or poor fixation. Retinal sensitivity function analyses performed by microperimetry have shown that translocated foveae have a higher median retinal sensitivity score than the retinal areas overlying the diseased RPE–choriocapillaris complex, but a lower median retinal sensitivity score than retinas over untouched RPE [34]. A prospective study by Mettu et al. [35] has shown that although 1 year after macular translocation surgery, retinal sensitivity scores improved, preoperative retinal sensitivity scores are not predictive of postoperative measures of retinal sensitivity or visual function. Preoperative cystoid macular edema, subretinal fluid accumulation and subretinal lesion were predictive of decreased median retinal sensitivity scores.

Several authors have reported on near visual function outcomes (reading acuity, contrast sensitivity reading, speeds and critical print size) after macular translocation surgery. Eckardt et al. [27], Lai et al. [36] and Toth et al. [30] reported improvements in near visual function after translocation and improvement in critical print size. These studies support the notion that intact RPE is able to recover the function of foveal photoreceptors. Uppal et al. [37] compared parameters of near visual function in a cohort of operated patients with a comparative cohort of individuals with normal visual function. The authors performed infrared eye tracking and microperimetry analyses in a selected group of patients after macular translocation and globe counter-rotation surgery. Macular translocation could approximate normal function for reading speed and fixation quality. Tracking of ocular movements revealed a greater number of horizontal and vertical saccades, longer latency and reduced velocity compared with an age-matched cohort group. Surgery succeeded in reducing the central scotoma and three patients showed normal median retinal sensitivity scores.

In a retrospective, consecutive case review, Ehlers et al. [38] reviewed the feasibility of macular translocation for submacular diseases other than AMD. From 1996 to 2009, 16 subjects underwent macular translocation for their underlying retinal disease. These conditions included Best disease, angioid streaks, pathologic myopia, punctate inner choroidopathy, presumed ocular histoplasmosis syndrome, central serous chorioretinopathy, adult-onset vitelliform macular dystrophy and North Carolina macular dystrophy. The preoperative visual acuity ranged from 20/50 to 20/500 with a mean of 20/135. The mean postoperative visual acuity ranged from 20/40 to 20/1000 (mean 20/110). The operation had the same complications as reported by previous studies. In total, 38% of the patients experienced more than three lines of vision and 31% achieved a final visual acuity if patients experienced more than 20/50 at the end of the follow-up period (range of 4–61 months).

Full macular translocation has been proposed as a valid treatment in the setting of retinal pigment epithelium tears in AMD. These can occur spontaneously or secondary to several treatments such as laser, photodynamic therapy, intravitreal triamcinolone and intravitreal VEGF modulating therapy. Prognosis of these lesions is grim with visual acuity decreasing to 20/200 or less. When a tear occurs, the interface between photoreceptors and retinal pigment epithelium is disrupted, which renders the lesion unresponsive to anti-VEGF therapies [39]. Translocation of the macula to another location is then a valid attempt in order to restore the interface of the neurosensory retina with the RPE–choroid complex. Polito et al. [39] described a retrospective consecutive case series of six patients who had undergone macular translocation for RPE tears secondary to neovascular AMD. Visual acuity increased by six lines at 1-year follow-up and mean visual acuity was 20/50 at 3 years. In one patient with more advanced disease, atrophy of the RPE extended to the new fovea. The authors pointed out that early surgical referral may have led to better visual outcomes in this small subset of patients. Other authors reported on the validity of macular translocation for RPE tears. Meyer et al. [40] reported a patient with RPE tear whose vision improved from 20/70 to 20/60 after macular translocation surgery, this improvement being maintained at 15 months. Gelisken et al. [41] described a patient with RPE tear whose vision improved from 20/200 to 20/50 at 22 months follow-up after macular translocation surgery; no major complications such as proliferative vitreoretinopathy and recurrence of choroidal neovascularisation were reported. Gibran et al. [42] reported a case in which a RPE tear developed after two bevacizumab injections – macular translocation surgery improved vision from 20/320 to 20/80 at 7-month follow-up. These studies suggest that macular translocation may be a valid option for patients with RPE tears secondary to AMD; all studies present some limitations as they are retrospective reports of single or small series of patients with no control group.

