# Anti–Vascular Endothelial Growth Factor With or Without Pneumatic Displacement for Submacular Hemorrhage

JOO YOUN SHIN, JI-MIN LEE, AND SUK HO BYEON

• PURPOSE: To compare the treatment outcomes of a combination of pneumatic displacement and intravitreal anti–vascular endothelial growth factor, and anti–vascular endothelial growth factor monotherapy for submacular hemorrhage resulting from exudative age-related macular degeneration.

• DESIGN: Retrospective, comparative, interventional case series.

• METHODS: Forty eyes treated with a combination therapy and 42 eyes treated with monotherapy for submacular hemorrhage resulting from exudative age-related macular degeneration with no significant difference in baseline central foveal thickness were compared. Central foveal thickness and best-corrected visual acuity (BCVA) at baseline, 1, 3, and 6 months after initial treatment were measured and compared between the 2 groups after adjustment of baseline central foveal thickness.

• RESULTS: Central foveal thickness ($P < .0001$) and BCVA (combination, $P < .0001$; monotherapy, $P = .022$) were improved after both treatments. Combination therapy showed more rapid improvement of central foveal thickness ($P = .009$) and BCVA ($P = .007$) within 1 month than monotherapy, but there was no difference at 6 months ($P = .385$ and $P = .303$, respectively). In eyes with subretinal hemorrhage thicker than 450 μm, visual outcome at 6 months was better in the combination therapy group than in the monotherapy group ($P = .021$), whereas BCVA showed no significant difference between groups in eyes with subretinal hemorrhage less than 450 μm ($P = .930$).

• CONCLUSIONS: Both treatments are useful options for submacular hemorrhage resulting from exudative age-related macular degeneration. Combination therapy may yield a better treatment outcome than monotherapy in eyes with thick subretinal hemorrhage. Nevertheless, the potential for adverse events resulting from pneumatic displacement should be considered. (Am J Ophthalmol 2015;159(5):904–914. © 2015 by Elsevier Inc. All rights reserved.)

SUBMACULAR HEMORRHAGE ASSOCIATED WITH exudative age-related macular degeneration (AMD) is a complication with potentially devastating effects on visual acuity.[1,2] Submacular hemorrhage frequently results in poor visual outcome because of the retinal toxicity of iron released from hemoglobin, its role as a physical barrier on diffusion of nutrients and metabolites, as well as the shearing of the outer segment photoreceptors from fibrin.[3,4] Subretinal fibrosis and disciform scar formation result in further visual loss.[5,6] Multiple treatments have been suggested, including pneumatic displacement with or without tissue plasminogen activator (tPA),[7,8] pars plana vitrectomy with or without subretinal tPA,[2,9] photodynamic therapy,[10] and intravitreal anti–vascular endothelial growth factor (VEGF) injection. However, there remains no consensus on the optimal management of patients with submacular hemorrhage.

Anti-VEGF agents can preserve or improve vision significantly and are used widely for treatment of exudative AMD.[11] Although patients with significant submacular hemorrhage were excluded from recent major randomized clinical trials, there is a good rationale for the efficacy of anti-VEGF therapy in such cases, including the effects on underlying neovascular membrane, the clearing effect of intravitreal and submacular hemorrhage,[12,13] and reducing the risk of recurrent hemorrhage and disciform scarring.[14] Several studies have suggested that anti-VEGF agents in combination with pneumatic displacement can improve the visual acuity in eyes with submacular hemorrhage secondary to exudative AMD.[15–21] In addition, recent studies have indicated improvement of visual acuity in submacular hemorrhage treated with anti-VEGF alone.[14,15,22–24]

Based on the mechanisms underlying these treatment options, a combination of pneumatic displacement with an anti-VEGF agent is used more frequently than anti-VEGF monotherapy for eyes with thicker submacular hemorrhage involving the fovea.[24] Because of this difference in baseline characteristics, it is difficult to compare the outcomes of these treatment groups, and little information is available regarding whether the combination of

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Jan 21, 2015.

From the Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, Seoul, South Korea.

Inquiries to Suk Ho Byeon, The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemun-Gu, Seoul, South Korea; e-mail: shbyeon@yuhs.ac



0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2015.01.024

displacement techniques with anti-VEGF provides any advantage over anti-VEGF alone. One study suggested that a combination of tPA and pneumatic displacement plus an anti-VEGF agent significantly improved visual acuity, whereas anti-VEGF monotherapy only stabilized the visual acuity.[15] In contrast, another study indicated no significant differences in visual acuity or central foveal thickness between ranibizumab monotherapy and combination therapy at 12 months after initial treatment.[23] In the present study, we analyzed a larger number of patients with thicker submacular hemorrhage compared with previous studies and compared the treatment outcome of combined pneumatic displacement plus anti-VEGF with anti-VEGF monotherapy for submacular hemorrhage associated with exudative AMD.

## METHODS

THIS RETROSPECTIVE, COMPARATIVE, INTERVENTIONAL case series study was performed at a single center (Severance Hospital, Seoul, South Korea) from January 2009 through March 2014. The research adhered to the tenets of the Declaration of Helsinki, and approval for the study was granted by the Institutional Review Board/Ethics Committee of Yonsei University (IRB no. 4-2014-0474). All patients provided their written informed consent.

• **PATIENTS:** A computerized search (clinical data repository system) was performed to identify patients diagnosed with both exudative AMD and submacular hemorrhage. We reviewed the medical data of these patients treated with anti-VEGF injection, either in combination with pneumatic displacement or as monotherapy. We analyzed patients who (1) were newly diagnosed with exudative AMD; (2) exhibited submacular hemorrhage involving the fovea of at least 1 disc diameter; (3) were treated with either a combination of pneumatic displacement and intravitreal anti-VEGF (combination therapy group) or anti-VEGF monotherapy (monotherapy group) at initial presentation, followed by 2 monthly intravitreal anti-VEGF injections; and (4) had a minimum follow-up period of 6 months. We excluded patients (1) who were younger than 50 years; (2) with submacular hemorrhages resulting from causes other than exudative AMD; (3) whose eyes were treated with tPA or photodynamic therapy during the 6-month follow-up period; (4) whose eyes had undergone vitrectomy surgery before initial presentation; (5) with evidence of end-stage AMD with severe scarring or atrophy at initial presentation; (6) whose duration of symptoms as a result of submacular hemorrhage was longer than 1 month or who had eyes with an old, yellowish discolored submacular hemorrhage; and (7) whose eyes had significant media opacity, including severe vitreous hemorrhage, at initial presentation.

