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RECURRENT CHOROIDAL NEOVASCULARIZATION AFTER MACULAR TRANSLOCATION SURGERY WITH 360-DEGREE PERIPHERAL RETINECTOMY

CLAXTON A. BAER, MD, PHD*, CATHERINE BOWES RICKMAN, PHD*[†], SUNIL SRIVASTAVA, MD*, GOLDIS MALEK, PHD*, SANDRA STINNETT, DRPH*[‡], and CYNTHIA A. TOTH, MD*[§]

*Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina

[†]Department of Cell Biology, Duke University Medical Center, Durham, North Carolina

[‡]Department of Bio-statistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina

[§]Department of Biomedical Engineering, Duke University Medical Center, Durham, North Carolina

Abstract

Purpose—To evaluate the pattern of age-related macular degeneration in the new foveal location after macular translocation surgery with 360 degree peripheral retinectomy for neovascular age-related macular degeneration.

Methods—Clinical data, fundus photos, and fluorescein angiograms of patients in the Duke Macular Translocation Study were reviewed with 2-year follow-up data.

Results—With 56 patients completing follow-up, no patient developed de novo choroidal neovascularization (CNV), geographic atrophy, or drusen in the new subfoveal retinal pigment epithelium bed. By 2 years, 14 patients (25%) developed recurrent CNV and 13 of these 14 recurrences clearly arose from the old CNV bed. Of the 13 recurrences clearly arising from the old bed, 12 of them had recurrent CNV that involved the margin of the bed closest to the repositioned fovea. Smokers were 5.3 times (95% confidence interval: 1.2–24) more likely to develop recurrent CNV over 2 years. Despite treatment, median visual acuity for the 14 eyes with recurrent CNV was 20/200 compared with 20/80 in eyes without recurrence.

Conclusions—Findings in this study support the hypotheses that the development of CNV occurs via a signaling mechanism from the fovea.

Keywords

age-related macular degeneration; choroidal neovascularization; macula; retina; translocation; signaling

Macular translocation with 360-degree peripheral retinectomy (MT360) is used to rotate the fovea away from a bed of choroidal neovascularization (CNV) or atrophy onto a bed of

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Reprint requests: Claxton A. Baer, MD, PhD, Cabarrus Eye Center, 201 LePhillip Court, Concord, NC 28025; cab8b@yahoo.com. Sunil Srivastava is currently at Emory Eye Center, 1365 B Clifton Road, NE, Atlanta, GA 30322.

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healthier retinal pigment epithelium (RPE) and choriocapillaris. Often, the fovea recovers function over this healthier RPE and the patient improves in distance and near visual acuity, reading speed and quality of life.¹⁻³ The Duke Macular Translocation Study is a prospective, noncomparative study of MT360 for neovascular age-related macular degeneration (AMD) in the second eye. Of the 64 patients enrolled in the study, median visual acuity of the study eye was 20/125 before treatment, and the median lesion size was nine macular photocoagulation study (MPS) disk areas (range 3–30 MPS disk areas). At 1 and 2 years after surgery, the median visual acuity of the study eyes improved to 20/80.^{1,4}

Although geographic atrophy has been reported in the new subfoveal RPE after MT360,^{5,6} there is little data regarding whether repositioning the macula off CNV will initiate the rapid onset or progression of AMD in the new subfoveal RPE bed that was previously outside the macula. The purpose of this study was to evaluate the RPE at the site of the translocated fovea for signs of new subfoveal drusen, geographic atrophy, or new CNV, and to evaluate factors associated with AMD clinical progression.

