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VISUAL FINDINGS IN NEOVASCULAR MACULAR DEGENERATION REFRACTORY TO BEVACIZUMAB AFTER INTRAVITREAL AFLIBERCEPT THERAPY

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ABSTRACT

Neovascular (wet) age-related macular degeneration (AMD) is associated with blindness in patient populations above 55 years of age, affecting approximately 2 million Americans. Intravitreal (IV) bevacizumab is widely employed in the treatment of wet AMD. Development of a novel pharmacologic intervention to match bevacizumab's indications is possible with the advent of aflibercept. This study evaluated the optical coherence tomographic (OCT) findings and intraocular pressure after IV aflibercept therapy in patients with wet AMD refractory to IV bevacizumab therapy. This retrospective review of 29 patient records (30 eyes) demonstrated that 73% of patients did not show an increase in OCT. Furthermore, 83% of patients did not demonstrate an increase in intraocular pressure (IOP) and all patients had an IOP of 20 or less after three months of therapy. This study further explores the mean change per patient in retinal thickness via OCT as well as intraocular pressure. The results of this study demonstrate that aflibercept can improve visual findings in patients refractory to bevacizumab and therefore we recommend that patients be switched to it. Further, it is safe to use in patients with glaucoma as it will not increase the IOP.

KEYWORDS: aflibercept, age-related macular degeneration.

INTRODUCTION

Age-related macular degeneration is the leading cause of visual loss in elderly patient populations. The prevalence of AMD in the United States is estimated to be 6.5% in patients over the age of 40.[1] There are currently two forms of AMD: neovascular and non-neovascular (dry). Dry AMD is currently the most common form of AMD in elderly patients and accounts for 90% of patients with AMD. To date there is nothing in clinical use to delay the progression of dry AMD. On the other hand, several gene-targeted therapies against vascular endothelial growth factor (VEGF) have been discovered that have revolutionized the treatment of neovascular AMD.[2] Furthermore, 90% of patients with severe visual loss have the neovascular form of AMD.[3]

AMD is a disease of the posterior segment of the eye affecting the macula lutea, a portion of the retina, which is the area that allows for vision. Wet AMD is due to a growth of choroidal neovascular membranes.[3] In wet AMD the photoreceptor outer segments of the eye are driven through cycles of shedding, degradation and resynthesis. This induces metabolic stress of the neurosensory retina and retinal pigment epithelium (RPE), which causes ischemia and inflammation to occur. This is in turn allows for the recruitment of cytokines and growth factors including VEGF which promote the growth of the choroidal neovascular membranes into the sub-retinal spaces which eventually causes vision loss.[4,5] It has been well documented and demonstrated that in wet AMD there are increased levels of VEGF.[6] Therefore, in order to prevent blindness in patients with wet AMD therapies have been developed that inhibit VEGF.

The most novel of these vascular therapies that inhibits VEGF is aflibercept. Current therapies for AMD only bind VEGF-A and not VEGF-B and placental growth factor (PIGF). Unlike these therapies, aflibercept is a recombinant fusion protein that binds PIGF, VEGF-A and VEGF-B. Studies have demonstrated that both PIGF and VEGF are present in choroidal neovascual membranes and therefore, both may contribute to promoting its growth into the sub-retinal spaces.[7] Furthermore, aflibercept shows a stronger binding affinity at 0.5 pM Kd for VEGF than other therapies for AMD including bevacizumab and ranibizumab. Therefore, it is thought to be more effective in blocking VEGF, which will inhibit the growth of the choroidal neovascular membranes.[8] Aflibercept has an unbound half-life of 1-3 days and a half-life of 18 days when bound to VEGF.[9] Ultimately, aflibercept has the

potential to be a stronger therapy for AMD since it is better able to inhibit VEGF and PIGF.

Currently, bevacizumab is the most widely used drug for the treatment of wet AMD in the United States. Bevacizumab has not been FDA approved for use in wet AMD and instead was approved for metastatic carcinoma of the colon and rectum. The majority of retina specialists in the United States use bevacizumab as an off-label therapy for wet AMD. It can be purchased at a significantly lower cost to its competitor ranibizumab. Bevacizumab is a humanized monoclonal antibody that has been shown to bind to all isoforms of VEGF-A, but not VEGF-B or PIGF. With its lower cost and affinity for VEGF, bevacizumab has been widely employed as an off-label therapeutic option for neovascular AMD. The multicenter, randomized Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study demonstrated the efficacy of bevacizumab in targeting VEGF to inhibit growth of choroidal neovascular membranes. This study demonstrated that after one year of treatment with bevacizumab there was improvement and stabilization in patients' vision. Just like aflibercept, bevacizumab is able to inhibit VEGF from promoting the growth of choroidal neovascular membranes into the sub-retinal space.[10,11,12,13]