During the study period, 189 eyes initially had submacular hemorrhage secondary to exudative AMD at presentation. After excluding eyes that had undergone vitrectomy at or before the initial presentation (20 eyes), photodynamic therapy during the follow-up period (7 eyes), use of tPA (4 eyes), less than 6 months of follow-up (15 eyes), severe scarring or atrophy at presentation (14 eyes), and other reasons (6 eyes), 76 eyes were treated with a combination of pneumatic displacement and anti-VEGF injection and 47 eyes were treated with anti-VEGF monotherapy. Because baseline central foveal thickness was different between the 2 treatment groups (886.2 ± 377.9 μm and 540.0 ± 219.3 μm, respectively; $P < .0001$), only eyes showing an overlapping range of central foveal thickness, between 380 and 850 μm, were included in the analysis. Finally, 40 eyes of 40 patients treated with a combination of pneumatic displacement and anti-VEGF (combination therapy group) and 42 eyes of 42 patients treated with anti-VEGF (monotherapy group) were analyzed.

Diagnoses of exudative AMD and submacular hemorrhage were based on the results of fundus examination, fluorescein angiography, indocyanine green angiography (ICGA; HRA2 [Heidelberg Engineering GmbH, Dossenheim, Germany]), and spectral-domain (SD) optical coherence tomography (OCT; Spectralis HRA+OCT [Heidelberg Engineering GmbH]) at either initial presentation or after resolution of hemorrhage. Patients were classified as having 1 of the 2 subtypes of exudative AMD: PCV or typical exudative AMD. PCV was diagnosed based on ICGA findings, on the presence of a branched vascular network, and on evidence of terminal polypoidal lesions, subpigment epithelial layer orange-red protrusions corresponding to the polypoidal lesions revealed by ICGA, or both. All other patients were considered to have typical neovascular AMD.

• **BASELINE EXAMINATION AND TREATMENT:** All patients underwent comprehensive ophthalmologic examinations, including best-corrected visual acuity (BCVA) using the Snellen visual acuity chart, slit-lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, fluorescein angiography, ICGA, and OCT at the initial visit. Follow-up visits were arranged monthly for BCVA, indirect ophthalmoscopy, and OCT. Fluorescein angiography and ICGA additionally were performed after the 3 monthly injections.

At initial presentation, all patients were given intravitreal injection of anti-VEGF agent, either 0.5 mg ranibizumab (Lucentis; Novartis, Basel, Switzerland) or 1.25 mg bevacizumab (Avastin; Genentech, Inc, South San Francisco, California, USA), under sterile conditions. In the combination group, intravitreal gas injection (either $SF_6$ or $C_3F_8$; mean volume, 0.3 mL) also was performed, and patients were instructed to remain in the prone position most of the time for at least 3 days. Thereafter, all patients

received 2 additional anti-VEGF injections each month. After 3 monthly loading injections, patients received additional anti-VEGF injection over the following 3-month period as necessary, if persistent or recurrent subretinal or intraretinal fluid was evident, new macular hemorrhage developed, or the extent of pigment epithelial detachment increased.

• **MAIN OUTCOME MEASURES:** The main outcome measures included BCVA and central foveal thickness at baseline and at 1, 3, and 6 months after the initial diagnosis. Thicknesses of the retina and submacular hemorrhage (either subretinal or sub-RPE hemorrhage) were measured at baseline and at 1 month after the initial treatment. For statistical analysis, Snellen BCVA was converted to logarithm of the minimal angle of resolution units.

Central foveal thickness, retinal thickness, and thickness of submacular hemorrhage were measured manually on the horizontal and vertical line scans intersecting the center of the fovea using the built-in caliper function of the SD OCT device. Central foveal thickness was defined as the distance between the internal limiting membrane and the Bruch membrane at the foveal center. We classified submacular hemorrhage into subretinal hemorrhage and subretinal pigment epithelium (RPE) hemorrhage according to the location of the hemorrhage. The thickness of subretinal hemorrhage was defined as the distance between the inner segment–outer segment line to the outer border of RPE, and the thickness of sub-RPE hemorrhage was defined as the distance from the inner border of RPE to the Bruch membrane, or to the outer border of fibrotic tissue at the fovea if definite sub-RPE fibrotic tissue was observed. The presumed RPE line obtained from a clearly visible RPE line was used when the RPE or Bruch membrane was not visible because of overlying thick hemorrhage. Retinal thickness was defined as the distance between the internal limiting membrane and the inner segment–outer segment line at the center of the fovea. The extent of hemorrhage was measured at baseline in square millimeters on a reference scan image obtained with SD OCT using the built-in caliper function. Thickness exceeding 1500 μm was considered as 1500 μm, and extent of hemorrhage exceeding 80 $mm^2$ on OCT images was regarded as 80 $mm^2$, because of the possibility of inaccurate measurement. All measurements and diagnoses were conducted by 2 retinal specialists (J.Y.S. and J.L.), and the average values were used for evaluation. The main outcome measures were analyzed as outlined below.

• **CHANGES IN CENTRAL FOVEAL THICKNESS AND BEST-CORRECTED VISUAL ACUITY OVER THE FOLLOW-UP PERIOD:** Central foveal thickness and BCVA measured at 1, 3, and 6 months after the initial treatment were compared with the respective baseline measurements in each treatment group. For comparison of treatment outcome between the groups, a linear mixed model was used with adjustment for baseline central foveal thickness. Post hoc analysis was performed to compare the treatment outcome at each time point and to compare the changes in central foveal thickness and BCVA from baseline.

• **CHANGES IN RETINAL THICKNESS AND SUBMACULAR HEMORRHAGE THICKNESS:** We measured the thickness of each structure at the foveal center separately—retina, subretinal hemorrhage, and sub-RPE hemorrhage—at baseline and 1 month after the initial treatment. Comparison of these measurements between baseline and 1 month after the initial treatment was performed using a paired *t* test, and a comparison of changes in these measurements between combination therapy and monotherapy groups was performed using an independent *t* test.

• **COMPARISON OF VISUAL OUTCOME ACCORDING TO CENTRAL FOVEAL THICKNESS AND SUBRETINAL HEMORRHAGE THICKNESS:** In the present study, the association between visual outcome at 6 months and baseline central foveal thickness and the association between visual outcome at 6 months and baseline subretinal hemorrhage thickness (locally weighted scatterplot smoothed curve; Supplemental Figure, available at AJO.com) showed that the differences in visual outcome between treatments tended to be greater in eyes with baseline central foveal thickness and baseline subretinal hemorrhage thickness values exceeding certain cutoff points. Therefore, cutoff points of baseline central foveal thickness and baseline subretinal hemorrhage thickness were chosen such that the visual outcome would be considered to be different between treatments. The data sets were searched for the point that best separated the 2 groups, which then was selected as the cutoff point the value that maximized the standard *t* statistics. If statistically significant, this was used as the cutoff point.[25] Eyes in each treatment group were divided into 2 subgroups according to the cutoff point. The BCVA at baseline and at 1 and 6 months after the initial treatment were compared between these subgroups.

