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Eddie F. Kadrmas, MD, PhD

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RETINA DIGEST®

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Association Between Retinal Vein Occlusion And Stroke

Due to recent studies showing that traditional risk factors such as hypertension, diabetes and cigarette smoking cannot explain stroke development, interest has shifted to retinal vasculature, including signs of hypertensive retinopathy and mild nonproliferative diabetic retinopathy along with retinal vein occlusion (RVO) as risk factors. Rim et al from Yonsei University College of Medicine, South Korea, used data from the Korean National Health Insurance Service (KNHIS) to evaluate the risk of stroke development after RVO.

Authors identified 1031 patients with newly diagnosed RVO in 2003, 2004 and 2005, along with a comparison group matched by age, gender, residential area and household income. Patients with preexisting RVO or stroke were excluded. All patients were tracked through 2010, and incidence of stroke (both ischemic and hemorrhagic) was recorded.

Patients in the RVO group were more apt to experience stroke ($p < .001$), hypertension ($p < .001$), diabetes mellitus ($p < .001$) and chronic kidney disease ($p < .001$) than were members of the comparison group. Table 1 shows the hazard ratio (HR) for stroke during the 8-year follow-up period using univariate and multivariate Cox regression models.

The RVO group showed an association with the propensity for stroke after multivariate analyses, as did comorbidities tested. Patients with RVO showed an increased risk of ischemic stroke and hemorrhagic stroke. RVO patients <50 years old had the highest risk for stroke, while patients aged ≥50 years showed a risk too.

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Table 1. Univariate and multivariate Cox regression analyses of overall survival after stroke

	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
RVO group	1.73 (1.45–2.06)	<.001	1.48 (1.24–1.76)	<.001
Hypertension	4.20 (3.40–5.20)	<.001	2.52 (2.01–3.15)	<.001
Diabetes mellitus	1.84 (1.58–2.15)	<.001	1.25 (1.06–1.46)	.006
Chronic kidney disease	3.07 (2.20–4.27)	<.001	2.02 (1.45–2.82)	<.001
Age (years)[a]				
40–49	6.89 (1.65–28.83)	.008	4.93 (1.17–20.69)	.029
50–59	12.76 (3.15–51.80)	<.001	7.54 (1.85–30.75)	.005
60–69	27.03 (6.73–108.59)	<.001	14.45 (3.57–58.54)	<.001
70–79	42.34 (10.52–170.45)	<.001	20.80 (5.12–84.54)	<.001
≥80	58.58 (14.26–240.66)	<.001	31.28 (7.56–129.40)	<.001

[a]*Comparison vs age <40 years. CI, confidence interval.*

RVO found through ophthalmologic examination can indicate future hypertension and stroke, especially in younger patients. Further studies examining this relationship and other factors need to be undertaken to confirm the findings of this study.

Rim TH, Kim DW, Han JS, Chung EJ. Retinal vein occlusion and the risk of stroke development: a 9-year nationwide population-based study. Ophthalmology *2015;122:1187-1194.*

Treating Neovascular Lesions and Visual Outcomes

Neovascular age-related macular degeneration (AMD) treatment was revolutionized by the use of vascular endothelial growth factor (VEGF) inhibitors, yet a protocol for the effective use of anti-VEGF drugs remains unclear. Current regimens require that lesions with evidence of activity undergo continued treatment. The presence of subretinal or intraretinal fluid, an indicator of persistent choroidal neovascularization (CNV), may be associated with progressive vision loss. A large number of eyes with AMD receiving anti-VEGF treatment show signs of persistently active CNVs.

Barthelmes et al from the University of Sydney, Australia, analyzed data collected from 27 ophthalmologists in Australia, New Zealand and Switzerland between 2007 and 2011. Patients in the study had wet AMD with ≥12 months' follow-up and ≥2 injections of ranibizumab. Variables analyzed included age, gender, visual acuity (VA) at each visit, lesion type, greatest linear dimension of the neovascular lesion identified by fundus fluorescein angiography, treatment at each visit and lesion status. Eyes were divided into 4 groups based on the grading of activity. Persistent activity was defined as activity at all visits; remaining eyes were ordered by amount of activity and divided into 3 equal groups classified as high, medium and low.

Mean patient age of 79.4 years and mean VA (measured in the number of letters read on a logarithm of the minimum angle of resolution [logMAR] chart) of 54.9 were similar across 4 groups; frequency of minimally classic and occult lesions increased in the more active groups. VA showed significant and clinically relevant (>5 logMAR letters) improvement in all groups at 12 months ($p < .001$). The mean annual number of injections for eyes in the low activity group increased over the term of the study, although improvements in VA were without a corresponding increase. Out of a total of 5305 injections recorded, 9 adverse effects were reported.

Study results showed that lesion activity had less effect on VA outcomes from intravitreal

therapy than expected. Subsequent studies showing similar results could suggest that less emphasis on using higher doses or treating persistently active lesions more frequently may be warranted.

Barthelmes D, Walton R, Campain AE, et al; Fight Retinal Blindness! Project Investigators. Outcomes of persistently active neovascular age-related macular degeneration treated with VEGF inhibitors: observational study data. Br J Ophthalmol *2015;99:359-364.*

The Role of Epiretinal Membrane in Neovascular AMD

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has led to improved vision for patients suffering from neovascular age-related macular degeneration (AMD). While studies have measured the impact of vitreomacular interface changes, such as posterior vitreous detachment, vitreomacular adhesion and vitreomacular traction, on the development and prognosis of neovascular AMD, no evidence has been published concerning the possible role of epiretinal membrane (ERM). Karaca et al from the Gazi University Medical Faculty, Turkey, conducted a retrospective observational case series of neovascular AMD patients treated with anti-VEGF therapy to measure the impact of ERM in this group.

