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Original Article

Ranibizumab for idiopathic epiretinal membranes A retrospective case series

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Abstract

Purpose: To study the effect of intravitreal ranibizumab on idiopathic epiretinal membranes (ERMs).
Methods: A retrospective cohort study on a consecutive series of ranibizumab intravitreal injections for epiretinal membranes was performed. Four cases were identified by reviewing a claims database linked to electronic medical records. All patients received a total of three 0.05 mg/0.05 ml ranibizumab intravitreal injections at a monthly interval. The primary outcome measure was the final best-corrected visual acuity (BCVA) at the end of the injection series, and the final central macular thickness (CMT).
Results: All four patients completed 3 months follow-up after the last ranibizumab injection. The mean baseline CMT was 509 microns (SD = 111). A trend was noticed for reduction in CMT (Δ = 41 microns) $P = 0.08$. Three patients improved by one line in their BCVA. The remaining patient maintained the same BCVA. No complications were noted.
Conclusion: In this study, intravitreal injection of ranibizumab marginally reduced retinal thickness in four patients with minimal improvement in visual acuity. No safety concerns were noticed. Further basic science and clinical studies may be warranted to assess the role of vascular endothelial growth factor and the effect of ranibizumab on idiopathic epiretinal membranes.

Keywords: Epiretinal membrane, Intravitreal injection, Metamorphopsia, Ranibizumab, Vascular endothelial growth factor

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Introduction

Epiretinal membrane (ERM) is a glial proliferation on the surface of the retina along the internal limiting membrane that may cause visual distortion, blurred vision, or decreased visual acuity when present in the macular area.[1] It can be idiopathic in origin, or a consequence of prior intraocular surgery, inflammation, retinal vasculopathy, or trauma.[1,2]

Surgical removal of epiretinal membrane by means of pars plana vitrectomy is usually performed in visually symptomatic patients with good post-operative visual outcomes, but many surgeons implement a minimum visual acuity of 20/50–20/60 as a cutoff point for performing surgery.[3,4] This threshold for surgery leaves no therapeutic option for those with symptomatic ERM and visual acuity of 20/40 or better. In addition, some patients who are symptomatic with advanced ERM might decline vitrectomy or are poor surgical candidates. ERM is a progressive condition; between 10–37% of eyes with ERMs will demonstrate a decrease in visual acuity over three years.[5,6]

Vascular Endothelial Growth Factor (VEGF) is a cytokine involved in multiple physiological processes, of clinical signifi-

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cance in both disease and health, and can act on cells other than the vascular endothelium.[7,8] Example of such processes include dendritic cell differentiation and function,[9] neural cell survival,[10] and trophic support of choriocapillaris.[11] Immunohistochemical studies have demonstrated VEGF and its receptors within both vascular and avascular ERM[7] with localization to the glial cells and retinal pigment epithelial (RPE) cells of the ERM. Angiogenesis and VEGF expression do not necessarily correlate when it comes to ERM proliferation.[8] Thus VEGF, in addition to being a powerful angiogenic and vascular permeability factor,[12] may play an important role in the stimulation of ERM formation.

Ranibizumab (Lucentis, Genentech, San Francisco, CA) has shown significant safety and efficacy in phase III trials in the treatment of age-related macular degeneration by inhibiting biologically active VEGF-A isoforms as proven by many randomized clinical trials.[13,14] Given the few alternatives for symptomatic ERM and the possibility that VEGF may play a role in the pathogenesis of ERM, we conducted a retrospective analysis of consecutive cases that received ranibizumab and looked into its effects on idiopathic ERM.

Methods

We reviewed an administrative claims database to identify patients with ERM who received ranibizumab. Four consecutive cases were identified. In all four cases, patients had a thorough informed consent performed and understood that the treatment they were to receive was off-label for this indication given their symptoms and as an alternative for those who refused surgical intervention. Patients underwent routine best corrected visual acuity (BCVA) testing and intraocular pressure measurement, fundus fluorescein angiography, and optical coherence tomography (OCT) scans with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California) both before and one month after the injection series. We used the built-in anatomic tracking software to measure the same central macular location at follow-up. Intravitreal injection of 0.5 mg/0.05 ml ranibizumab was done via a 30-gauge needle inserted 3.5 mm from the limbus, administered monthly for three months under sterile conditions using topical 5% povidone-iodine drops and 10% povidone-iodine lid scrub. Topical xylocaine gel to anesthetize the eye and a sterile lid speculum were used in the process. All patients were followed for at least three months after the last injection. The outcome measures were BCVA, and thickness of the central area with a 1 mm diameter on OCT – central macular thickness – (CMT). The approval of the Research Ethics Board was obtained for this study.