• **OTHER STATISTICAL ANALYSES:** Patient characteristics, including age, sex, duration of symptoms, antithrombotic or anticoagulant use, lens status (phakic or pseudophakic), anti-VEGF agents, and the number of anti-VEGF injections during the follow-up period, were retrieved from medical charts. For comparison of variables between the combination and monotherapy groups, an independent *t* test and Fisher exact test were used. Recurrence of submacular hemorrhage or adverse events after treatment, including vitreous hemorrhage, retinal detachment, or endophthalmitis, also was retrieved from medical charts. Statistical analysis was performed using SAS software version 9.2 (SAS Institute, Inc, Cary, North Carolina, USA). In all analyses, $P < .05$ was taken to indicate statistical significance.

**TABLE 1.** Baseline Characteristics of Patients With Submacular Hemorrhage Secondary to Exudative Age-Related Macular Degeneration

| Characteristic | Pneumatic Displacement With anti-VEGF | Anti-VEGF Monotherapy | *P* Value |
|---|---|---|---|
| Age (y) | 72.0 ± 8.3 | 74.6 ± 6.8 | .127 |
| Male sex, no. (%) | 26 (65.0) | 27 (64.3) | >.999 |
| Duration of symptom (d) | 11.4 ± 10.4 | 13.8 ± 11.5 | .342 |
| Antithrombotic/anticoagulant use, no. (%) | 7 (17.5) | 10 (23.8) | .589 |
| Phakic lens status, no. (%) | 33 (82.5) | 34 (81.0) | >.999 |
| No. of anti-VEGF injections | 4.3 ± 1.1 | 4.6 ± 1.2 | .345 |
| Diagnosis, no. (%) | | | |
| Typical AMD | 21 (52.5) | 17 (40.5) | .376 |
| PCV | 19 (47.5) | 25 (59.5) | |
| BCVA (logMAR) | 1.21 ± 0.71 | 1.14 ± 0.63 | .670 |
| Central foveal thickness (μm) | 590.9 ± 157.9 | 560.1 ± 152.7 | .386 |
| Extent of hemorrhage ($mm^2$) | 23.5 ± 21.8 | 23.4 ± 22.3 | .997 |

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; PCV = polypoidal choroidal vasculopathy; VEGF = vascular endothelial growth factor.

## RESULTS

• **BASELINE CHARACTERISTICS:** There were no significant differences between the combination therapy group and monotherapy group in terms of demographics or baseline characteristics (Table 1). The mean duration of symptoms was 11.4 ± 10.4 days in the combination therapy group and 13.8 ± 11.5 days in the monotherapy group ($P = .342$). Baseline central foveal thickness was 590.9 ± 157.9 μm in the combination therapy group and 560.1 ± 152.7 μm in the monotherapy group. There were no differences in baseline BCVA or central foveal thickness between the 2 groups ($P = .670$ and $P = .386$, respectively). Diagnosis (either typical AMD or PCV) also was not different between the 2 treatment groups ($P = .376$).

For initial treatment, 23 eyes in the combination therapy group and 29 eyes in the monotherapy group were treated with ranibizumab ($P = .360$). In the combination therapy group, pneumatic displacement was performed with $SF_6$ in 20 eyes and $C_3F_8$ in 20 eyes. The number of anti-VEGF injections within 6 months was not significantly different between the 2 groups ($P = .345$).

• **CHANGES IN CENTRAL FOVEAL THICKNESS OVER THE FOLLOW-UP PERIOD:** Central foveal thickness improved significantly after both combination therapy (Figure 1) and monotherapy (Figure 2) during the 6-month follow-up period (both $P < .0001$; Figure 3). Central foveal thickness decreased from 590.9 ± 157.9 μm at baseline to 279.2 ± 196.2 μm at 6 months in the combination therapy group and from 560.1 ± 152.7 μm at baseline to 311.5 ± 190.2 μm at 6 months in the monotherapy group. To minimize the effect of differences in baseline central foveal thickness, comparisons between the 2 groups were performed after adjustment for the initial central foveal thickness, although baseline central foveal thickness was not significantly different between the 2 groups. From baseline to 1 month after initial treatment, decrease in central foveal thickness was significantly greater in the combination therapy group than in the monotherapy group ($P = .009$), but the differences were not significant between baseline and 3 months and between baseline and 6 months after initial presentation ($P = .127$ and $P = .385$, respectively).

• **CHANGES IN VISUAL ACUITY OVER THE FOLLOW-UP PERIOD:** Changes in BCVA over the follow-up period are shown in Figure 3. Logarithm of the minimal angle of resolution BCVA improved from 1.21 ± 0.71 to 0.76 ± 0.59 at 6 months in the combination therapy group and from 1.14 ± 0.63 to 0.94 ± 0.61 at 6 months in the monotherapy group. In the combination therapy group, BCVA improved significantly from baseline to 1 month ($P < .0001$), to 3 months ($P = .0003$), and to 6 months ($P < .0001$). Meanwhile, in the monotherapy group, BCVA showed no significant difference from baseline at 1 month ($P = .905$) or 3 months ($P = .079$), but showed significant improvement from baseline at 6 months after initial treatment ($P = .022$). Comparisons between the 2 groups were performed after adjustment for initial central foveal thickness. BCVA was not significantly different between the 2 groups at baseline ($P > .999$), 3 months ($P = .579$), or 6 months ($P = .474$) after initial treatment, but the combination therapy group showed better visual acuity at 1 month after initial treatment compared with the monotherapy group ($P = .017$). The changes in BCVA from baseline to 1 month were significantly greater in the combination therapy group than in the monotherapy group ($P = .007$), whereas there was no significant difference between the 2 groups from baseline to 3 months ($P = .361$)

