Changes in Aqueous Vascular Endothelial Growth Factor and Pigment Epithelium-derived Factor after Ranibizumab Alone or Combined with Verteporfin for Exudative Age-related Macular Degeneration

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• PURPOSE: To investigate changes in aqueous vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) in choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) after ranibizumab (Lucentis; Genentech Inc, South San Francisco, California, USA) monotherapy or combined with photodynamic therapy (PDT).

• DESIGN: Prospective, interventional, case-control study.

• METHODS: We recruited 34 patients with CNV secondary to AMD and 10 controls. Baseline examinations, including visual acuity (VA), central macular thickness (CMT), fluorescein angiography, and indocyanine angiography, were performed, and the measurements of VA and CMT were repeated 1 month after treatments. Seventeen of 34 patients received a single intravitreal injection of 0.5 mg ranibizumab, and the remaining 17 patients underwent combined PDT on the same day. Aqueous samples were collected at the time of injection and 1 month after treatment and were measured by enzyme-linked immunosorbent assay. Main outcomes measures were the changes in VA and CMT and the changes in VEGF and PEDF levels.

• RESULTS: Demographic features, lesion characteristics, and mean changes in VA and CMT were similar between the two groups. Aqueous VEGF and PEDF levels were reduced significantly 1 month after treatment in all patients. The reduction levels of VEGF and PEDF were similar between the two groups. There was a positive correlation between the reduction levels of aqueous VEGF and the reduction levels of aqueous PEDF. The reduction levels of VEGF and PEDF were correlated positively with the decrease in CMT, but were not positively correlated with the improvements in VA.

• CONCLUSIONS: Ranibizumab therapy for CNV secondary to AMD is associated with reduced levels of aqueous VEGF and PEDF regardless of combined therapy with PDT. The reduction levels of VEGF and PEDF are correlated with anatomic improvements in the macula.

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EXUDATIVE AGE-RELATED MACULAR DEGENERATION (AMD) associated with choroidal neovascularization (CNV) is the main cause of severe visual loss in individuals older than 55 years.[1] The angiogenic shift in the choriocapillaris and retinal pigment epithelium (RPE) may be involved in the development of CNV.[2,3] Vascular endothelial growth factor (VEGF) plays a key role in the initiation and growth of CNV.[4,5] Pigment epithelium-derived factor (PEDF) counterbalances the effect of VEGF and modulates the formation of CNV.[6,7] Aqueous levels of VEGF and PEDF have been reported to be markedly increased in patients with CNV secondary to AMD.[8]

Photodynamic therapy (PDT) with verteporfin has been a standard treatment for subfoveal CNV secondary to AMD.[9] However, 30% to 40% of PDT-treated patients still sustain severe visual loss, and other subtypes, except predominantly classic lesions, seem to benefit if the lesions size is small.[10] Retreatments by PDT often are required because enhanced VEGF expression and reduced PEDF expression after PDT may promote regrowth of CNV.[11,12] Ranibizumab (Lucentis; Genentech Inc, South San Francisco, California, USA) blocks the action of VEGF and has been proven to improve vision by at least 15 letters in one-third of patients with CNV secondary to AMD.[13,14] Bevacizumab (Avastin; Genentech Inc) intravitreal injections have been reported to be associated with a decrease in aqueous VEGF and an increase in PEDF in CNV secondary to AMD.[15] This study was undertaken to investigate aqueous changes in VEGF and PEDF levels in patients with CNV secondary to AMD after intravitreal injection of ranibizumab alone or combined therapy with PDT.

METHODS

THIS WAS A PROSPECTIVE, INTERVENTIONAL, CASE-CONtrol study of sequential changes in aqueous levels of VEGF and PEDF after a single intravitreal injection of ranibizumab alone (monotherapy) or combined with PDT (com-

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TABLE 1. Baseline Clinical Features of Enrolled Patients with Exudative Age-Related Macular Degeneration

Variable (Mean ± SD)	Monotherapy (n = 17)	Combined Therapy (n = 17)	*P* value
Age (years)	71 ± 11	72 ± 6	.77
Gender (female/male)	5/12	6/11	.71
Visual acuity (logMAR)	0.92 ± 0.60	0.97 ± 0.51	.84
Smoking (no.)	10	11	.72
Hypertension (no.)	12	13	.70
Central macular thickness (μm)	345 ± 106	362 ± 99	.45
Lesion characteristics			
Predominantly classic (no.)	8	10	.49
Lesion size (μm)	3053 ± 945	3200 ± 710	.64
RAP (no.)	2	2	.99

LogMAR = logarithm of the minimum angle of resolution; RAP = retinal angiomatous proliferation; SD = standard deviation.

Size more than 2 disc areas.