The development of Optical Coherance Tomography (OCT), a new noninvasive imaging technique, has recently revolutionized the world of vision. OCT allows for the measurement of retinal thickness through high resolution, cross-sectional images of the retinal nerve fiber layer and optic nerve head topography. OCT uses low coherence interferometry of light to determine the thickness of a patient's macula. Increase in retinal thickness causes vision loss and eventually blindness in AMD. This new imaging technique allows an Ophthalmologist to determine if a patient's retina has changed in thickness on the level of microns, which allows for evaluation of retinal interfaces.[14]

Intraocular pressure (IOP) is another measurement used to determine the pressure in the eye. Prior to intravitreal injections, ophthalmologists measure the IOP in the eye to ensure that the patient will be able to tolerate the injection. Many studies have demonstrated that bevacizumab and ranibizumab injections have caused a sustained elevation in IOP. Good et al demonstrated that 9.9% of patients who were given bevacizumab showed a sustained increase in IOP.[15] 3.45% of patients with AMD in another study demonstrated sustained elevated IOP after injections with bevacizumab or ranibizumab, and none of these patients had a history significant for glaucoma.[16] IOP is an important measurement that must be taken prior to using intravitreal injections.

The purpose of this study is to determine if intravitreal aflibercept therapy can show improvement in anatomy and cystic edema in patients with wet AMD who are refractory to bevacizumab treatment. Intraocular pressure in these patients will also be measured to determine if aflibercept therapy can be used in patients with glaucoma. Additionally, this study will determine if there is a correlation between number of prior bevacizumab injections and visual improvement after switching to aflibercept. This study will determine if vision loss from wet AMD can be prevented in the elderly population. Furthermore, this study can help physicians determine if they should switch their patients with wet AMD who are not responding on bevacizumab to aflibercept therapy.

MATERIALS AND METHODS

An institutional review board exemption was granted by Sterling IRB. 29 patient records (30 eyes) (male: 9, female: 20, mean age: 79.82 years) were used for this retrospective review. Patients were identified in this study numerically. All patients were above 55 years of age and were from the greater Phoenix area. Patient records were reviewed via Centry City EMR from their first aflibercept injection until 3 months post treatment. Every patient in the study had a history notable for wet AMD and had received at least one IV bevacizumab injection a minimum of 4 weeks prior to initiating IV aflibercept therapy.

Aflibercept (2 mg IV injection) was administered by trained Ophthalmologists at Associated Retina Consultants in Phoenix, AZ once every 4 weeks to the study population for a period of 3 months. An OCT machine (Cirrus HD-OCT Model 4000) was used to obtain high-resolution images of retinal thickness before each IV aflibercept dose. IOP was also measured prior to initiating each aflibercept dose using a tonopen (Reichert, NY, USA). Visual acuity was converted to logarithm of minimum angle of resolution (logMAR) for data analysis.

A paired samples t-test was used for data analysis with retinal thickness and IOP as the dependent variables and pretreatment, 1, 2, and 3-month time points as the independent variables. Visual acuity was also correlated with OCT in patients who showed a decrease in OCT. A t-test was used to determine if the number of bevacizumab injections correlated with OCT improvement. A p value of <0.05 was considered the standard of statistical significance.

RESULTS

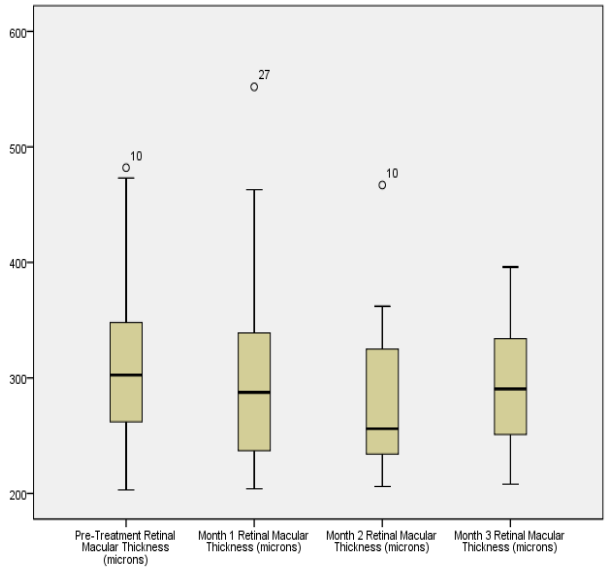

Figure 1: Change In Mean Retinal Thickness After Aflibercept Therapy.

