Retention of good visual acuity in eyes with neovascular age-related macular degeneration and chronic refractory subfoveal subretinal fluid

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optical coherence tomography (OCT) has revolutionized the classification of CNV which was previously defined by fluorescein angiography alone. Vascular endothelial growth factor A (VEGF-A) is a diffusible cytokine implicated in inducing angiogenesis and increased vascular permeability in the setting of neovascular AMD. Blockade of VEGF-A has become an effective treatment for the management of CNV secondary to AMD. The employment of anti-VEGF therapy has improved long term visual outcomes by reducing the risk of fluid accumulation and hemorrhage.

However, in a small subset of patients, successful resolution of anatomic features such as the presence of sub or intra-retinal fluid may be difficult. Current clinical practice advocates treatment with anti-VEGF to achieve complete or near complete resolution of foveal threatening fluid to minimize risk of structural damage to retinal photoreceptors. However, the relationships between morphologic features and visual prognosis after intravitreal anti-VEGF treatment are complex and not well characterized. Integrity of retinal photoreceptor cells may be dependent on a combination of factors that interact to modify the retinal pigment epithelium and photoreceptor layer.

The purpose of this study is to assess the clinical characteristics of eyes with neovascular AMD receiving continuous intravitreal anti-VEGF therapy that retain good visual acuity despite chronic, persistent, subfoveal subretinal fluid (SRF).

Methods

This study design was approved by Western institutional review board (Olympia, WA, USA). It complied with the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki.

Study eyes were identified from a consecutive series of 186 NVAMD patients treated with intravitreal anti-VEGF therapy seen for regular follow-up visits over a 3-month period by a single physician (KBF). All patients had active choroidal neovascularization documented by SD-OCT and fluorescein angiography (Topcon, Tokyo, Japan) prior to the initiation of intravitreal anti-VEGF therapy. To be included in this study, eyes were required to have chronic subfoveal subretinal fluid (defined as fluid present at >80% of all follow-up visits for >1 year) secondary to NVAMD despite continuous anti-VEGF therapy, and good long-term visual acuity of 20/40 or better. All patients had undergone a complete ophthalmic examination including a slit-lamp examination, dilated fundus biomicroscopy, and eye-tracked imaging with Spectralis SD-OCT (Heidelberg Engineering, Vista, California, USA) at each office visit. Eyes with concomitant retinal disease including diabetic retinopathy, pathologic myopia, angioid streaks, and retinal vascular occlusions were excluded. A retrospective chart review was performed to obtain data on demographics and treatment history (photodynamic therapy, number and type of anti-VEGF injections).

Spectralis SD-OCT was used to obtain measurements of subfoveal choroidal thickness. Choroidal thickness was manually measured beneath the foveal center from the posterior edge of the retinal pigment epithelium to the choroid/sclera junction using a linear measuring tool built-into the review software. SD-OCT scans were also qualitatively assessed for integrity of the ellipsoid zone and external limiting membrane, presence of cystoid macular edema, location of subretinal fluid, and characterization of choroidal neovascularization subtype (1 – sub-RPE, 2 – subretinal, 3 – intraretinal/retinal angiomatous proliferation or mixed) in all patients.

Results

From the 186 consecutive NVAMD patients seen over 3 months, a total of 9 (4.8%) patients (10 eyes) with chronic subretinal fluid were identified for this study (Table 1). The mean patient age was 78 years (range 55–91). Of these subjects, 3 were male and 6 were female. All patients were white. In addition to neovascular AMD, the only other ocular comorbidity shared by these patients was the presence of nuclear sclerotic cataracts. 5 eyes of 4 patients had nuclear sclerotic cataracts and the remaining 5 eyes of 5 patients had undergone uncomplicated cataract surgery with posterior chamber intraocular lens placement.

SD-OCT data showed the presence of vascularized pigment epithelial detachment (PED) consistent with type 1 neovascularization in all eyes and baseline fluorescein angiography was consistent with type 1 neovascularization in all eyes (Fig. 1A–D). All 10 eyes had subfoveal subretinal fluid, and 1 eye also had an additional area of subretinal fluid located temporal to the fovea. The mean duration of persistent subretinal fluid was 5.2 years (range 1.3–11.0). Only 1 eye had or developed cystoid macular edema detected by SD-OCT. At least partial preservation of the foveal ellipsoid zone and external limiting membrane was identified in all patients. No eyes had or developed the presence of foveal or non-foveal geographic atrophy over the follow-up period.

