Anti-VEGF-refractory Exudative Age-related Macular Degeneration: 
Differential Response According to Features on Optical Coherence Tomography

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Purpose: To describe optical coherence tomography (OCT) characteristics of neovascular age-related macular degeneration (AMD) patients refractory to intravitreal anti-vascular endothelial growth factor (VEGF) injections (ranibizumab, bevacizumab) and their responses to alternative anti-VEGF agents or photodynamic therapy (PDT).

Methods: A retrospective review of 267 neovascular AMD patients treated with intravitreal anti-VEGF injections. 

Results: Twenty patients (7.5%) were refractory to anti-VEGF injections (stationary or increased retinal exudation despite three or more monthly injections). They were grouped into either the extensive intraretinal fluid group (IRF group, 9 patients) or the subretinal fluid only group (SRF group, 11 patients) according to OCT findings. In the IRF group, response rates to subsequent treatment were 0% (0 / 7) for bevacizumab, 50% (3 / 6) for ranibizumab and 50% (3 / 6) for PDT ± anti-VEGF. Three out of four bevacizumab-refractory patients showed response to ranibizumab as a secondary treatment. In the SRF group, response rates were lower with 0% (0 / 7) for bevacizumab, 22.2% (2 / 9) for ranibizumab and 28.6% (2 / 7) for PDT ± anti-VEGF. One out of four bevacizumab-refractory patients responded to ranibizumab. The visual outcome was worse in the IRF group (median 20 / 1,000) than in the SRF group (median 20 / 100).

Conclusions: In anti-VEGF-refractory neovascular AMD, patients with extensive IRF refractory to bevacizumab can be responsive to ranibizumab while patients with SRF may be refractory to both, suggesting a different pathophysiology and intraocular pharmacokinetics.

Key Words: Bevacizumab, Drug resistance, Macular degeneration, Optical coherence tomography, Ranibizumab
(Avastin, Genentech Inc.) has also been reported to be beneficial in many previous studies, and the efficacy is suggested to be comparable to ranibizumab [3-7]. The usage of optical coherence tomography (OCT) has also increased steadily with the increased use of intravitreal anti-VEGF injections and has enabled accurate and early assessment of the anatomical response to treatment [8]. However, not every patient improves with anti-VEGF therapy; about 25% to 40% has been reported to experience improvements in vision with ranibizumab therapy [1,2]. The anatomical response rates are usually higher, but anatomical response does not always lead to visual improvement, and visual improvement usually cannot be achieved without anatomical improvement [9]. In previous studies, more than 90% of patients treated with ranibizumab showed resolution of all fluid after three consecutive injections [8]. However, features of patients who are likely to be resistant to anti-VEGF antibody treatment are currently unknown. Increasing experience with variable treatment methods of AMD has revealed a differential response to these treatments among patients, with some responding better to certain treatments than others. Clinical factors that have been associated with a poor response to anti-VEGF treatment include the presence of polypoidal choroidal vasculopathy (PCV) [10] and vitreomacular traction [11]. However, no studies have analyzed the morphologic and clinical features of cases refractory to specific anti-VEGF injections in detail. We hereby report the morphologic features on OCT of patients who were refractory to intravitreal bevacizumab or ranibizumab injections and their responses to other subsequent treatments.

Materials and Methods

Medical records of 267 consecutive patients treated with intravitreal anti-VEGF injection for neovascular AMD by a single clinician (SJW) between May 2007 and August 2010 at Seoul National University Bundang Hospital were reviewed. Best-corrected visual acuity (BCVA), fluorescein angiography (FA), OCT (Stratus OCT, Carl Zeiss Ophthalmic Instruments, Dublin, CA, USA; Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany), and indocyanine green angiography (ICGA; Heidelberg Retina Angiography, Heidelberg Engineering) were performed at the time of diagnosis. Patients were initially treated with three monthly injections of ranibizumab 0.5 mg/0.05 mL or bevacizumab 1.25 mg/0.05 mL, and at one month, BCVA and OCT assessments were done. The choice of the initial anti-VEGF agent was dependent on the availability in Korea at the time the individual patients were treated. Reinjection was performed according to the patient’s BCVA and anatomical response as seen on OCT. Patients who showed worsening visual acuity, partial response, no response, or worsening on OCT were recommended reinjection.