Autologous retinal pigment epithelial choroid patch graft

Autologous RPE–choroid patch graft has been investigated as a surgical option for AMD [43–49]. Patch grafts, also known as full thickness grafts or patch transplants, consist of RPE, Bruch membrane and choroid [50]. Transplantation of patch grafts, in the literature often referred as translocation of patch grafts, is used in patients with dry or nonexudative and wet or exudative AMD [43–60]. This technique is also used in AMD patients with RPE tears that occurred spontaneously or as a result of a treatment [55,61].

During the last decades, different techniques of RPE–choroid patch graft have been performed in animals and humans [52]. Rejection has been seen in allogeneic patch transplantations in humans. A lower rate of rejection has been reported for patients with nonexudative or dry AMD than exudative or wet AMD. Mechanisms such as a disturbed retinal–blood barrier, the amount of transplanted RPE cells and the major histocompatibility complex molecule expression are possible mediators in rejection episodes [51,52,62].

Immunosuppressive therapy is required to improve RPE–choroid patch graft survival [51-59]. Tezel et al. [59] employed a technique with allogeneic RPE cells in patients with exudative AMD. Immunosuppression appeared to prevent rejection but did not improve visual function. Autologous RPE tissue is used so as to prevent graft rejection. Peyman et al. was one of the first to report a full-thickness autologous graft in patients with end-stage AMD [58].

In exudative AMD, patch surgery consists of a standard three-port pars plana vitrectomy, with or without inducement of posterior vitreous detachment, with or without direct phacoemulsification in phakic eyes, excision of CNV membranes by means of a small retinotomy with or without injection of a balanced salt solution (to induce a retinal detachment), use of perfluorocarbon liquid in some cases, followed by autologous full-thickness RPE–choroid translocation. As endotamponade (heavy) silicone oil, gas tamponade or air–fluid exchange can be used. Silicone oil, if used, may be subsequently removed after 3–9 months and when necessary the surgery may be performed in combination with phacoemulsification [43,45,49,54,55,57,60,63]. Grafts can be excised from the edge of the RPE defect [46] or from the mid-peripheral retina [43,45,47,48,60]. The latter technique is more often performed so as to minimize damage to the macular area, and because this area contributes less to functional vision. Treumer et al. [47] reported the use of a round patch to prevent curling of the graft.

In nonexudative AMD, patch surgery consists of a standard three-port pars plana vitrectomy, separation of RPE from the central retina by buffered saline solution, retinotomy, midperiphery autologous full-thickness RPE translocation and silicone oil exchange. The silicone oil may be removed after a minimum of 3 months and when necessary performed in combination with a phacoemulsification [44,47,50,56].

Autologous RPE–choroid patch grafts in patients with exudative AMD

Stanga et al. [46] described in a retrospective noncomparative interventional study the results of a subfoveal RPE–choroid patch graft translocation cut from the edge of the RPE defect. Nine patients underwent intervention, none had received treatment for exudative AMD. The follow-up time was 12–32 months. In seven of the nine patients, it was possible to translocate the RPE–choroid patch successfully during the operation, in one patient, it was not possible to translocate the graft under the fovea and in one patient, the graft got inverted during translocation. One patient developed a retinal detachment due to severe proliferative vitreoretinopathy. Four patients developed nuclear cataract during follow-up. No significant improvement of visual acuity was observed; no loss of vision was reported except in the patient who developed a retinal detachment. All seven patients with adequate translocation could detect a flashing light at the fovea and had preferred fixation at the fovea. A photopic 10-2 perimetry and a photopic fine matrix showed loss of foveal sensitivity, but central vision was present. Increases in autofluorescence were not noted with confocal laser scanning ophthalmoscopy in the area devoid of native RPE. Visual outcomes for treated patients, albeit disappointing, proved that this procedure might have a role in the treatment of AMD.

Meurs et al. [48] published a prospective interventional case series with six patients with subfoveal choroidal membranes (more than one disk diameter) with a follow-up of 7–13 months. Surgical technique involved a mid-peripheral full-thickness RPE–choroid patch. Visual acuity ranged preoperatively between 20/400 and 20/200. Postoperatively, the last recorded visual acuity ranged from 20/200 to 20/64. Bleeding from the excision site of the subfoveal membrane in all patients was noted intraoperatively in all patients. The RPE patch showed a brown furry flat appearance on biomicroscopial analysis. With the optical coherence tomography monitor, it was noted that four patients had preferred fixation in the region correspondent to the patch. Confocal scanning laser ophthalmoscopy analysis showed normal levels of autofluorescence in the patch region of the four patients. Postoperatively, one patient developed an extrafoveal subretinal hemorrhage and in one patients, submacular fluid was observed.