The study included 90 patients aged ≥50 years and newly diagnosed with neovascular AMD who had been treated with intravitreal anti-VEGF therapy (ranibizumab or bevacuzimab) during a 3-year period. Data collected included age, gender, best-corrected visual acuity (BCVA), lesion characteristics (including type of neovascular AMD), follow-up time, number of injections, injection intervals, signs of neovascular AMD control and vitreomacular interface characteristics. Patients were divided into 3 groups based on the results of slit-lamp biomicroscopy and spectral domain optical coherence tomography performed at their first visit.

- **Group 1**: concurrent vitreomacular adhesion (n = 43)
- **Group 2**: complete posterior vitreous detachment (n = 29)
- **Group 3**: ERM in addition to vitreomacular adhesion (n = 18)

Mean follow-up for all groups was at least 2 years.

Group 3 patients required 11.6 ± 2.9 anti-VEGF injections with a mean injection interval of 6.12 weeks. This represented both a significantly greater number of injections and shorter mean interval between injections than in the other groups. The mean longest interval was also shortest for these patients. Findings showed no difference between the groups for BCVA or for change from baseline in BCVA at any time point. Neither was any difference found between the groups in central foveal thickness or lesion size (Table 2).

Table 2. Baseline characteristics of the patients in 3 groups

	Group 1 (n = 43)	Group 2 (n = 29)	Group 3 (n = 18)	p value (ANOVA)*
BCVA (baseline; logMAR)	0.5 (0.1–1)	0.5 (0.1–1)	0.3 (0–1)	.204
CFT (µm; baseline)	252 (140–651)	271 (126–1000)	255 (175–600)	.525
Lesion size (cm^2; baseline)	9.97 (0.21–71.37)	10.23 (0.65–33.12)	11.29 (1.38–37.31)	.230
Number of injections	8.32 ± 4.7	6.87 ± 3.3	11.6 ± 2.9	<.001
Injection intervals (weeks)	7.59 (4–10.7)	7.2 (4–12.2)	6.12 (4–9.1)	<.032
Longest interval between injections (weeks)	10.7	12.2	9.1	<.012

**ANOVA, analysis of variance; logMAR, logarithm of the minimum angle of resolution; CFT, central foveal thickness.*

The comparatively poor response to anti-VEGF therapy showed the impact that the presence of ERM can have on the management of patients with neovascular AMD. The reason why the presence of ERM in neovascular AMD influences the number of injections and the injection interval is unclear. The authors hypothesized that the presence of ERMs may act as a physical barrier to the penetration of anti-VEGF medications.

Karaca EE, Kepez Yıldız B, Çubuk MÖ, Özdek Ş. Epiretinal membranes in neovascular age-related macular degeneration: effect on outcomes of anti-vascular endothelial growth factor therapy. Retina *2015;35:1540-1546.*

Endophthalmitis Risk with Intravitreal Injections

With >1 million intravitreal injections for treatment of diseases such as age-related macular degeneration, uveitis, diabetic macular edema and macular edema secondary to retinal vein occlusion reported in the United States in 2009 alone, there is concern about possible complications. Infectious endophthalmitis is one of the most worrisome of these complications. Dossarps et al from Burgundy University, France, conducted a large multicenter retrospective study of endophthalmitis cases in 25 ophthalmic centers throughout France. Their goals were to report the incidence of endophthalmitis and to describe the prophylactic measures, the clinical and microbiological spectrum, and the management and outcome of endophthalmitis following intravitreal injections.

From January 2008 through June 2013, the centers reported a total of 316,576 intravitreal injections; treatments included ranibizumab, bevacizumab, triamcinolone acetonide and the dexamethasone implant. Before injection, each eye received one drop of tetracaine as a local anesthetic, followed by a 2-minute application of 5% periocular and conjunctival povidone-iodine. Either a lid speculum or a disposable conjunctival mold was used. Ophthalmologists wore sterile gloves, face masks, surgical hats and gowns, as did their assistants.

The centers reported 65 presumed cases of infectious endophthalmitis, for an overall incidence of 0.021% (95% confidence interval [CI], 0.016%–0.026%). The factors of the intravitreal injection procedure associated with increased incidence of endophthalmitis were the use of a disposable conjunctival fixed mold and use of antibiotic or antiseptic prophylaxis.

On average, initial presentation took place 4 days after the injection. The first intravitreal antibiotic injection took place on the same day as presentation in all but 3 cases, with a second injection performed in 60% of eyes an average of 2 days later. Treatment also included subconjunctival injections of betamethasone in 39 cases and systemic corticosteroids in 22 cases. In the 23 eyes that had a positive bacterial culture, 18 were positive for coagulase-negative staphylococci. Visual acuity at 3-months' follow-up was better than at baseline but poorer than it was before the infection.

This retrospective study found that although the incidence of endophthalmitis after intravitreal injection is low, the overall prognosis is poor. Universal application of these results may be limited by differences in protocols; in the United States, for example, the use of sterile drape, face mask, surgical hat, sterile gloves and surgical gown remains uncommon.

Dossarps D, Bron AM, Koehrer P, et al; FRCR Net (French Retina Specialists Net). Endophthalmitis after intravitreal injections: incidence, presentation, management, and visual outcome. Am J Ophthalmol *2015;160:17-25.*

SPRING 2016

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- Causes of photopsias in patients
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