Methods

Patients who had MT360 with silicone oil tamponade for neovascular AMD as part of the prospective, Duke University Medical Center Institutional Review Board-approved Macular Translocation Study between July 1999 and March 2002 were included in this study. Details of study criteria, procedures, and visual outcome data have been published.¹ In general, superior translocation of the macula was preferred for several reasons. Superior translocation creates a superior rather than inferior eccentric scotoma; the extraocular muscle surgery is more effective with advancing the inferior oblique rather than the superior oblique; the superior RPE is less likely to have been associated with preoperative subretinal hemorrhage; and if there is a postoperative inferior retinal detachment it would be less likely to extend into the macula. Occasionally, inferior translocation was performed if the RPE and choroid appeared healthier inferiorly compared with the usual superior location.

Patients had eye examinations including fundus photographs and fluorescein angiograms before surgery and at 6, 12, and 24 months afterwards. For the 64 study patients, review of demographic, study, and clinical data were performed. Fundus photographs and fluorescein angiograms were reviewed and scored for new drusen, new geographic atrophy, and recurrence of CNV. For those patients with recurrent CNV, the location of the recurrence was determined relative to the original lesion by centering a large “X” over the old CNV bed in fluorescein angiogram frames, dividing the bed into superior, temporal, inferior, and nasal quadrants (Figure 1). The location of the recurrent CNV was described relative to these quadrants, with the percentage of the CNV in each quadrant calculated.

Logistic regression was used to assess the significance of the relationship between smoking history, size of the CNV lesion, distance of translocation (distance between the old fovea location and the repositioned fovea), distance between the closest margin of the old CNV bed and repositioned fovea, and duration of vision loss. Any patient who reported smoking within 6 months of surgery was designated a smoker. To determine whether there was a disproportionate distribution of CNV recurrences over the four quadrants of the CNV bed, a chi-square goodness of fit test was carried out, assuming equal distributions in the quadrants were expected.

Results

Sixty-one patients at 1 year and 56 patients at 2 years completed the follow-up. The fovea was translocated off the CNV bed in all eyes. The median distance of translocation was 3.8

mm (range, 1.8–5.4 mm), and the median distance between the foveal center and the closest margin of the old CNV bed was 1.5 mm (range, 0.1–3.5 mm). None of the patients had new drusen in the RPE under the translocated fovea at 1 or 2 years. No patient developed a clear-cut site of small or large geographic atrophy. No patient developed definite de novo subfoveal CNV in the new fovea.

Twelve of 61 (20%) patients developed recurrent CNV over the first year, all from the old CNV bed. At 2 years, two additional patients developed recurrence for a cumulative recurrence rate of 14 out of 56 patients (25%) over 2 years. As shown in Figure 2, the majority of CNV recurrences occurred within the first 9 months.

Recurrent CNV occurred almost exclusively from the old CNV bed (13 out of 14). In one patient there was a likely, but not unequivocal, connection to the old CNV bed (Figure 3). In all 13 patients that had recurrence from the old CNV bed, the recurrent CNV always crossed the margin of the old CNV bed (Figure 4). Twelve of the 13 recurrences (92%) involved the superior margin of the CNV bed and for 8 of these recurrences, this was the only margin involved (e.g., see Figure 5). This distribution of CNV recurrences was significantly ($P < 0.001$) disproportionate over the quadrants as measured by a chi-square goodness of fit test. Sixty of 64 patients (94%) had superior translocation of the retina. The remaining four patients had inferior rotation of the retina and none of these patients developed recurrent CNV.

At 2 years, recurrence of CNV correlated with a history of smoking. Five out of nine smokers had recurrent CNV compared with 9 out of 47 nonsmokers. The odds of having a recurrence were 5.3 times greater for smokers than nonsmokers (95% confidence interval: 1.2–23.7).