A patient was considered not responsive to therapy if he or she showed stationary or increased intraretinal or subretinal exudation despite more than three repeated injections, even if an initial partial response could be observed temporarily. Patients showing partial reduction of intraretinal or subretinal fluid were considered as responsive, while those with vitreomacular traction on OCT were recommended vitrectomy. The change in pigment epithelial detachment was not considered in assessing treatment response. The patients were usually switched to an alternative treatment method, such as PDT, the other anti-VEGF agent injection or a combination of PDT and bevacizumab/ranibizumab injection. The choice of the alternative treatment regimen was based on the findings on FA, OCT, and ICGA. PDT or PDT combined with bevacizumab or ranibizumab injection was preferred in patients showing features of PCV: branched vascular networks terminating in polypoidal dilatations in the choroidal vasculature on ICGA. PDT was done as in previous reports [12], with verteporfin (Visudyne; Novartis AG, Bulach, Switzerland) 6 mg/m² infused over 10 minutes, with 689 nm wavelength light applied at a fluence of 50 J/cm² over 83 seconds starting 15 minutes after the infusion began. Responses to these secondary and further treatments were also assessed. Eyes with choroidal neovascularization (CNV) resulting from diseases other than AMD, such as pathologic high myopia or angioid streaks, were excluded from the study.

Patient data including gender, age at presentation, eye laterality, past medical and ocular history, BCVA (at presentation and at last follow-up), and initial OCT findings, such as intraretinal vacuoles, intraretinal separation, CNV size, and subretinal fluid (SRF), were analyzed. Patients were grouped according to these findings, and treatment responses on OCT, treatment changes, responses to subsequent treatments, total number of treatments, and follow-up duration were assessed.
Results

Of the 267 patients reviewed, 20 (7.5%) were defined as non-responsive based on morphologic features on OCT. The clinical characteristics of these patients are summarized in Table 1. Mean age at diagnosis was 70.6 ± 8.9 years (range, 53 to 87 years), and 4 were female. The initial diagnosis was occult CNV in 8 cases, and the other 12 cases had features of PCV on ICGA. Four patients had previously received PDT, but the time of PDT was at least one year before the administration of the anti-VEGF treatment. Seven patients refractory to ranibizumab injection were identified, while 13 patients were refractory to bevacizumab. Five patients refused further treatment, two of whom were followed. Nine patients received PDT or PDT combined with intravitreal anti-VEGF injection as a secondary treatment, and 6 switched to another anti-VEGF injection (one patient switched to bevacizumab from ranibizumab, and 5 patients switched to ranibizumab). BCVA improved in 4 cases, was stable in 3 cases, and worsened in 10 cases. Mean total number of treatments received was 9.7 ± 5.1 times (range, 3 to 20 times). The average follow-up period was 31.5 ± 18.9 months (range, 4 to 72.7 months).

On analysis of initial OCT features, the patients could be grouped into two distinctive groups according to their OCT findings. Nine patients were found to have a large amount of intraretinal fluid (IRF) splitting and separating the retina, with large hyporeflective spaces with no structures visible in between (IRF group). The other 11 patients showed CNV with SRF only (SRF group), and their retinal structures (including photoreceptor layers) appeared relatively intact on OCT.

In the 9 patients with extensive IRF (IRF group), 6 were diagnosed with PCV (66.7%). Two were refractory to ranibizumab, while the other 7 were refractory to bevacizumab. Treatment response rates to subsequent therapies were 0% for bevacizumab (0 / 7), 50% for ranibizumab (3 / 6), and 50% for PDT ± anti-VEGF (3 / 6). Of the 2 refractory to ranibizumab, one had an ERM but refused further treatment. The other patient showed features of PCV on ICGA and was refractory to the combined PDT and ranibizumab injection as well as to the subsequent repeated ranibizumab injections (case 1). Of the 7 patients refractory to bevacizumab, one had an ERM, which was successfully removed with vitrectomy. Five had PCV, three of whom showed dramatic reduction of the massive IRF with PDT or combined PDT and bevacizumab injection, including 1 patient who was also refractory to ranibizumab (case 4). The other 2 patients who showed insufficient responses to PDT or combined PDT and bevacizumab injection were successfully treated with ranibizumab injection. Of the 2 patients who did not have PCV features on ICGA, one showed good response to ranibizumab (case 3), and the other refused further treatment. Overall, three out of 4 patients (75%) had a favorable response after switching to ranibizumab from bevacizumab in the IRF group.