Reliable measurements of choroidal thickness were attained in all cases. Mean baseline subfoveal choroidal thickness was measured to be 285.3 μm (range 100–573 μm) and the mean follow-up subfoveal choroidal thickness was

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Age</th>
<th>Duration of subretinal fluid (Years)</th>
<th>Baseline best corrected visual acuity</th>
<th>Follow-up best corrected visual acuity</th>
<th>Baseline choroidal thickness (μm)</th>
<th>Choroidal neovascularization subtype (1, 2, 3)</th>
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</thead>
<tbody>
<tr>
<td>Patient 2</td>
<td>87</td>
<td>9.5</td>
<td>20/25</td>
<td>20/25</td>
<td>289</td>
<td>1</td>
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<tr>
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<td>91</td>
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<td>20/30</td>
<td>20/30</td>
<td>231</td>
<td>1</td>
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<tr>
<td>Patient 4</td>
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<td>1.5</td>
<td>20/30</td>
<td>20/30</td>
<td>326</td>
<td>1</td>
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<tr>
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<td>7.0</td>
<td>20/30</td>
<td>20/30</td>
<td>427</td>
<td>1</td>
</tr>
<tr>
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<td>68</td>
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<td>20/25</td>
<td>258</td>
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<tr>
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<td>4.9</td>
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<td>20/25</td>
<td>238</td>
<td>1</td>
</tr>
</tbody>
</table>
239.7 μm (range 83–470 μm). Data for normal age-matched choroidal thickness were obtained from another study which measured choroidal thickness in 42 eyes of 42 healthy subjects. These subjects had no history of retinal or choroidal pathology, and patients with myopic refractive error of greater than 6.0 diopters were excluded. The average subfoveal choroidal thickness in this group of healthy patients was measured to be 256.8 ± 75.8 μm (Fig. 2).

All eyes were being treated with intravitreal anti-VEGF therapy in order to control their disease (Table 2). Eyes had received a mean of 36.5 injections (range 17–66) of either bevacizumab (intra-vitreal 1.25 mg/0.05 ml), ranibizumab (intra-vitreal 0.5 mg/0.05 ml), or aflibercept (2.0 mg/0.05 ml). Only a single eye had received verteporfin photodynamic therapy (PDT) prior to the initiation of intravitreal therapy, with a total of 5 treatment sessions, including one session of combined PDT and intra-vitreal triamcinolone acetonide. At the most recent follow-up, 7 eyes were receiving intravitreal monthly aflibercept and the remaining 3 eyes were receiving monthly intravitreal ranibizumab. Criteria for retreatment included persistent subretinal or intraretinal fluid by OCT with or without the presence of clinically identified hemorrhage.

Discussion

This study illustrates that good long-term visual outcomes are possible in certain eyes with persistent subretinal fluid secondary to type 1 neovascularization in the setting of NVAMD. While morphologic features detected by SD-OCT are typically used to guide intravitreal anti-VEGF therapy, their relationship to visual prognosis may be complex and incompletely characterized.

Jaffe et al. investigated the association of macular morphology with visual acuity in eyes with neovascular AMD treated with intravitreal ranibizumab or bevacizumab for 1 year. The results of their study indicated that residual intraretinal fluid in the macula, mainly intraretinal fluid involving the fovea, had a significant negative effect on visual acuity, whereas subretinal or sub-retinal pigment epithelial (RPE) fluid was not found to have a significant negative effect on visual function. Previous studies have also reported that cystoid macular edema has an adverse impact on visual acuity when associated with subfoveal CNV. The etiology of this specific negative effect of intraretinal fluid (not subretinal or sub-RPE...
Following photolysis, vascular AMD treated with anti-VEGF therapy for one year. Anti-VEGF treatment due its potential atrophic effects on RPE is a significant concern in NVAMD patients with chronic photoreceptor degeneration and resultant poor visual prognosis. Risk of geographic atrophy and resultant poor visual prognosis. In this investigation, patients with type 1 neovascularization causing persistent subretinal fluid refractory to anti-VEGF therapy were able to achieve good long-term visual outcomes. Increased subfoveal choroidal thickness and type 1 neovascularization may exert a protective effect on photoreceptor integrity and may result in better visual outcomes.

Financial interest disclosure

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None of the authors have a proprietary interest.

Conflict of interest

The authors declared that there is no conflict of interest.

References

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