Treumer et al. [47] published an interventional case series of nine patients with exudative AMD who had undergone a RPE–choroid patch translocation from the midperiphery with a follow-up of 6–12 months. Mean preoperative visual acuity was 1.37logMAR (range 0.7–1.8) and postoperatively was 1.24logMAR (range 0.4–1.6). Visual acuity improved moderately in seven patients (mean logMAR 0.26) although one must consider that in this series seven patients underwent a combined phacoemulsification during surgery. Visual acuity decreased in two patients due to proliferative vitreoretinopathy with retinal detachment and postoperative development of CNV. In 5 of the 10 patients, microperimetry measurements showed perception of light stimuli and predominantly stable fixation on the RPE patch, such ability was maintained until the end of the follow-up. There were no intraoperative complications. Postoperative complications included retinal detachment, subtle macular pucker and epiretinal membrane formation. The authors concluded that autologous mid-peripheral

RPE–choroid patch appeared to be a feasible and a comparatively safe procedure although longer follow-up time is required.

In the prospective interventional study of Maaijwee *et al.* [45], 83 patients with exudative AMD underwent a midperiphery (12 o'clock) RPE–choroid graft patch with a minimal follow-up ranging from 1 to 4 years. Preoperative mean visual acuity was 0.95 logMAR (range 1/300–20/32) and after 4 years, it was 0.74 logMAR (range 20/800–20/32). A loss of less than three ETDRS lines was observed in 76% of patients 1 year after surgery and 82% of patients 4 years after surgery. In 17% of the patients, intraoperative complications were reported, the most frequent trauma to the subfoveal choroid with bleeding (six patients), loss of the graft through sclerotomies with the need to prepare a second graft and tearing of the retinotomy with bleeding (two patients). Postoperative complications were recurrent or persistent CNV membranes (13%), retinal detachment due to severe proliferative vitreoretinopathy or due to a rhegmatogenous cause (8%) and some degree of retinal puckering or cellophane maculopathy after removal of silicone oil in 90% of the patients. In nine patients, postoperative hemorrhages including subchoroidal, subretinal and vitreous hemorrhages were noted. Other complications included acute glaucoma (five patients), nonischemic retinal vein occlusion (one patient), retinal artery occlusion (one patient) and optic disc atrophy (one patient). Fixation on the graft was present in 62 patients up to the last examination. The graft had a brown velvety appearance in 60 eyes. Despite the mentioned complications, the authors concluded that RPE–choroid graft transplantation may stabilize or improve vision in patients with exudative AMD.

Heussen *et al.* [55] described translocation of a midperiphery RPE–choroid graft patch in 30 patients with exudative AMD. Visual acuity ranged preoperatively from 20/40 to 20/800. Postoperatively visual acuity ranged from 20/25 to light perception. Between 6 and 12 months, distance acuity remained stable or improved in 82% of the patients. There was an improvement between 6 months (1.4 log RAD) and 1 year (1.1 log RAD) of reading acuity as determined by the Radner test. All major complications occurred in the early operative period. A macular pucker developed in 1 patient and 11 patients experienced CNV recurrences. Microperimetry analyses did not differ between 6 and 12 months postoperatively. Autofluorescence of the graft decreased significantly in all patients from 6 to 12 months postoperatively. Of the 17 eyes with visual acuity worse than 1.0 logMAR, fixation analysis was performed in 11 patients and only 3 patients showed fixation on the patch itself. The authors concluded that patch grafting may be useful in patients with large subretinal hemorrhages in spite of the risk of late CNV formation.

In the prospective cohort study of Van Zeeburg *et al.* [60], 130 patients with exudative AMD with subfoveal CNV membranes underwent a midperiphery (at 6- or 12 o'clock) RPE–choroid graft translocation. The follow-up time was up to 7 years. Mean preoperative visual acuity was 20/250. Four years postoperatively, 15% of the eyes had a visual acuity above 20/200 and 5% of the eyes had a best-corrected visual acuity over or equal to 20/40. Reported postoperative complications included proliferative vitreoretinopathy (13 patients), CNV recurrence (13 patients), local retinal detachment (four patients) and hypotony (three patients). Loss of 24 patients during follow-up was recognized as an important limitation of this study. The authors concluded that patch grafting may maintain macular function and can be a good alternative treatment for patients with AMD.