In the 11 patients with SRF only (SRF group), five were refractory to ranibizumab, while 6 were refractory to bevacizumab. Treatment response rates to subsequent therapies were lower than the IRF group; 0% for bevacizumab (0 / 7), 22.2% for ranibizumab (2 / 9), and 28.6% for PDT ± anti-VEGF (2 / 7). In patients who were refractory to ranibizumab, all other treatments were also unsuccessful, except for 1 case, which had features of PCV on ICGA in which SRF disappeared after repeated ranibizumab injections following PDT (case 14). Of the 6 patients refractory to bevacizumab, PCV was found in 3 patients; two were successfully managed with PDT or combined PDT and bevacizumab injection, one of which ranibizumab injection was also unsuccessful, and the other patient was treated with additional ranibizumab injection. Of the 3 patients with no features of PCV on ICGA, one showed an insufficient response to repeated ranibizumab injection, and 1 showed recurrence despite combined PDT and bevacizumab injection and additional repeated ranibizumab injection. The remaining patient refused further treatment. Switching to ranibizumab in bevacizumab-refractory patients showed a favorable response in only 1 out of 4 patients (25%) in the SRF group for whom ranibizumab had initially failed before combined treatment with PDT and bevacizumab had been done.

Final visual acuities were all 20 / 200 or better in patients in the SRF group (median, 20 / 100; range, 20 / 200 to 20 / 40), while the final visual acuities were all 20 / 200 or worse in patients in the IRF group (median, 20 / 1,000; range, counting fingers to 20 / 200). Figs. 1 and 2 show the representative cases in each group.

Discussion

Twenty (7.5%) of 267 neovascular AMD patients treated
| No | Sex | Age | Eye | Initial VA | Last VA | Follow-up (mon) | Initial OCT | Dx | Initial Tx & response | Second Tx & response | Third Tx & response | Fourth Tx & response | Final effective Tx method | Total no. of Tx |
|----|-----|-----|-----|------------|---------|-----------------|-------------|----|---------------------|---------------------|---------------------|---------------------|-----------------------------|-----------------|
| 1  | M   | 65  | L   | 20/500    | 20/500  | 54.6            | IRF         | PCV | PDT                 | Ranibizumab (-) | Ranibizumab (-) | Ranibizumab (-) | None                        | 9               |
| 2  | M   | 78  | R   | 20/500    | 20/1,000| 5               | IRF, ERM   | Occult CNV | PDT | Ranibizumab (-) | Refused            | ?                             | ?                           | 3               |
| 3  | M   | 68  | L   | 20/600    | 20/200  | 71.3            | IRF         | Occult CNV | PDT | Ranibizumab (+) | -                  | Ranibizumab          | -                  | PDT                          | 12              |
| 4  | M   | 75  | L   | 20/60    | 20/500  | 26.4            | IRF         | PCV   | PDT | Ranibizumab (-) | PDT (+)           | -                  | -                  | PDT                          | 13              |
| 5  | M   | 82  | L   | 20/200    | 20/1,000| 26.1            | IRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (+) | -                  | -                  | -                            | 7               |
| 6  | M   | 67  | L   | 20/150    | 20/1,000| 72.7            | IRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (+) | -                  | -                  | -                            | 20              |
| 7  | M   | 65  | L   | 20/500    | 20/1,000| 29.3            | IRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (-) | Ranibizumab (+) | -                  | PDT                          | 14              |
| 8  | F   | 87  | L   | CF        | CF       | 35.5            | IRF, ERM   | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (-) | Ranibizumab (+) | -                  | PDT                          | 16              |
| 9  | M   | 73  | L   | 20/1,000  | 20/1,000| 4               | IRF         | Occult CNV | PDT | Ranibizumab (-) | Refused            | -                  | -                  | -                            | 3               |
| 10 | M   | 60  | L   | 20/100    | 20/200  | 20.8            | IRF         | Occult CNV | PDT | Ranibizumab (-) | Refused            | -                  | -                  | -                            | 3               |
| 11 | M   | 76  | L   | 20/50    | 20/100  | 28.8            | SRF         | Occult CNV | PDT | Ranibizumab (-) | PDT & ranibizumab (-) | Ranibizumab (-) | -                  | -                            | 6               |
| 12 | M   | 61  | R   | 20/33    | 20/50   | 34.2            | SRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (-) | -                  | -                  | -                            | 12              |
| 13 | F   | 64  | R   | 20/100    | 20/40   | 26.9            | SRF         | PCV   | PDT | Ranibizumab (-) | Refused            | -                  | -                  | -                            | 10              |
| 14 | M   | 62  | R   | 20/50    | 20/150  | 50.6            | SRF         | PCV   | PDT | Ranibizumab (-) | PDT (+)           | Ranibizumab        | -                  | PDT                          | 15              |
| 15 | F   | 71  | L   | 20/40    | 20/40   | 22.7            | SRF         | PCV   | PDT | Ranibizumab (-) | PDT (+)           | -                  | -                  | -                            | 11              |
| 16 | M   | 67  | L   | 20/150   | 20/100  | 37.8            | SRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (-) | Ranibizumab (+) | -                  | PDT                          | 16              |
| 17 | M   | 80  | R   | 20/150   | 20/200  | 19.6            | SRF         | Occult CNV | PDT | Ranibizumab (-) | -                  | -                  | None                        | 7               |
| 18 | M   | 83  | R   | 20/50    | 20/100  | 31.7            | SRF         | PCV   | PDT | Ranibizumab (-) | PDT & bevacizumab (+) | -                  | -                  | PDT                          | 4               |
| 19 | F   | 75  | L   | 20/35    | 20/40   | 24.8            | SRF         | Occult CNV | PDT | Ranibizumab (-) | PDT & bevacizumab (-) | Ranibizumab (-) | -                  | -                            | 9               |
| 20 | M   | 53  | R   | 20/60    | 20/100  | 7               | SRF         | Occult CNV | PDT | Ranibizumab (-) | Refused            | -                  | -                  | -                            | 3               |