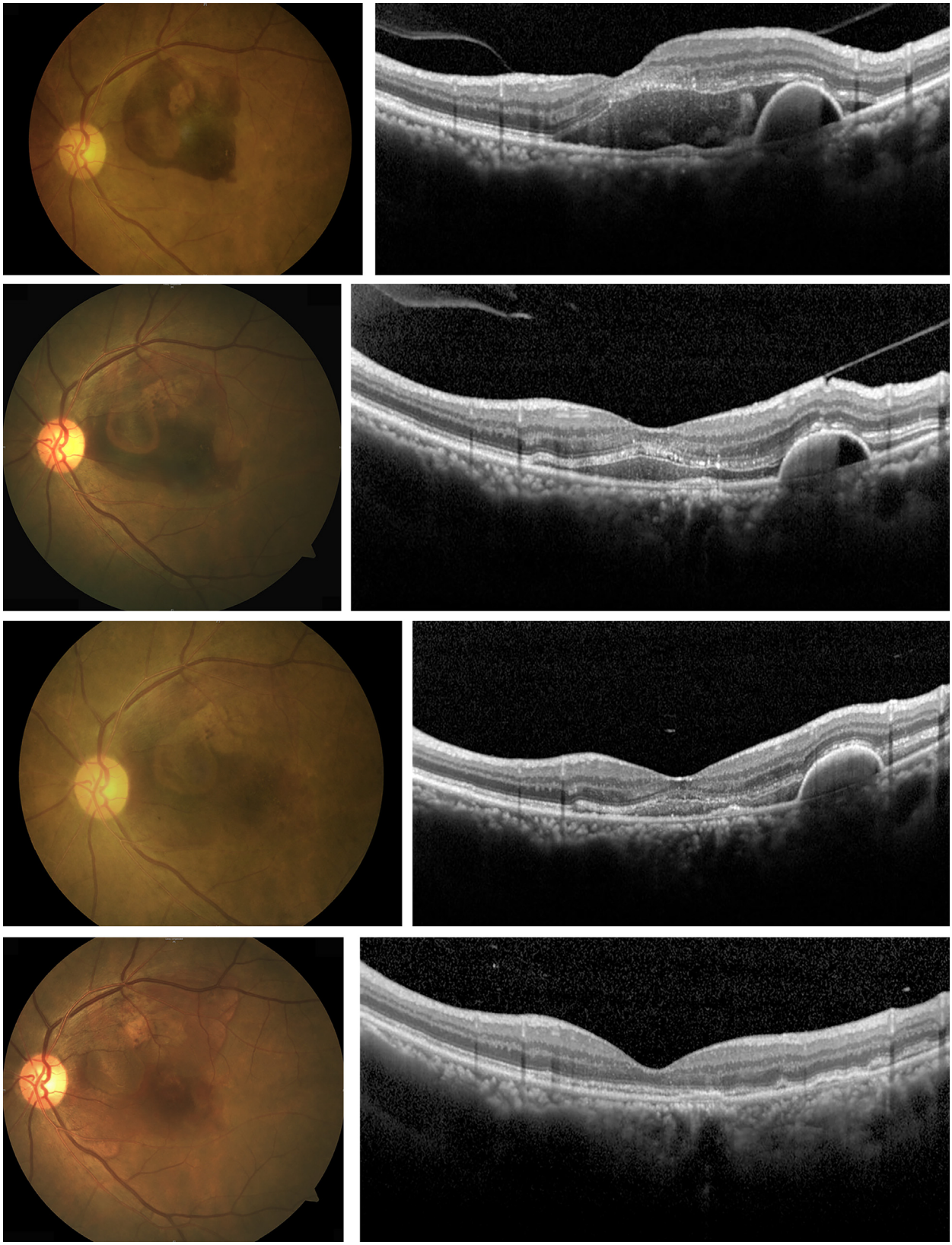


**FIGURE 1. Fundus photography and optical coherence tomography (OCT) findings of an eye treated with a combination of pneumatic displacement and anti–vascular endothelial growth factor (VEGF) injection for submacular hemorrhage resulting from exudative age-related macular degeneration. At the time of diagnosis, (Top left) fundus photography and (Top right) OCT demonstrated submacular hemorrhage centered superior to but involving the fovea, and visual acuity was 20/60. After pneumatic displacement with**

or from baseline to 6 months after the initial treatment ($P = .303$).

• **CHANGES IN RETINAL THICKNESS AND SUBMACULAR HEMORRHAGE THICKNESS:** The thicknesses of submacular hemorrhage and the retina were decreased significantly 1 month after initial treatment in both the combination therapy group (subretinal hemorrhage, $P < .0001$; sub-RPE hemorrhage, $P = .018$; retinal thickness, $P = .001$) and monotherapy group ($P < .0001$, respectively). In terms of subretinal hemorrhage, changes in subretinal hemorrhage thickness were greater in the combination therapy group than in the monotherapy group ($P = .002$). Sub-RPE hemorrhage did not show significant differences at baseline or 1 month after initial treatment ($P = .508$ and $P = .987$, respectively), and changes in thickness of sub-RPE hemorrhage also were not significantly different between the 2 groups ($P = .554$). Retinal thickness showed no differences at baseline ($P = .238$) or 1 month after initial treatment ($P = .319$), and changes in retinal thickness were not significantly different between the 2 groups ($P = .481$; Table 2).

• **COMPARISON OF VISUAL OUTCOME ACCORDING TO BASELINE CENTRAL FOVEAL THICKNESS AND SUBRETINAL HEMORRHAGE THICKNESS:** The eyes in each treatment group were divided into 2 subgroups according to the baseline central foveal thickness of 550 μm. There were 19 and 23 eyes with central foveal thickness less than 550 μm in the combination and monotherapy groups, respectively. In eyes with central foveal thickness less than 550 μm, there were no significant differences in BCVA at baseline ($P = .945$), 1 month ($P = .161$), or 6 months ($P = .468$) between the 2 treatment groups. In eyes with central foveal thickness exceeding 550 μm, BCVA of the combination therapy group was better than that of the monotherapy group at 1 month after initial treatment ($P = .039$), but there were no significant differences between the 2 groups at baseline ($P = .639$) or 6 months ($P = .169$) after initial treatment.

The eyes with subretinal hemorrhage also were divided into subgroups according to the baseline subretinal hemorrhage thickness of 450 μm. Twenty-four eyes in the combination therapy group and 31 eyes in the monotherapy group showed subretinal hemorrhage thickness of less than 450 μm. In eyes with subretinal hemorrhage thickness of less than 450 μm, there were no differences in BCVA at baseline ($P = .625$), 1 month ($P = .191$), or 6 months ($P = .930$) between the 2 treatment groups. In eyes with subretinal hemorrhage exceeding 450 μm, BCVA was not different at baseline ($P = .669$), but was better in the combination therapy group than in the monotherapy group at 1 month ($P = .014$) and at 6 months ($P = .021$; Table 3).

• **RECURRENCE AND OTHER OCULAR ADVERSE EVENTS:** During the 6-month follow-up period, submacular hemorrhage recurred in 3 eyes in the combination therapy group and in 3 eyes in the monotherapy group. Recurrence occurred at 3, 5, and 6 months after initial treatment in the combination therapy group and at 2, 5, and 6 months in the monotherapy group. RPE tears developed in 5 eyes in the combination therapy group and in 7 eyes in the monotherapy group. Tears of the RPE were observed within 1 month after initial treatment in all eyes in the combination therapy group and at a mean of 1.86 months after initial treatment in the monotherapy group. Severe vitreous hemorrhage requiring vitrectomy developed in 3 eyes in the combination therapy group and in 2 eyes in the monotherapy group. Rhegmatogenous retinal detachment (2 eyes) and hemorrhagic retinal detachment with choroidal hemorrhage (1 eye) developed in the combination therapy group, whereas no other severe ocular adverse events or systemic events occurred in the monotherapy group.

## DISCUSSION

IN THE PRESENT STUDY, WE COMPARED THE TREATMENT outcome between combination therapy with pneumatic displacement plus anti-VEGF and anti-VEGF monotherapy for the management of submacular hemorrhage secondary to AMD. We analyzed a larger number of patients with thicker submacular hemorrhage compared with previous studies. In addition, to minimize the effect of differences in baseline central foveal thickness between the treatments, we included eyes with an overlapping range of central foveal thickness measurements and adjusted for initial central foveal thickness in the analysis.