Degenring *et al.* [43] evaluated in a retrospective study results of 12 eyes that had undergone a translocation of a midpheripheral (temporal/temporal inferior) RPE–choroid full-thickness graft in patients with exudative AMD with a mean follow-up of 11.1 months. Before surgery, median visual acuity was counting fingers (range perception of hand movements 20/125), and during follow-up, vision increased to a maximum median of 1/10 (range hand movements 20/40). At the end of follow-up, vision dropped until 1/40 (range hand movements 20/50). In eight of the 10 eyes, the translocated graft had a vital appearance and was perfused. Intraoperative complications were bleeding from the CNV extraction side (three eyes) and from the graft excision side (two eyes). The margins of the graft were slightly folded inward in one eye. In 41.6% of all eyes, there were surgery-associated complications, two eyes had rhegmatogenous retinal detachment and three eyes developed proliferative vitreoretinopathy. Revision surgery had not be done in 30% of the eyes. Postoperatively one eye developed an embolic occlusion of the central artery of the retina. After surgery, no persistent or recurrent CNV membranes was observed. The authors concluded that their data did not support the indication of autologous graft transplantation in patients with exudative AMD due to the high rate of adverse complications in the postoperative course.

In the prospective interventional cohort study of Maclaren *et al.* [57], 12 patients with exudative or wet AMD underwent removal of the CNV membranes and superior equatorial full-thickness RPE–choroid patch translocation with a 6-month follow-up. Preoperatively, the mean logMAR visual acuity was 0.82 (range 0.40–1.20) and 6 months postoperatively, it decreased to mean 1.16 (range 0.30–1.60). In three patients, complications were not reported; this group of patients showed a mean improvement of logMAR visual acuity from 0.88 to 0.79. In one patient, it was necessary to trim the RPE–choroid graft intraoperatively, and a relatively large strip was removed en bloc from the eye. Loss of sheets of RPE cells and an intact Bruch's membrane with electron microscopy was seen in this patient. Postoperative complications were proliferative vitreoretinopathy (six patients), retinal detachment (five patients) and hemorrhages affecting the graft (four patients). No recurrences of CNV were detected. The authors concluded that in some cases of exudative or wet AMD, the use of free RPE–choroid graft patch can improve vision, albeit the high rate of postoperative complications.

Autologous RPE–choroid patch grafts in patients with dry or nonexudative AMD

The use of autologous RPE–choroid patch graft for patients afflicted with dry or nonexudative AMD has been studied less extensively than for exudative or wet AMD.

A prospective nonrandomized study by Joussen et al. [56] analyzed the outcomes of a lower midperiphery full-thickness RPE–choroid graft (area 4–8 disc diameters outside the vascular arcades) in 12 patients with geographical atrophy with vision loss with a 6 months follow-up. Preoperatively, visual acuity ranged from 20/800 to 20/40 (mean 0.6 ± 0.4 logMAR) and reading vision ranged from 1.1 to 0.5 (mean 0.8 ± 0.2 logMAR). Six months postoperatively, visual acuity ranged from 20/2000 to 20/32 (mean 0.98 ± 0.6 logMAR). A significant distance visual loss (more than 15 letters) was reported in 33% of patients at 6 months follow-up. Severe visual loss occurred in 2 of the 12 eyes (17%) at 6-month follow-up. Only 9 of the 12 patients could read preoperatively, 8 of the 12 patients could read 6 months postoperatively. Almost in all eyes, revascularization was visible on indocyanine green angiography as early as 3 weeks postoperatively. Four eyes had an unstable or extrafoveal fixation preoperatively, two of these eyes stabilized during follow-up. A few intraoperative complications were mentioned such as macular hole formation and problems inserting and positioning the RPE graft. Postoperative complications included retinal detachment due to proliferative vitreoretinopathy (five eyes), subretinal hemorrhage, fibrinous reaction after silicone oil (one eye), failure or delay in revascularization (two eyes) and macula pucker formation (two eyes). The authors concluded that RPE–choroid patch grafts in dry or nonexudative AMD patients are associated with a high risk of complications and visual loss. Another earlier prospective nonrandomized study of Joussen et al. [44] used a midperiphery full-thickness RPE–choroid graft in 3 patients with geographical atrophy and 40 patients with exudative AMD. There was no subgroup analysis of visual acuity. Intraoperative and postoperative complications occurred in all patients of the nonexudative AMD group. Intraoperative complications included retinal adherences in two patients and macular hole formation in one patient. Postoperatively, two patients suffered a retinal detachment due to proliferative vitreoretinopathy and one patient suffered from a massive subretinal hemorrhage.