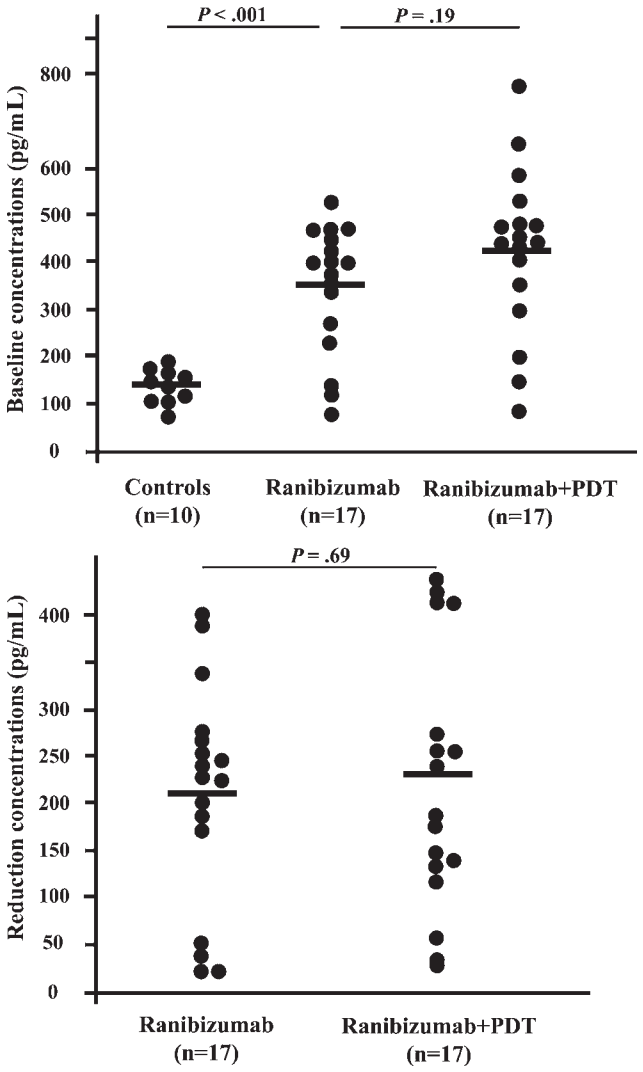

FIGURE 1. Graphs showing vascular endothelial growth factor (VEGF) levels in aqueous humor in 34 patients with exudative age-related macular degeneration (AMD) after ranibizumab monotherapy or combined ranibizumab with photodynamic therapy (PDT). (Top) Baseline concentrations of aqueous VEGF. (Bottom) Reduction concentrations of aqueous VEGF from baseline levels 1 month after treatments. Bar indicates the mean VEGF concentration in each group.

bined therapy) for CNV secondary to AMD. We recruited 34 consecutive patients who had CNV secondary to AMD at Department of Ophthalmology, the Chonnam National University Hospital, Gwangju, Korea, from December 1, 2007 through November 30, 2008. The inclusion criteria were as follows: 50 years of age or older; subfoveal CNV lesions secondary to AMD, either predominantly classic or occult with no classic component; total area of CNV encompassed within the lesion more than 50% of the total lesion area; greatest linear dimension no more than 5400 μm; best-corrected visual acuity (BCVA) score using a Snellen visual acuity (VA) chart from 20/400 to 20/40; and central macular thickness (CMT) as assessed by optical coherence tomography (OCT) of more than 300 μm. The exclusion criteria were as follows: the size of subretinal blood or pigment epithelial detachment more than 50% of the total lesion size; other causes of CNV such as polypoidal choroidal vasculopathy, angioid streak, inflammation, or myopia; any prior treatment for CNV secondary to AMD; and subfoveal fibrosis or atrophy.

All patients received a single intravitreal injection of ranibizumab. After disinfection with a povidone iodine solution, a sterile drape was placed over the eye. A sterile lid speculum was inserted and ranibizumab 0.5 mg (0.05 mL) was administered using a 30-gauge needle through a pars plana approach under aseptic conditions after topical anesthesia. Seventeen of 34 patients underwent combined PDT with the intravitreal injection of ranibizumab at the same day. Patients received standard verteporfin therapy (infusion over 10 minutes at a dose of 6 mg/m^2; activating light applied 15 minutes after the start of infusion at a wavelength of 689 nm, light dose of 50 J/cm^2, and fluence of 600 mW/cm^2). The treatment method was not randomized because we did not perform PDT for patients who had pigment epithelium detachment or submacular hemorrhage of more than 1 disc area. Patients with media opacities of the cornea, lens, and vitreous also received ranibizumab monotherapy. All patients underwent complete ophthalmic examinations, including VA, slit-lamp examination, funduscopy, fluorescein angiography, indocyanine angiography, and OCT (Carl Zeiss Ophthalmic System Inc, Dublin, California, USA). BCVA was measured by Snellen VA that was converted into logarithm of the minimum angle of resolution units for statistical comparison. The CMT was measured by OCT at a scan