Pretreatment mean retinal thickness was 320.3um and mean retinal thickness after one, two and three months of therapy was 303.3um, 281.0um (p=.001), and 293.1um (p<.05) respectively. 21 out of 30 (70%) eyes showed a decrease in retinal macular thickness while 1 out of 30 (3%) demonstrated no change in retinal macular thickness. 8 out of 30 (27%) eyes showed an increase in retinal macular thickness. Visual acuity was correlated with OCT in patients that showed decreased OCT (n = 21). Pretreatment to month 3 showed statistical significance p <.05.

Table 1: Mean Retinal Thickness Results After Aflibercept Therapy.

	Pretreatment	Month 1	Month 2	Month 3
Mean	320.3	303.3	281.0	293.1
95% CI	+/- 28.9	+/- 30.7	+/- 22.780	+/- 18.9
SD	77.3	82.1	61.0	50.6
Minimum	203.0	204.0	206.0	208.0
25th Percentile	262.0	237.0	234.0	251.0
Median	302.5	287.5	256.0	290.5
75th Percentile	348.0	339.0	325.0	334.0
Maximum	482.0	552.0	467.0	396.0

Table 1 shows that the pretreatment mean retinal thickness was 320.3um and mean retinal thickness after one, two and three months of therapy was 303.3um, 281.0um (p=.001), and 293.1um (p<.05) respectively. 21 out of 30 (70%) eyes showed a decrease in retinal macular thickness while 1 out of 30 (3%) demonstrated no change in retinal macular thickness. 8 out of 30 (27%) eyes showed an increase in retinal macular thickness. Visual acuity was correlated with OCT in patients that showed decreased OCT (n = 21). Pretreatment to month 3 showed statistical significance p <.05.

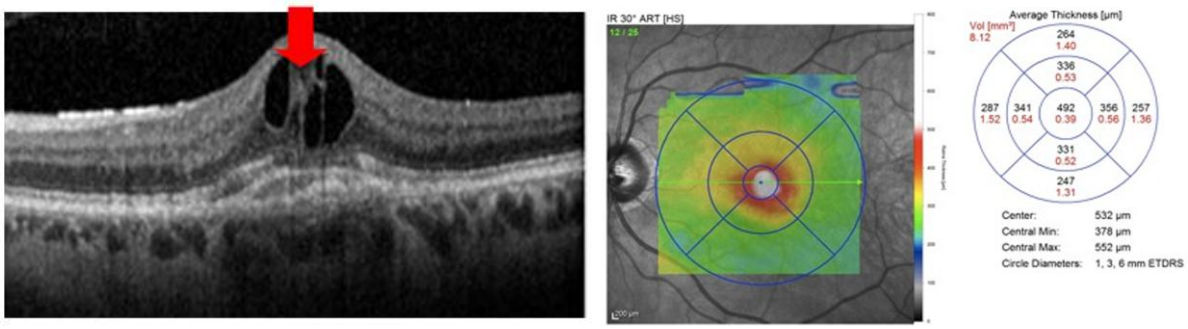

Figure 2: Patient #15's Pretreatment OCT.

The above figure is patient #15's OCT taken prior to initiating aflibercept therapy. Figure 2 demonstrates the pretreatment intraretinal cystoid macular edema.

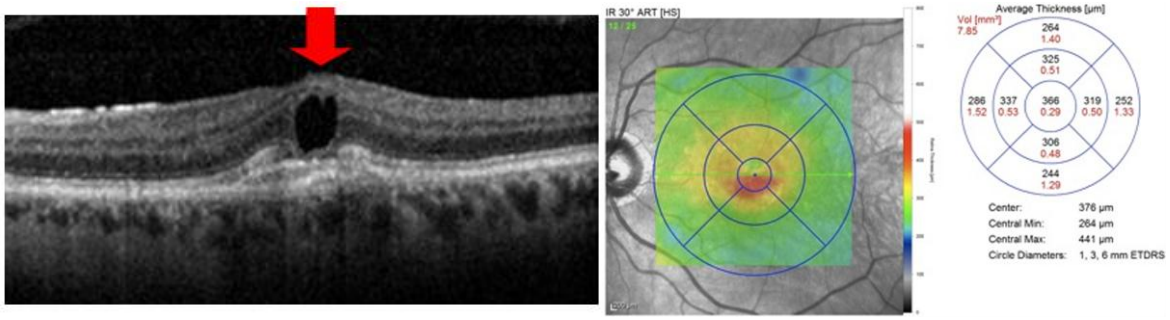

Figure 3: Patient #15's Posttreatment OCT

The above figure is patient #15's OCT taken after three months of aflibercept therapy. Figure 3 demonstrates a decrease in the cystoid edema and central retinal thickness after three months of therapy.