Both combination therapy and monotherapy significantly improved visual acuity and central foveal thickness during the 6-month follow-up period in this study, consistent with previous studies of combined pneumatic displacement plus anti-VEGF therapy[15–21] and with anti-VEGF monotherapy.[14,15,22,23,26–28] These observations suggest that both treatments are useful options for submacular hemorrhage secondary to exudative AMD. However, the resolution rate of hemorrhage was significantly different between the 2 treatment groups, and the most significant difference was observed within 1 month after initial treatment. Combination therapy showed rapid improvement in BCVA and central foveal thickness after initial treatment, whereas monotherapy showed gradual visual and anatomic improvement. This difference can be

**anti-VEGF injection at (Second row) 1 day and (Third row) 4 days later, a decrease of the hemorrhage was observed on fundus photography (Second and Third row left) and (Second and Third row right) OCT. (Bottom) Eleven days after treatment, submacular hemorrhage was resolved from the fovea and visual acuity improved to 20/25.**

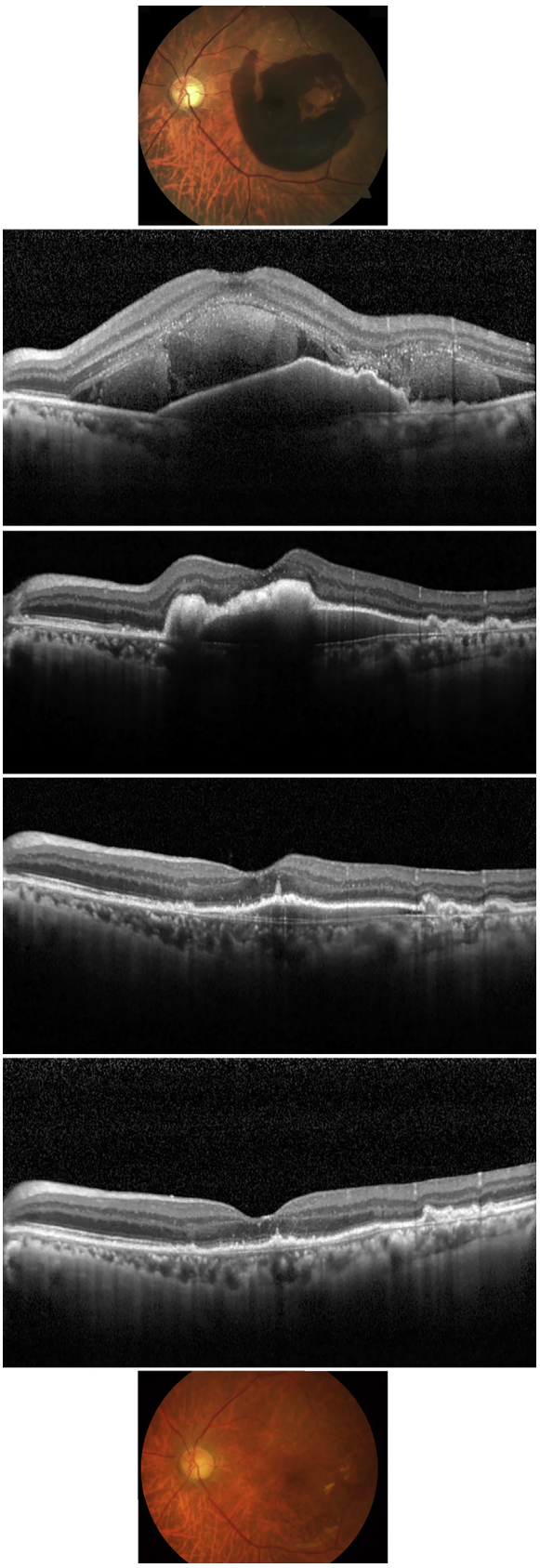


FIGURE 2. Fundus photography and optical coherence tomography (OCT) findings of an eye treated with intravitreal anti–vascular endothelial growth factor (VEGF) monotherapy for submacular hemorrhage resulting from exudative age-related macular degeneration. At the time of diagnosis, (Top) fundus photography and (Second row) OCT demonstrated submacular hemorrhage involving fovea and visual acuity was 20/50. One month after anti-VEGF injection, (Third row) OCT showed remaining organized subretinal hemorrhage as hyperreflective material. Two additional intravitreal anti-VEGF injections were performed, and gradual resolution of submacular hemorrhage was observed on OCT at (Fourth row) 2 months and (Fifth row) 3 months after the initial treatment. Four months after the initial treatment, (Bottom) fundus photography showed completely resolved submacular hemorrhage and visual acuity was 20/60.

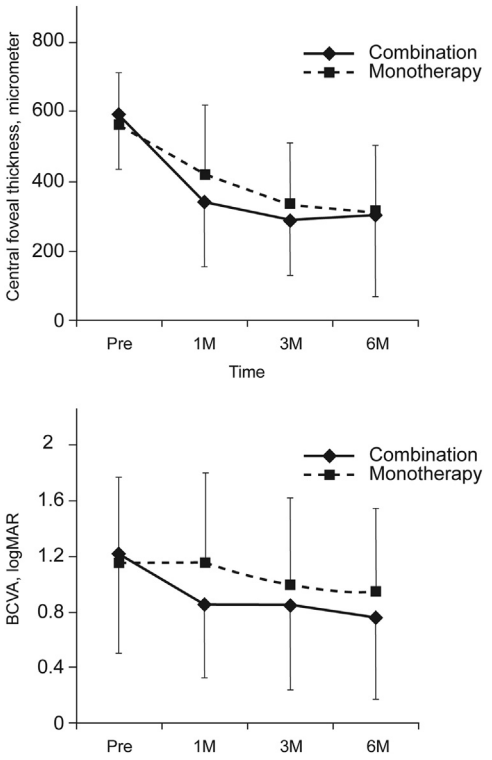



FIGURE 3. Graphs showing (Top) changes in central foveal thickness and (Bottom) best-corrected visual acuity (BCVA) in eyes treated with either a combination of pneumatic displacement and anti–vascular endothelial growth factor (VEGF) or anti-VEGF monotherapy for submacular hemorrhage resulting from exudative age-related macular degeneration. Combination = combination of pneumatic displacement and anti-VEGF; logMAR = logarithm of the minimal angle of resolution; M = months; monotherapy = anti-VEGF monotherapy.

helpful in guiding management decisions, particularly in patients who require rapid visual recovery. Comparison of changes in subretinal hemorrhage thickness, sub-RPE hemorrhage thickness, and retinal thickness between treatments indicated that the difference in treatment outcome