Results

Four patients, two females and two males, with a mean age of 72.5 years (range: 60–84 years) received intravitreal ranibizumab injection for idiopathic ERM. Prior to starting these injections, their average CMT was 509 ± 111 microns (mean ± SD). Their mean BCVA (logMAR) was 0.62 ± 0.27 [Snellen equivalent, 20/80]. At the end of the third month follow-up after the third injection of ranibizumab, the mean CMT was 468.75 ± 86.27 microns (Figs. 1 and 2). Mean BCVA (logMAR) was 0.56 ± 0.22 [Snellen equivalent, 20/70]. No complications were encountered from injections or during the three month follow-up. Table 1 summarizes the pre-and

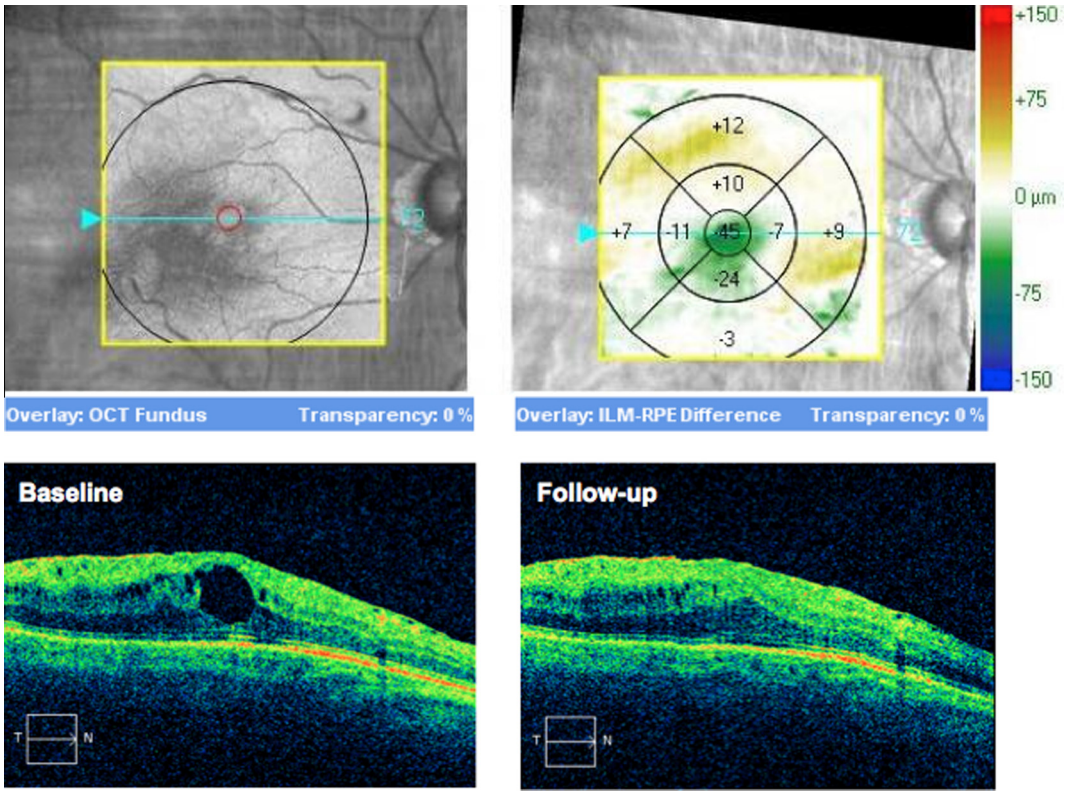

Figure 1. Optical coherence tomography (OCT) for Patient 1 showing reduction in central macular thickness after ranibizumab injections by 45 microns (left, before treatment; right, three months after third injection). Note the disappearance of the central macular cyst.