In the aforementioned study of Treumer et al. [47], one patient with geographical atrophy and nine patients with exudative AMD underwent a RPE–choroid patch translocation from the midperiphery under the macula. The one patient with geographical atrophy developed CNV 3 months after surgery.

Caramoy et al. [50] described the results of a prospective nonrandomized case series in which 10 patients with dry or nonexudative AMD underwent a full-thickness RPE–choroid graft (2–3 years follow-up). This study used the same surgical technique as Joussen et al. [44]. No recurrence of geographical atrophy was reported. The mean vision decreased from 20/80 at baseline (range 20/800–20/40) to 20/125 (range 20/800–20/32) at 6 months and 20/200 (range hand movements 20/32) at last follow-up. Prior to surgery, 7 of the 10 patients were able to read, 5 of the 10 patients were able to read at 2–3 years follow-up. Microperimetry analyses demonstrated central fixation in 5 of 10 eyes before surgery; 2–3 years after surgery, two eyes used the graft for fixation. Autofluorescence of the graft was present in all eyes throughout the follow-up period, in some patients, the autofluorescence decreased slightly throughout the follow-up period. Postoperative complications included retinal detachment due to proliferative vitreoretinopathy (three eyes), macula pucker and cystoid macula edema (three eyes), iritis and branch retinal vein occlusion (one eye), occult CNV at the border of the graft (three eyes) and secondary ocular hypertension (two eyes). The authors concluded that surgery may be useful in selected patients with stable fixation.

Retinal pigment epithelial cell suspension

Retinal pigment epithelial cell suspension is a transplantation technique that delivers RPE cells under the fovea [52].

Meurs et al. [49] reported the results of subfoveal injection of RPE cells in eight patients afflicted by AMD and subfoveal neovascular membranes (range two to four disk diameters) with a follow-up of 3–16 months. The procedure involved the following steps: a standard three-port pars plana vitrectomy, transretinal injection of Ringer's solution in the subretinal space, submacular injection of poly-L-lysine (0.2 ml, 0.1 mg/ml) and subsequently (after 5 min) subfoveal injection of autologous peripheral RPE cells (8×10^4 to 16×10^4). Solution with poly-l-lysine solution was used to promote cell adhesion. Snellen visual acuity did not show improvement in any patient up to 12 months postoperatively. Retinal detachment occurred in three patients due to proliferative vitreoretinopathy. Only in one patient, a pigmented area was noted in the extraction bed of the neovascular membrane. The authors concluded that this surgical procedure had a high rate of postoperative complications and no measurable positive effects on functional outcome.

In a randomized clinical cohort study of Falkner-Radler-et al. [54], 14 patients with exudative AMD were randomly assigned to receive either RPE–choroid graft patch or RPE cell suspension transplantation with 24 months follow-up. The anatomic and functional outcomes were comparable in both groups. Only one patient from the RPE cell suspension transplantation gained three or more lines in best-corrected visual acuity (same outcome in two patients treated with RPE–choroid graft patch), whereas a loss of vision occurred in one patient in each group.

Based on these results, and notwithstanding the low number of patients treated, RPE cell suspension transplantation does not seem to be a suitable approach for visual recovery in AMD patients.

Expert commentary

Visual outcome in patients with AMD remains poor if left untreated, especially in patients who developed extensive subretinal hemorrhages. Toxicity of blood under the neuroepithelium and chronic subretinal fluid accumulation eventually led to irreversible damage to the neurosensorial retina.