VA = visual acuity; OCT = optical coherence tomography; Dx = diagnosis; Tx = treatment; IRF = intraretinal fluid; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; ERM = epiretinal membrane; CNV = choroidal neovascularization; CF = counting fingers; SRF = subretinal fluid.
with anti-VEGF agents (bevacizumab or ranibizumab) showed refractory responses in our study. Few studies to date have assessed the anatomical response rate of anti-VEGF injections in neovascular AMD. In the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) studies of ranibizumab, 25% and 40% patients had visual improvement [1,2], respectively, and more than 90% have been reported to have experienced resolution of all fluid after three consecutive monthly injections [8]. With bevacizumab, Lux et al. [13] reported 45% of patients to be refractory to visual improvement with bevacizumab. Not many studies have compared treatment results of ranibizumab and bevacizumab. Considering the larger size and higher complexity of bevacizumab compared with ranibizumab, it can be speculated that the anatomical response rate might be lower; however, recent reports showed a similar outcome with ranibizumab and bevacizumab. Fong et al. [6] found similar visual results with the two forms of anti-VEGF antibodies in a comparative retrospective case series. A recent multicenter prospective randomized clinical trial also reported similar visual outcomes with ranibizumab and bevacizumab [14].

Cho et al. [10] and Stangos et al. [15] previously determined that eyes refractory to therapy showed features of PCV on ICGA. Twelve out of 20 patients (60%) in our study also had features of PCV. However, one new notable finding was that patients showing refractory responses to anti-VEGF injections could be grouped into two distinctive categories according to their OCT findings. One group showed extensive IRF. This group included more patients refractory to bevacizumab, and these patients tended to have a better response to ranibizumab when switched from bevacizumab. However, visual improvement was limited, and the final visual acuity was poor in this group. The proposed mechanism of this refractoriness to bevacizumab and responsiveness to ranibizumab could be due to the different molecular size and associated transport of these molecules through the retina to the subretinal space. Because it is smaller, ranibizumab is known to diffuse across the retina and was found diffusely across the retina after intravitreal injection [16]. Bevacizumab also effectively reaches the subretinal space; however, the distribution of the antibody in the retina after intravitreal injection is different from ranibizumab. The strokes radius of a full-length IgG (bevacizumab) is around 5.5 nm [17], while that of the Fab fragment (ranibizumab) is about one-third. Considering the pore diameters of the internal limiting membrane (10 to 25 nm) [18] and the external limiting membrane (3.0 to 3.6 nm) [19], which are the physical barriers of the retina, transport of bevacizumab should be different from that of ranibizumab [20]. In animal experiments [20-22], intraretinal penetration of bevacizumab after intravitreal injections showed a columnar pattern, spanning the full layer of the retina and possibly implicating the important role of active transport by Müller cells [22]. In contrast, intravitreal injection of ranibizumab showed free, random penetration across the entire retina, reaching the choriocapillaries [16]. The decreased response to bevacizumab in patients with extensive separation of the intraretinal tissue with fluid may also further support that Müller cells might be the major transport route for bevacizumab. Disruption of the Müller cells in areas with extensive IRF may have led to impaired bevacizumab transport across this area, producing poor anatomical responses