**TABLE 2.** Changes in Submacular Hemorrhage Thickness and Retinal Thickness After Initial Treatment in Eyes With Submacular Hemorrhage Secondary to Exudative Age-Related Macular Degeneration

| Location | Pneumatic Displacement With anti-VEGF | Anti-VEGF Monotherapy | *P* Value |
|---|---|---|---|
| Subretinal hemorrhage (μm) | | | |
| No. | 37 | 40 | .604 |
| Baseline | 360.7 ± 134.5 | 299.7 ± 146.1 | .061 |
| 1 mo | 101.4 ± 134.2 | 148.1 ± 150.8 | .156 |
| Change | 259.3 ± 140.0 | 151.6 ± 155.0 | .002[a] |
| Sub-RPE hemorrhage (μm) | | | |
| No. | 13 | 11 | .530 |
| Baseline | 288.5 ± 146.4 | 336.1 ± 199.1 | .508 |
| 1 mo | 178.6 ± 124.5 | 179.6 ± 162.5 | .987 |
| Change | 109.9 ± 144.3 | 156.5 ± 231.9 | .554 |
| Retinal thickness, μm | | | |
| No. | 40 | 42 | NA |
| Baseline | 161.9 ± 98.7 | 189.6 ± 109.1 | .238 |
| 1 mo | 140.6 ± 87.3 | 161.8 ± 101.4 | .319 |
| Change | 21.3 ± 36.6 | 27.7 ± 44.1 | .481 |

NA = not applicable; RPE = retinal pigment epithelium; VEGF = vascular endothelial growth factor.
[a]$P < .05$.

**TABLE 3.** Comparison of Visual Outcomes According to Central Foveal Thickness and Subretinal Hemorrhage Thickness

| Subgroup | BCVA (logMAR) | | *P* Value |
|---|---|---|---|
| | Pneumatic Displacement With Anti-VEGF | Anti-VEGF Monotherapy | |
| Baseline CFT (μm) | | | |
| <550 | | | |
| Baseline | 0.95 ± 0.79 | 0.96 ± 0.54 | .945 |
| 1 mo | 0.71 ± 0.50 | 0.93 ± 0.50 | .161 |
| 6 mo | 0.62 ± 0.55 | 0.73 ± 0.48 | .468 |
| >550 | | | |
| Baseline | 1.47 ± 0.53 | 1.37 ± 0.67 | .639 |
| 1 mo | 0.99 ± 0.53 | 1.44 ± 0.73 | .039[a] |
| 6 mo | 0.91 ± 0.60 | 1.20 ± 0.67 | .168 |
| Baseline SRH (μm) | | | |
| <450 | | | |
| Baseline | 1.13 ± 0.77 | 1.03 ± 0.62 | .625 |
| 1 mo | 0.86 ± 0.58 | 1.08 ± 0.68 | .191 |
| 6 mo | 0.82 ± 0.67 | 0.84 ± 0.57 | .930 |
| >450 | | | |
| Baseline | 1.32 ± 0.62 | 1.43 ± 0.55 | .669 |
| 1 mo | 0.77 ± 0.38 | 1.29 ± 0.54 | .014[a] |
| 6 mo | 0.60 ± 0.34 | 1.25 ± 0.68 | .021[a] |

BCVA = best-corrected visual acuity; CFT = central foveal thickness; logMAR = logarithm of the minimal angle of resolution; SRH = subretinal hemorrhage thickness; VEGF = vascular endothelial growth factor.
[a]$P < .05$.

within 1 month mainly was the result of the change in subretinal hemorrhage thickness. Intravitreal gas effectively displaced the subretinal hemorrhage, and therefore more rapid recovery was possible in the combination therapy group than in the monotherapy group. In contrast, changes in sub-RPE hemorrhage thickness and retinal thickness were not significantly different between these treatment options, suggesting an effect of anti-VEGF. Sub-RPE hemorrhage is known to be resistant to pneumatic displacement,[24] and therefore anti-VEGF monotherapy can be considered in patients with submacular hemorrhage mainly located in the sub-RPE space.

Few studies[15,23] have compared the treatment outcome between anti-VEGF monotherapy and pneumatic displacement plus anti-VEGF combination therapy. Sacu and associates reported that a combination of tPA plus pneumatic displacement and an anti-VEGF drug significantly improved visual acuity, whereas anti-VEGF monotherapy only stabilized visual acuity.[15] Visual acuity improved in 80% in the combination therapy group compared with 60% in the monotherapy group, but this pilot study had a relatively small sample size with thin submacular hemorrhage of less than 300 μm in mean central foveal thickness. A recent study showed no significant difference in treatment outcome between ranibizumab monotherapy and combination therapy with pneumatic displacement, and the results were derived from eyes with mean central foveal thickness and submacular hemorrhage thickness thinner than those in our study (mean central foveal thickness, 478 μm; submacular hemorrhage thickness, 269 μm).[23] Because pneumatic displacement in combination with an anti-VEGF agent has been used for eyes with thicker submacular hemorrhage involving the fovea than anti-VEGF monotherapy,[14] studies regarding anti-VEGF monotherapy[15,26–28] included relatively thin submacular hemorrhage and mean central foveal thickness ranging from 299 to 334 μm, which may be associated with improved visual outcome. Kim and associates also reported visual improvement after anti-VEGF monotherapy in an analysis of a larger number of eyes (91 eyes) with thick submacular hemorrhage (mean central foveal thickness, 596.8 μm), but efficacy was limited in eyes with large hemorrhage, which suggested the need for more aggressive treatment in such cases.[22] These results suggest that the effectiveness of anti-VEGF monotherapy may be limited in cases with thicker retinal hemorrhage.

The presence of submacular hemorrhage separating the retina from the RPE has been suggested to block the

essential 2-way exchange of nutrients and metabolites and to induce retinal damage and visual loss.[3–5] Toxic damage from iron or tractional changes from clot retraction also were proposed to lead to retinal damage.[3,4] Retinal degeneration over areas of dense fibrin occurs at approximately 3 to 14 days in an experimental model,[4] thus highlighting the importance of early management of submacular hemorrhage. Based on the mechanism of damage, physical displacement of the submacular hemorrhage out of the fovea using gas can speed visual recovery and prevent irreversible blood-induced damage to the outer retina; this effect may be greater in eyes with thick submacular hemorrhage. This is consistent with our observation that combination therapy resulted in better visual outcome than monotherapy in eyes with thick subretinal hemorrhage. Pneumatic displacement also may enhance penetration of the anti-VEGF agent into the choroidal neovascularization lesion by decreasing the hemorrhage thickness,[22] and therefore may lower the incidence of disciform scar formation.[14] Therefore, surgeons should take subretinal hemorrhage thickness into consideration when comparing the treatment outcome and in designing treatment strategies between combination therapy (pneumatic displacement with anti-VEGF) and anti-VEGF monotherapy for patients with submacular hemorrhage resulting from exudative AMD.