The incidence of recurrent CNV was related to both the distance of translocation and the size of the original CNV lesion at 2 years. Mean (median) distance of translocation for the 14 patients with CNV recurrence was 3.3 mm (3.2 mm) compared with 3.8 mm (3.9) for those with no recurrence. For every 1 mm increase in translocation distance, the odds of recurrence of CNV by 2 years decreases by 0.44 (95% confidence interval: 0.19–1.0, $P = 0.055$). Mean (median) original lesion sizes for the 14 patients with CNV recurrence were 3.8 mm (3.7 mm) compared with 4.7 mm (4.5 mm) for those with no recurrence. The odds of recurrence decreased by 0.47 (95% confidence interval: 0.25–0.88, $P = 0.019$) for every 1 mm increase in lesion diameter. There was a moderate relationship between lesion size and translocation distance. For every 0.5 mm increase in lesion radius, translocation distance increased 0.36 mm ($R^2 = 0.31$). In contrast, the odds of recurrence of CNV were not related to the distance between the closest margin of the old CNV bed and the repositioned fovea ($P = 0.955$; median distance was 1.5 mm), or the duration of vision loss ($P = 0.104$; median duration of visual loss was 2 months).

Recurrent CNV was treated in 12 of the 14 eyes either with argon laser photocoagulation following MPS guidelines for extra or juxtafoveal CNV or with verteporfin photodynamic therapy. Ten of the 14 recurrences extended subfoveally. At 2 years, median visual acuity for the 14 eyes with recurrent CNV (with or without treatment) was 20/200 (range 20/40 to light perception) compared with 20/80 (range 20/25 to hand motion) for the 42 eyes without recurrence.

Discussion

With MT360, the fovea is moved off a diseased area with CNV onto a “healthier new bed.”^{7,8} A concern with macular translocation surgery that has been raised previously⁸ is whether the RPE-Bruch’s membrane-choriocapillaris of the new bed will develop AMD

once stressed by the overlying photoreceptor density of the repositioned fovea. Previous studies clearly show pathology of early AMD outside the fovea in AMD patients.^{9,10} In the current study, none of the 56 patients completing 2 years of follow-up developed new changes of either early or late forms of AMD in the “new macula.” These 56 patients did not develop de novo drusen, RPE atrophy or de novo CNV in the new RPE-Bruch’s membrane-choriocapillaris bed beneath the translocated fovea.

Although no new CNV developed in the foveal bed, 14 of the 56 eyes (25%, 95% confidence interval: 14–36%) developed recurrent CNV originating from or near the site of previous CNV removal during the 2 years after MT360. Cigarette smoking, the strongest known environmental risk factor for the development of advanced AMD,^{11–16} has also been strongly associated with risk of recurrence of CNV.¹⁷ In this study, the odds of developing recurrent CNV after MT360 were 5.3 times higher in patients that were smokers than for nonsmokers. At 2 years, there was a recurrence rate of 56% in smokers compared with a recurrence rate of 19% for those that did not smoke. These data suggest that it is very important to discuss the increased risk of recurrent CNV for patients who are considering MT360 and who also smoke.

Recurrence of CNV is a major challenge for all treatments of neovascular AMD. The 25% rate of CNV recurrence after MT360 is relatively low compared with other treatments for neovascular AMD. With laser photocoagulation of CNV in AMD, persistent or recurrent neovascularization was seen in 51% of eyes with subfoveal CNV at 2 years of follow-up.¹⁸ In the Submacular Surgery Trials for patients with neovascular AMD, there was a 52% rate of recurrence of neovascularization at 2 years after surgical removal of the CNV.¹⁹

For each of the above treatments, there is no repositioning of the neurosensory retina, leaving it associated with the macular RPE and choroid. In contrast, with limited macular translocation, the fovea is moved a short distance (median of 960 μm) from the CNV site and the CNV is not removed.²⁰ The rate of CNV recurrence reported at 9 months (43%) and at 1 year (45.3%) after limited translocation surgery is close to that for submacular surgery.^{21,22}

We hypothesize that signaling from the fovea is the impetus for recurrent CNV following current treatment paradigms for neovascular AMD and that the influence of this effect is inversely related to the final distance of the posttreatment fovea from the original lesion. This is strongly supported by the lower rate of CNV recurrence following MT360 than after many other treatments for neovascular AMD. After submacular surgery, the fovea remains over the CNV bed. After limited macular translocation, the fovea is moved a short distance, leaving it positioned over a portion of the original CNV 39% of the time.²⁰ Because the fovea ends up in closer proximity of the site of the original CNV following both of these treatment paradigms, fovea-derived factors would predict the higher recurrence rates found in these studies when compared with MT360. With MT 360, the median distance of translocation (3.7 mm) is more than 3 times the median distance of translocation in limited macular translocation.