in such patients, while ranibizumab could cross by diffusion. In contrast, the other group with isolated SRF only showed refractoriness to ranibizumab and bevacizumab similarly, with some response to PDT, indicating that this subgroup might represent a completely different disease group with a different mechanism of refractoriness to anti-VEGF therapy and a different pathophysiology, possibly one that is less associated with VEGF but more with other factors, such as platelet-derived growth factor, pigment epithelium derived factor or other cytokines. The OCT features of anti-VEGF-refractory patients in other diseases, such as macular edema, will need to be evaluated by further studies.

Additionally, the IRF group showed a worse visual outcome than the SRF group. The poor vision in the IRF group can be explained by the more severe disruption of the photoreceptor layers and inner retinal structures, which could be inferred from the spectral-domain OCT (Spectralis OCT) findings. In a previous study of patients with diabetic macular edema who were treated with intravitreal triamcinolone injection, the visual prognosis was worse for those with cystoid macular edema, while patients with SRF showed a better visual prognosis [23].

The rationale to continue treatment despite the failure of anti-VEGF injections requires additional consideration, as our analysis revealed that little visual improvement can be
Fig. 1. Case 7. A 65-year-old male diagnosed with polypoidal choroidal vasculopathy (A, fundus photography; B, fluorescein angiography). His initial visual acuity was 20 / 500, and findings compatible with polypoidal choroidal vasculopathy were observed on indocyanine green angiography (C). Optical coherence tomography (D) showed extensive intraretinal fluid. He was refractory to six sequential bevacizumab injections and was treated with combined photodynamic therapy and bevacizumab injections twice without success (E, optical coherence tomography). The patient received ranibizumab injections monthly, effectively decreasing the intraretinal fluid (F, optical coherence tomography), although his visual acuity was limited to 20 / 1,000.

Fig. 2. Case 11. A 76-year-old male diagnosed with occult choroidal neovascularization (A, fundus photography; B, fluorescein angiography). His visual acuity was 20 / 50, and he showed no evidence of polypoidal choroidal vasculopathy on indocyanine green angiography (C). Optical coherence tomography (D) revealed subretinal fluid only. The patient was refractory to three sequential ranibizumab injections and received combined photodynamic therapy and ranibizumab injections, which also had no effect (E, optical coherence tomography). He was prescribed additional ranibizumab injections, but the SRF still remained (F, optical coherence tomography). At the last follow-up visit, his visual acuity was 20 / 100.
achieved, especially in the IRF group with a poor visual outcome. However, in our previous experiences, treatment should not be discontinued in these non-responsive patients until anatomical stabilization is achieved, although there seems to be little to gain in visual improvement. In neovascular AMD patients with large amounts of IRF who refused treatment, the IRF gradually expanded or led to extensive bleeding, resulting in a more severe visual field defect and increased visual impairment, as shown in Fig. 3. Therefore, anatomical stabilization using PDT or ranibizumab can be valued even in the IRF group to prevent further visual decline and the expansion of visual field defects. Also, the natural course of patients with isolated SRF only needs further study in the future, and additional evidence to support continuous treatment in these patients will also be required because these patients tend to have relatively good vision despite the presence of persistent fluid.