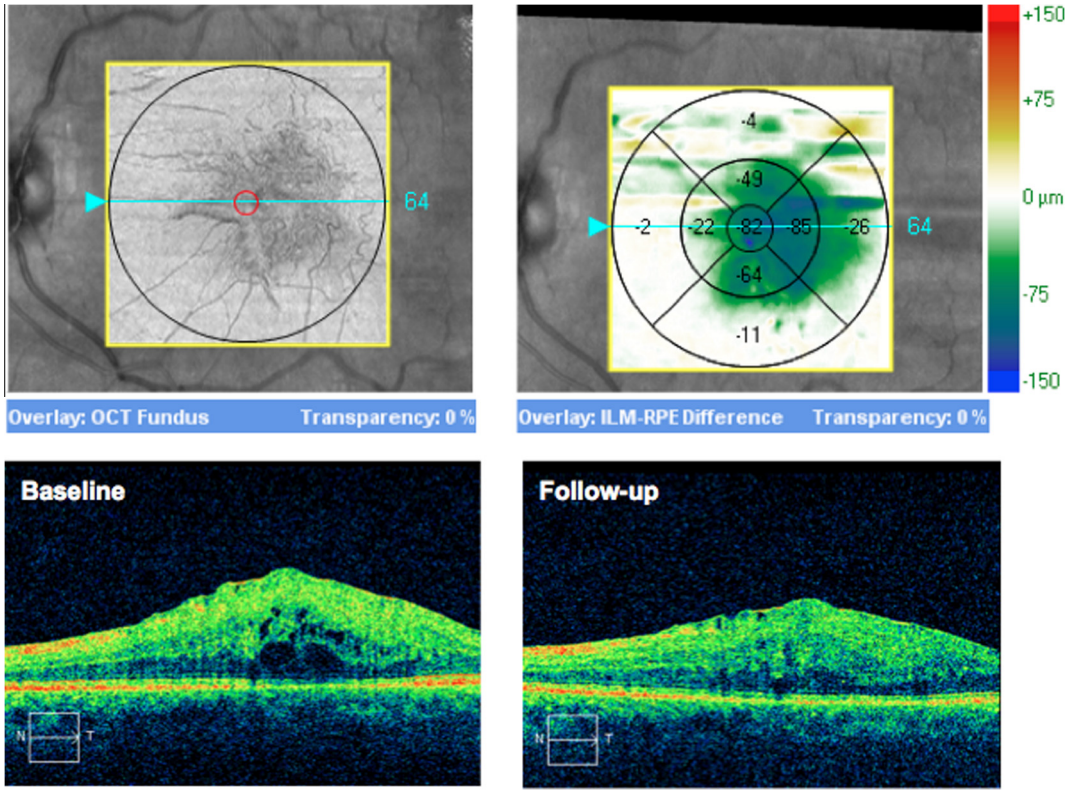

Figure 2. OCT images showing reduction of CMT by 82 microns and shrinking of cystoid spaces in Patient 3.

Table 1. Summary of cases.

	Sex/Age(yrs)	CMT		BCVA	
		Pre-injection	Post-injection	Pre-injection	Post-injection
Patient 1	Male/68	558	513	6/24	6/21
Patient 2	Female/78	359	344	6/15	6/15
Patient 3	Male/84	619	537	6/60	6/45
Patient 4	Female/60	500	481	6/18	6/15

CMT = Central macular thickness, BCVA = Best corrected visual acuity.

post-injection values. A trend was present for a reduction in central macular thickness (mean Δ in CMT = 41 microns ± 24.91, $P = 0.08$).

Discussion

Based on immunopathologic studies, VEGF may play an important role in the development of ERM.[7,8] In our present study, we evaluated the CMT and BCVA for patients with idiopathic ERM before and after intravitreal injection of ranibizumab. We found a trend in the reduction in CMT of patients with idiopathic ERM after injection of three doses of ranibizumab. This reduction appears to be related to a decrease in macular edema, presumably related to ranibizumab's effect on vascular permeability. The membrane was still visible in all cases and showed no appreciable change at the resolution level of spectral domain-OCT. BCVA improved by one line in three patients and was maintained at the same level in the remaining patient. No ocular or systemic adverse events were noted.

There are no published data evaluating the effect of ranibizumab on idiopathic ERMs. However, Luttrull and Spink[15] showed that anti-VEGF injection for eyes with age-related subfoveal neovascularization and ERM followed by surgical removal of the ERM might offer further improvement in visual acuity. Kon-Jara concluded that the presence of ERM with wet age-related macular degeneration results in poorer visual outcomes when treated with ranibizumab (Kon-Jara V, Chaudhry N, Tabandeh H, et al. Visual and Anatomic Outcomes of Intravitreal Anti-VEGF Therapy for Exudative AMD with Significant Epiretinal Membrane. Poster presented at: American Society of Retina Specialists Annual Meeting, 2010; Vancouver). Watanabe et al.[16] demonstrated a correlation between metamorphopsia detected in ERMs and the actual thickness on OCT. Of note, Kuiper et al.[17] reported that anti-VEGF treatment could alter the angiogenic signal into a pro-fibrotic one by altering the balance between connective tissue growth factor (CTGF) and VEGF in diabetic retinas. A similar mechanism may explain fibrosis and contraction after anti-VEGF administration for retinopathy of prematurity.[18] Idiopathic ERMs are usually avascular membranes, thus we

presume that they are exempted from this fibrotic response to anti-VEGF.

Conclusion

In this small case series, we report that ranibizumab may have a role in treating ERM by reducing associated macular edema. The mean change in CMT approached statistical significance, and there was improvement in visual acuity in three out of four patients, although a placebo effect cannot be ruled out. The conclusions of this study are preliminary given the small sample size. We believe a larger, prospective clinical trial is warranted to evaluate ranibizumab for the treatment of idiopathic ERM. Currently the lucentis for epiretinal membrane (LERM) study is ongoing.[19] Results of the study should provide more insight into the role of ranibizumab in treating ERM.

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