The transplantation of an autologous retinal choroidal patch graft is another surgical technique used to treat macular degeneration.^{23–26} The largest of these series was a prospective nonrandomized study of 45 eyes of 43 patients with 6 months of follow-up.²⁶ Most of these 45 eyes had neovascular AMD with only 3 being operated on for geographic atrophy. In 24 of the 45 eyes, severe fibrosis of the patch occurred postoperatively affecting the central fovea. An additional nine eyes had a “slight form of fibrosis at the edges of the patch.” In their discussion, the authors claim that there was no recurrent CNV found in their study, however, in our opinion it is difficult to differentiate fibrosis from CNV. For this

reason it is difficult for us to make a comparison of CNV recurrence rates among these two techniques.

The foveal signaling hypothesis is also supported by the inverse correlation between CNV recurrence and distance of translocation. The distance of translocation and the lesion size are related parameters since during MT360 the surgeon observes the size of the CNV bed and purposely translocates the fovea off this site producing a greater translocation distance in eyes with larger lesions. In this study, translocation distance increased on average 0.36 mm for every 0.5 mm increase in lesion radius. For every 1 mm increase in lesion size, odds of CNV recurrence decreased by 47% and for every 1 mm increase in translocation distance odds of recurrence decreased by 44%. An alternate explanation could be that a smaller CNV lesion is younger, and therefore the stimulus for initiation of the CNV is still present and active within the eye. However, the larger lesions do result in greater distance of translocation which moves the fovea further away from the original site or sites where the CNV crossed Bruchs membrane or was initiated.

Additional support for the hypothesis that the fovea signals recurrence of CNV is that recurrence of CNV originating from within the old CNV bed almost always involved the edge of the bed closest to the repositioned fovea. Under the more metabolically active fovea (compared with the rest of the retina) there may be a higher concentration of pro-angiogenic factors and a lower concentration of antiangiogenic factors. This would lead to an increased concentration of angiogenic factors and a decreased concentration of antiangiogenic factors at the edge of the CNV bed closest to the repositioned fovea, possibly explaining why almost every CNV recurrence involved that margin. A similar finding was also seen in the extrafoveal MPS in which 90% of the CNV recurrence detected after MPS laser for extrafoveal CNV was contiguous with the laser scar. Of the contiguous recurrences, 97% of them involved the foveal half of the laser scar and for 85% of them the foveal half was the only side that was affected.¹⁶

Macular translocation surgery with 360 degree peripheral retinectomy outcomes provide unique insight into the pathogenesis of AMD. In addition to implicating the foveal retina in the development of neovascular AMD, the foveal retina also appears to signal the development of recurrent geographic atrophy (GA) in patients having MT360 for GA via a different mechanism.^{5,6,27} GA recurred in three of four eyes in patients who had undergone MT360 surgery for GA at our center.⁵ In each case, the atrophy occurred de novo under the repositioned fovea and the resultant lesion was similar in shape and size to the original GA. In contrast, no patient in this series of MT360 for CNV developed geographic atrophy, and the CNV recurrence originated from the old bed, not de novo subfoveally. Recurrent CNV was only seen in patients that underwent MT360 for CNV, not for GA, and recurrent GA was restricted to patients who had MT360 for GA.⁵ The above findings suggest that neovascular AMD and geographic atrophy occur via distinct mechanisms. Support for a direct role of photoreceptors in GA comes from studies of recessive Stargardt macular dystrophy, which is clinically similar to dry AMD and is caused by mutations in the gene encoding a photo-receptor-specific adenosine-5'-triphosphate binding cassette transporter, ABCA4.²⁸ Examination of *ABCA4* for a potential role in AMD suggested an association with AMD,²⁹ but this is controversial.³⁰