In this study, recurrence of hemorrhage, RPE tears, and severe vitreous hemorrhage developed in both treatment groups, but rhegmatogenous retinal detachment and choroidal hemorrhage with hemorrhagic retinal detachment developed only in the combination therapy group. It is possible that these complications were part of the natural history of disease, particularly in eyes with large submacular hemorrhage, and that these adverse events were reported after both pneumatic displacement[8] and intravitreal anti-VEGF injection,[29] although the reported occurrence rates were different. Because of the retrospective design and small sample size of our study, statistical comparisons are not meaningful, and further prospective studies are needed to address these questions. However, retinal tear formation is a well-known complication of intravitreal gas injection, occurring in 7% to 23% of eyes after pneumatic retinopexy[8,30]; the reported rate of retinal detachment was much lower after intravitreal ranibizumab injection. In addition, pneumatic displacement may promote migration of submacular hemorrhage into the vitreous cavity,[8] thus increasing vitreous hemorrhage compared with anti-VEGF monotherapy,[23] although our results did not show a difference in occurrence. Choroidal hemorrhage may occur when a fragile vessel is exposed to sudden compression and decompression events, and risk factors for choroidal hemorrhage include advanced age, hypertension, atherosclerosis, high myopia, trauma, and increased intraoperative intraocular pressure.[31] Although our patients had a number of these risk factors, including advanced age, hypertension, and atherosclerosis, and choroidal hemorrhage developed 2 months after gas injection, we cannot exclude the possibility that intraocular pressure fluctuation during or after gas injection resulted in choroidal hemorrhage. Therefore, eyes receiving combination therapy consisting of pneumatic displacement and anti-VEGF agent(s) may require increased attention regarding these adverse events.

This study had several limitations, including its retrospective design, small number of patients, relatively short follow-up period, and the possibility of selection bias. To overcome the selection bias and minimize the effects of differences in baseline hemorrhage thickness between the treatment groups, we included eyes with an overlapping range of central foveal thicknesses and adjusted for central foveal thickness in the analysis. Another limitation was the use of 2 anti-VEGF agents and 2 types of gas in the analysis; however, a recent trial indicated equivalent efficacy between bevacizumab and ranibizumab.[32] Also, there was no difference in the type of anti-VEGF agent or type of gas between subgroups divided according to the baseline central foveal thickness and submacular hemorrhage thickness. Additionally, although we adjusted for central foveal thickness, other variables, including baseline subretinal hemorrhage thickness, were not adjusted for in the analysis. Although we analyzed eyes with thicker central foveal thickness than previous studies, our results still came from a limited range of central foveal thicknesses measuring between 380 and 850 μm. Further prospective studies with larger numbers of patients and a wider range of hemorrhage therefore are necessary.

A combination of pneumatic displacement with both anti-VEGF and anti-VEGF monotherapy are useful treatment options for submacular hemorrhage resulting from exudative AMD. Combination therapy may yield more rapid recovery and better treatment outcome than monotherapy, particularly in eyes with thick subretinal hemorrhage; nevertheless, the potential for adverse events resulting from pneumatic displacement should be considered. SD OCT can provide more detailed and quantitative information regarding the thickness and location of submacular hemorrhage and can assist in designing the treatment plan for such patients. Further studies will help to optimize customized treatments for submacular hemorrhage secondary to exudative AMD.

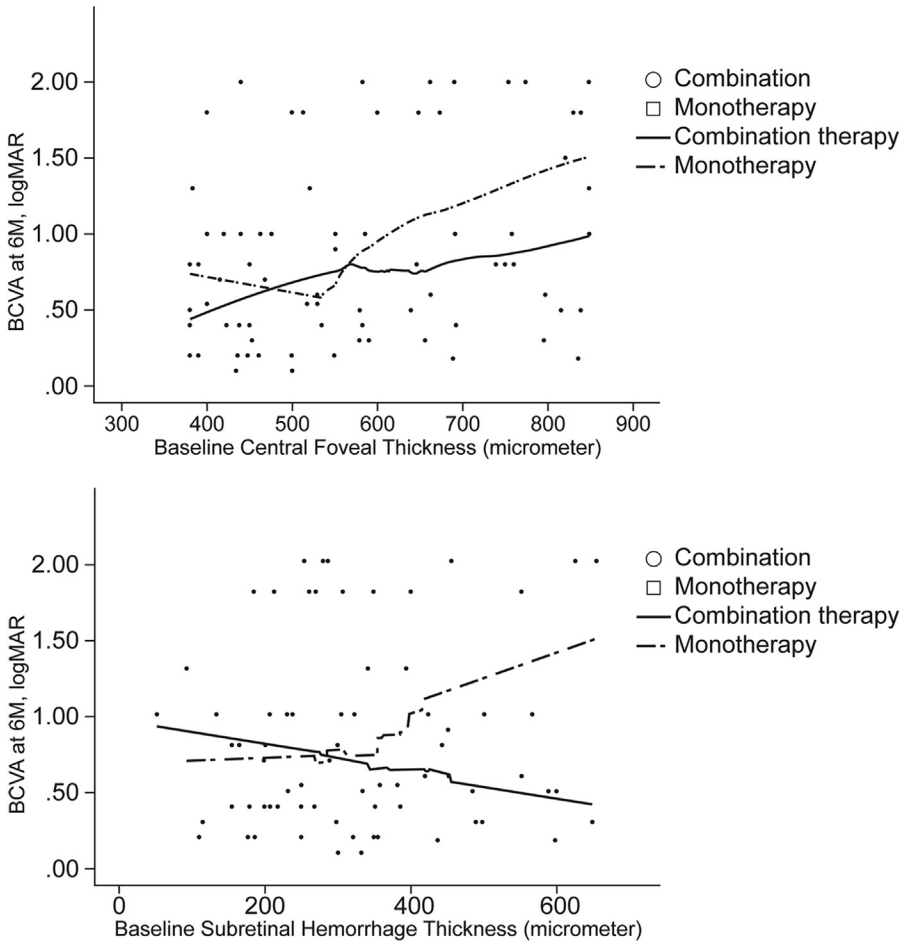
ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. Supported by Grant 2013R1A1A2007865 from the Basic Science Research Program through the National Research Foundation of South Korea (NRF) funded by the Ministry of Education. The funding organizations had no role in the design or conduct of this research. The authors were independent in reporting the study data and interpretation of the data. Involved in Design of study (J.Y.S., S.H.B.); Conduct of study (J.Y.S., J.L., S.H.B.); Collection, management, analysis, and interpretation of data (J.Y.S., J.L., S.H.B.); Preparation of manuscript (J.Y.S., J.L., S.H.B.); and Review or

approval of manuscript (J.Y.S., J.L., S.H.B.). Each author is responsible for the integrity of the entire study and manuscript. Each author has seen and agrees with each of the changes made to this manuscript in the revision and to the way his and her name is listed. The authors thank Jung Hwa Hong, Biostatistics Collaboration Unit, Yonsei University College of Medicine, for statistical support and Dong-Su Jang, MFA, Medical Illustrator, Medical Research Support Section, Yonsei University College of Medicine, for his help with the illustrations.