With the advent of anti-VEGF therapy, prognosis for exudative AMD has clearly improved, and progression toward end-stage AMD characterized by fibrovascular macular scar formation has slowed down. In patients with subretinal hemorrhages secondary to exudative AMD, monotherapy with anti-VEGF therapy may be a suitable first approach in some selected patients. In a recent published series by Shienbaum et al. [64], improvements in ETDRS letter score (more than 17 letter gain) were reported at 1-year follow-up after a period of treatment with intravitreal anti-VEGF injections. However, complications such as RPE tears may occur and not all patients respond well to anti-VEGF therapy. In such cases, surgery stands as the last valid attempt to preserve vision and halt progression. In this paper, four surgical approaches for exudative or wet and nonexudative or dry AMD have been described.

Minimally invasive surgical techniques have been reported. Intravitreal injection of gas with rTPA and anti-VEGF without gas could be the first choice in cases of thin submacular hemorrhages with small diameter (<1500 m) to obviate the relative risk of submacular hemorrhage recurrence and vitreous hemorrhages. If after 24 h the clot is not displaced, or in cases of larger hemorrhages, an additional injection of rTPA (at doses ≤ at 50 μg) to liquefy the clot for displacement by the pre-existing gas bubble can be performed. If the intravitreal approach does not result in an improvement of vision due to subretinal fibrosis or persistence of subretinal blood or in cases with large (>1500 μ) and thick submacular hemorrhage or if the procedure ends up with complication such as vitreous hemorrhage, recurrent submacular hemorrhage or a retinal detachment, a surgical approach would be advisable. In sum, surgical intervention with vitrectomy should be preferred for massive submacular hemorrhages, RPE submacular tears or nonresponders to medical treatment with progressive visual reduction.

Although most studies on surgical management of exudative AMD have been reported before the era of anti-VEGF therapy, results can be extrapolated to the present time since the surgical techniques currently used do not differ greatly from the ones used in the past. Selection criteria for surgical intervention in AMD have been redefined, with most patients being considered for surgery after other attempts (i.e., medical therapy) have failed.

Both macular translocation and autologous RPE-choroid graft patch appear to achieve a comparable visual outcome although both are associated with important complications.

The number of complications such as proliferative vitreoretinopathy and retinal detachment has been reduced in more recent studies due to improved techniques and the availability of new instrumentarium for the surgery. Retinal pigment epithelium–choroid patch graft could be offered for patients retaining a good vision in the fellow eye and macular translocation for functionally monocular patients (in which vision in the fellow eye is lost irreversibly). These techniques allow the removal of the submacular fibrovascular complex that is partially responsible for visual deterioration in patients with end-stage AMD. In a not yet published series of 60 patients from our vitreoretinal surgery unit, an improvement in visual acuity occurred in 50% of the patients operated with full macular translocation and in 27% of patients after RPE–choroid graft patch. More randomized comparative studies evaluating the efficacy of the aforementioned surgical approaches are required in the future.

Five-year view

Extraordinary advances in the medical treatment of AMD will result in more confined patient selection for surgery. Surgical intervention will remain a valid option for the treatment of complications of medical treatment and for patients who do not respond to medical treatment. Introduction of drug delivery devices may increase the need of new surgical procedures aimed to implant such devices.

Improvements in instrumentation have made vitreoretinal surgical techniques safer while enabling the standardization of complex techniques like macular translocation and RPE–choroid graft patch. Next-generation vitreoretinal instruments will bring even more advantages in the management of complex diseases in which surgery currently has no role. The use of intraoperative optical coherence tomography will make surgical procedures more precise and reproducible, allowing better decision-making process and giving prognostic information after surgery. Engineering of RPE cell layers or stem cells that can be transplanted or injected in patients with nonexudative and exudative AMD in order to regenerate the diseased RPE in early stages of the disease is one of the potential future approaches that may greatly improve the prognosis of this debilitating condition.

Key issues

- Age-related macular degeneration remains a leading cause of blindness worldwide.
- Surgery for end-stage exudative AMD is a valid approach aimed to preserve vision or halt progression when other treatment modalities have failed.
- Injection of tPA and gas is one of the available options in case of difficulty to treat submacular hemorrhages secondary to AMD.
- Surgical treatments such as macular translocation or RPE–choroid graft patch are relatively safe, albeit invasive procedures for the treatment of end-stage exudative or wet AMD and for patients who do not respond to anti-VEGF therapy.

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