In conclusion, at 2 years after MT360 for neovascular AMD, data from a moderate-sized prospective case series demonstrate that the new subfoveal bed does not develop signs of AMD (drusen, GA, or CNV). However, recurrent CNV is seen in 25% of patients and almost always recurs from the old CNV bed. Three findings from this study implicate signaling from the foveal retina in the development of recurrent CNV: 1) The MT360 CNV recurrence rate is relatively low compared with treatments where fovea is not moved or

moved to a lesser extent; 2) The recurrence of CNV is inversely related to distance of translocation; and 3) The recurrence of CNV is most common at the edge closest to fovea. Based on the results of this study, we recommend close follow-up after MT360 with relatively frequent fluorescein angiograms to detect recurrent CNV so that it can be treated before expansion to the fovea, particularly in patients that smoke. Attention to the foveal side of the CNV bed is warranted. Frequent surveillance is especially important during the first postoperative year when recurrence is most likely to occur. Early recognition and new methods to treat recurrent CNV may prevent vision loss in this subgroup of patients and improve overall outcomes after macular translocation surgery. Also given that recurrence of CNV decreases with increase in distance of translocation, we recommend avoiding minimal distance of translocation to reduce rates of recurrent CNV.

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Fig. 1. Schematic of repositioned retina (black optic nerve head plus arcades) relative to original CNV lesion (gray region). The original CNV bed was divided into quadrants by placing an X in the center of the CNV bed. For each recurrence of CNV from the old CNV bed, the proportion of recurrent CNV within each quadrant was determined. S, superior; N, nasal; I, inferior; T, temporal.

Fig. 2.
Recurrent CNV as a function of time after macular translocation surgery.

Fig. 3.

Fluorescein angiograms (FA) of the patient with recurrent CNV in whom the site of origin of the recurrent CNV is unclear. Early frames of FA in left column (**A, C, E**), late frames in right column (**B, D, F**). Preoperative fluorescein angiogram shown at top (**A, B**). At fourteen months after MT360 there is late staining at the position of the old CNV bed (**C, D**) and a site of poorly defined early recurrence off the superotemporal margin of the CNV bed. At 18 months of follow-up, classic appearing recurrent CNV is seen temporal to the foveal (arrow, **E**). In the late frames of the fluorescein angiogram at 18 months of follow-up (**F**), an occult recurrence is seen juxtafoveally (top arrow) with a probable connecting region just superior to the margin of the old CNV bed (bottom arrow).

Fig. 4.

Origination site of recurrent CNV from the old CNV bed. For each recurrence of CNV from the old CNV bed, the proportion of recurrent CNV within each quadrant was determined (see Fig. 1). Twelve of the 13 recurrences from the old CNV bed involved the superior margin of the old CNV bed. For 8 of these patients the superior margin was the only margin involved. For all 13 of these patients the retina was rotated superiorly as part of the MT360 procedure. The superior margin is therefore the margin of the old CNV bed that is closest to the repositioned fovea. This prevalence of recurrence at the margin closest to the repositioned fovea suggests a signaling mechanism from the fovea in the development of CNV.

Fig. 5.

Fluorescein angiograms of a patient with recurrent CNV that involves the superior margin of the old CNV bed. Early frames of FA in left column (**A**, **C**, **E**), late frames in right column (**B**, **D**, **F**). Preoperative fluorescein angiogram shown at top (**A**, **B**). Two months after MT360 (**C**, **D**) there is late staining of the old CNV bed. At 12 months postoperatively (**E**, **F**), recurrent CNV has extended across the superior margin of the old CNV bed into the fovea (arrow, **F**). At 2 months, an area of late staining may represent a fibrovascular nidus of the recurrent CNV (arrow, **D**).