## REFERENCES


1. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. *Retina* 1996;16(3):183–189.
2. Bressler NM, Bressler SB, Childs AL, et al. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. *Ophthalmology* 2004;111(11):1993–2006.
3. Glatt H, Machemer R. Experimental subretinal hemorrhage in rabbits. *Am J Ophthalmol* 1982;94(6):762–773.
4. Toth CA, Morse LS, Hjelmeland LM, Landers MB. Fibrin directs early retinal damage after experimental subretinal hemorrhage. *Arch Ophthalmol* 1991;109(5):723–729.
5. Berrocal MH, Lewis ML, Flynn HW. Variations in the clinical course of submacular hemorrhage. *Am J Ophthalmol* 1996;122(4):486–493.
6. Scupola A, Coscas G, Soubrane G, Balestrazzi E. Natural history of macular subretinal hemorrhage in age-related macular degeneration. *Int Ophtalmol* 1999;213(2):97–102.
7. Hassan AS, Johnson MW, Schneiderman TE, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. *Ophthalmology* 1999;106(10):1900–1906. discussion 1906–1907.
8. Ohji M, Saito Y, Hayashi A, Lewis JM, Tano Y. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. *Arch Ophthalmol* 1998;116(10):1326–1332.
9. Vander JF, Federman JL, Greven C, Slusher MM, Gabel VP. Surgical removal of massive subretinal hemorrhage associated with age-related macular degeneration. *Ophthalmology* 1991;98(1):23–27.
10. Bakri SJ, Nickel J, Yoganathan P, Beer PM. Photodynamic therapy for choroidal neovascularization associated with submacular hemorrhage in age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2006;37(4):278–283.
11. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1419–1431.
12. Soliman W, Lund-Andersen H, Larsen M. Resolution of subretinal haemorrhage and fluid after intravitreal bevacizumab in aggressive peripapillary subretinal neovascularization. *Acta Ophthalmol* 2006;84(5):707–708.
13. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina* 2006;26(3):275–278.
14. Shienbaum G, Garcia Filho CA, Flynn HW, Nunes RP, Smiddy WE, Rosenfeld PJ. Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. *Am J Ophthalmol* 2013;155(6):1009–1013.
15. Sacu S, Stifter E, Vécsei-Marlovits PV, et al. Management of extensive subfoveal haemorrhage secondary to neovascular age-related macular degeneration. *Eye* 2009;23(6):1404–1410.
16. Hasler PW, la Cour M, Villumsen J. Pneumatic displacement and intravitreal bevacizumab in the management of subretinal haemorrhage caused by choroidal neovascularization. *Acta Ophthalmol* 2007;85(5):577–579.
17. Höhn F, Mirshahi A, Hattenbach L-O. Combined intravitreal injection of bevacizumab and SF6 gas for treatment of submacular hemorrhage secondary to age-related macular degeneration. *Ophthalmologe* 2010;107(4):328–332.
18. Mayer WJ, Hakim I, Haritoglou C, et al. Efficacy and safety of recombinant tissue plasminogen activator and gas versus bevacizumab and gas for subretinal haemorrhage. *Acta Ophthalmol* 2013;91(3):274–278.
19. Meyer CH, Scholl HP, Eter N, Helb H-M, Holz FG. Combined treatment of acute subretinal haemorrhages with intravitreal recombined tissue plasminogen activator, expansile gas and bevacizumab: a retrospective pilot study. *Acta Ophthalmol* 2008;86(5):490–494.
20. Kitahashi M, Baba T, Sakurai M, et al. Pneumatic displacement with intravitreal bevacizumab for massive submacular hemorrhage due to polypoidal choroidal vasculopathy. *Clin Ophthalmol* 2014;8:485–492.
21. Papavasileiou E, Steel DH, Liazos E, McHugh D, Jackson TL. Intravitreal tissue plasminogen activator, perfluoropropane ($C_3F_8$), and ranibizumab or photodynamic therapy for submacular hemorrhage secondary to wet age-related macular degeneration. *Retina* 2013;33(4):846–853.
22. Kim JH, Chang YS, Kim JW, Kim CG, Yoo SJ, Cho HJ. Intravitreal anti-vascular endothelial growth factor for submacular hemorrhage from choroidal neovascularization. *Ophthalmology* 2014;121(4):926–935.
23. Cho HJ, Koh KM, Kim JH, et al. Intravitreal ranibizumab injections with and without pneumatic displacement for treating submacular hemorrhage secondary to neovascular age-related macular degeneration. *Retina* 2015;35(2):205–212.
24. Steel DH, Sandhu SS. Submacular haemorrhages associated with neovascular age-related macular degeneration. *Br J Ophthalmol* 2011;95(8):1051–1057.
25. Miller R, Siegmund D. Maximally selected chi square statistics. *Biometrics* 1982;38(4):1011–1016.
26. Cho HJ, Koh KM, Kim HS, Lee TG, Kim CG, Kim JW. Anti-vascular endothelial growth factor monotherapy in the treatment of submacular hemorrhage secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2013;156(3):524–531.
27. Chang MA, Do DV, Bressler SB, Cassard SD, Gower EW, Bressler NM. Prospective one-year study of ranibizumab for predominantly hemorrhagic choroidal neovascular lesions in age-related macular degeneration. *Retina* 2010;30(8):1171–1176.

28. Stifter E, Michels S, Prager F, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. *Am J Ophthalmol* 2007; 144(6):886–892.
29. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* 2009;116(1):57–65.
30. Hilton GF, Kelly NE, Salzano TC, Tornambe PE, Wells JW, Wendel RT. Pneumatic retinopexy. A collaborative report of the first 100 cases. *Ophthalmology* 1987;94(4):307–314.
31. Obuchowska I, Mariak Z. Risk factors of massive suprachoroidal hemorrhage during extracapsular cataract extraction surgery. *Eur J Ophthalmol* 2005;15(6):712–717.
32. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012; 119(7):1388–1398.




**SUPPLEMENTAL FIGURE. Locally weighted scatterplot curves showing (Top) the association between visual outcome at 6 months and baseline central foveal thickness and (Bottom) the association between visual outcome at 6 months and baseline subretinal hemorrhage thickness. The association between visual outcome at 6 months and baseline central foveal thickness and the association between visual outcome at 6 months and baseline subretinal hemorrhage thickness show that the differences in visual outcome between treatments tend to be greater in eyes with baseline central foveal thickness and baseline subretinal hemorrhage thickness values exceeding certain cut-off points. BCVA = best-corrected visual acuity; combination therapy = combination of pneumatic displacement and anti-vascular endothelial growth factor; logMAR = logarithm of the minimal angle of resolution; M = months; monotherapy = anti–vascular endothelial growth factor monotherapy.**