This study had limitations, including the retrospective and observational nature of the study and the small number of patients that was not large enough for statistical analysis. In addition, the treatment protocol was non-randomized and non-standardized, and heterogeneous patients were included, with some having a previous treatment history with PDT. However, this study still was significant in that it showed the distinct morphologic OCT features of cases refractory to anti-VEGF and the possible differential treatment outcomes according to those OCT features. Neovascular AMD may therefore be a heterogeneous group of diseases showing a common clinical presentation. Today, we are more equipped than we were 10 years ago, with many more treatment options for neovascular AMD. Individual features on FA, OCT and ICGA (when possible), and their association with refractoriness to certain treatments should be considered when deciding on the treatment method in patients with neovascular AMD. This study raised the possibility that patients with extensive IRF refractory to bevacizumab can be responsive to ranibizumab, while patients with SRF may be refractory to both, suggesting a different pathophysiology and intraocular pharmacokinetics. Further large-scale studies that focus on evaluating the differential response by types of exudation on OCT in anti-VEGF-refractory AMD patients may aid in the selection of treatment options.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.
Acknowledgements

This study was partly supported by the Translational Research Program (A111161) funded by the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea.

References

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-31.

2. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-44.

3. Abraham-Marin ML, Cortes-Luna CF, Alvarez-Rivera G, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration: a pilot study. *Graefes Arch Clin Exp Ophthalmol* 2007;245:651-5.

4. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:363-72.e5.

5. Costa RA, Jorge R, Calucci D, et al. Intravitreal bevacizumab for choroidal neovascularization caused by AMD (IBeNA Study): results of a phase 1 dose-escalation study. *Invest Ophthalmol Vis Sci* 2006;47:4569-78.

6. Fong DS, Custis P, Howes J, Hu JW. Intravitreal bevacizumab and ranibizumab for age-related macular degeneration: a multicenter, retrospective study. *Ophthalmology* 2010;117:298-302.

7. Rich RM, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006;26:495-511.

8. Fung AE, Lahmani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;143:566-83.

9. Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. *Am J Ophthalmol* 2007;144:627-37.

10. Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2009;148:70-8.el.

11. Mojana F, Cheng L, Bartsch DU, et al. The role of abnor-

mal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. *Am J Ophthalmol* 2008;146:218-27.

12. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. *Arch Ophthalmol* 1999;117:1329-45.

13. Lux A, Llacer H, Heussen FM, Joussen AM. Non-responders to bevacizumab (Avastin) therapy of choroidal neovascular lesions. *Br J Ophthalmol* 2007;91:1318-22.

14. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364:1897-908.

15. Stangos AN, Gandhi JS, Nair-Sahni J, et al. Polypoidal choroidal vasculopathy masquerading as neovascular age-related macular degeneration refractory to ranibizumab. *Am J Ophthalmol* 2010;150:666-73.

16. Gaudreault J, Fei D, Beyer JC, et al. Pharmacokinetics and retinal distribution of ranibizumab, a humanized antibody fragment directed against VEGF-A, following intravitreal administration in rabbits. *Retina* 2007;27:1260-6.

17. Kofoid-Enevoldsen A, Foyle WJ, Fernandez M, Yudkin JS. Evidence of impaired glomerular charge selectivity in nondiabetic subjects with microalbuminuria: relevance to cardiovascular disease. *Arterioscler Thromb Vasc Biol* 1996;16:450-4.

18. Nishihara H. Studies on the ultrastructure of the inner limiting membrane of the retina: distribution of anionic sites in the inner limiting membrane of the retina. *Nihon Ganka Gakkai Zasshi* 1991;95:951-8.

19. Bunt-Milam AH, Saari JC, Klock IB, Garwin GG. Zonulae adherentes pore size in the external limiting membrane of the rabbit retina. *Invest Ophthalmol Vis Sci* 1985;26:1377-80.

20. Kim H, Robinson SB, Csaky KG. FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye. *Mol Vis* 2009;15:2803-12.

21. Heiduschka P, Fietz H, Hofmeister S, et al. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. *Invest Ophthalmol Vis Sci* 2007;48:2814-23.

22. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006;26:262-9.

23. Brasil OF, Smith SD, Galor A, et al. Predictive factors for short-term visual outcome after intravitreal triamcinolone acetonide injection for diabetic macular oedema: an optical coherence tomography study. *Br J Ophthalmol* 2007;91:761-5.