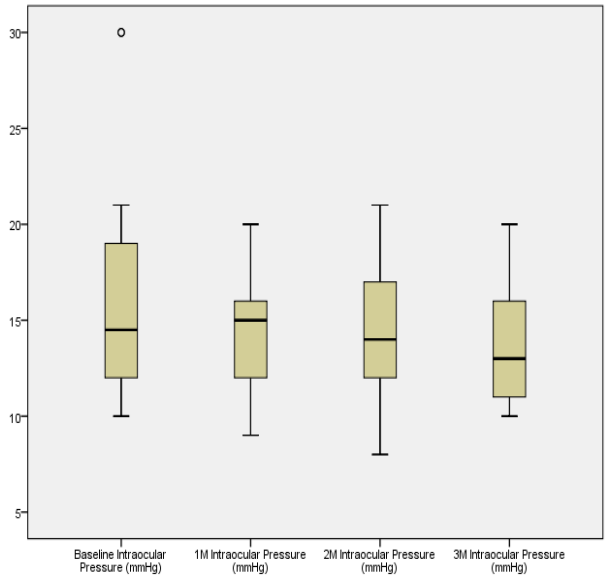

Figure 4: Change In Intraocular Pressure (Iop) After Aflibercept Therapy.

Pretreatment mean IOP was 16.1 mmHg and mean IOP after one, two and three months of therapy was 14.5 mmHg, 14.3 mmHg, and 14.0 mmHg respectively. All two-tailed t-test comparisons demonstrated a p value that was greater than .05 except baseline to three months of therapy, which was less than .05. After three months of therapy all patients had an IOP of 20 or less. 20 out of 30 eyes (66.7%) showed a decrease in IOP after therapy while 5 out of 30 eyes (16.7%) showed no change after therapy. 5 out of 30 eyes (16.7%) showed an increase in IOP after therapy, but all still had IOPs of 20 or less.

Table 2: Intraocular Pressure (Iop) Results After Aflibercept Therapy.

	Pretreatment	Month 1	Month 2	Month 3
Mean	16.1	14.5	14.3	14.03
95% CI	+/- 2.0	+/- 1.2	+/- 1.2	+/- 1.2
SD	5.2	3.2	3.2	3.2
Minimum	10.0	9	8.0	10.0
25th Percentile	12.0	12.0	12.0	11.0
Median	14.0	15.0	14.0	13.0
75th Percentile	19.0	16.0	17.0	16.0
Maximum	30.0	20	21.0	20.0

Table 2 shows that the pretreatment mean IOP was 16.1 mmHg and mean IOP after one, two and three months of therapy was 14.5 mmHg, 14.3 mmHg, and 14.0 mmHg respectively. All two-tailed t-test comparisons demonstrated a p value that was greater than .05 except baseline to three months of therapy, which was less than .05. After three months of therapy all patients had an IOP of 20 or less. 20 out of 30 eyes (66.7%) showed a decrease in IOP after therapy while 5 out of 30 eyes (16.7%) showed no change after therapy. 5 out of 30 eyes (16.7%) showed an increase in IOP after therapy, but all still had IOPs of 20 or less.

An average of 7.8 bevacizumab injections was given prior to switching to aflibercept. A 2-tailed t-test did not show a statistically significant correlation between the number of bevacizumab injections and a decrease in OCT ($p > .05$).

DISCUSSION

This retrospective review studied the visual outcomes in patients with neovascular AMD who were not responding to bevacizumab therapy and were switched to aflibercept. Overall 73% of patients did not demonstrate an increase in retinal macular thickness. This study demonstrates the efficacy of aflibercept in patients with AMD refractory to bevacizumab, which is in line with other studies that have recently been published.[8,17,18] This may be because aflibercept binds VEGF-A, VEGF-B and PIGF while bevacizumab only binds VEGF-A[7]. Also, aflibercept has a higher binding affinity than bevacizumab which may also attribute to its better outcome[8]. Furthermore, this study shows that patients who are not responding to other anti-VEGF therapies such as bevacizumab have a good chance of responding to aflibercept and showing improvement in their anatomy and a decrease in cystic edema. This study demonstrated that visual acuity correlated with OCT after 3 months of therapy.[17,18]

Hoang et al found that a greater number of anti-VEGF intraocular injections with bevacizumab or ranibizumab demonstrated an increased risk for sustained elevation of IOP. They did not however study IOP changes with aflibercept.[19] Our study measured the IOP outcome in patients before each aflibercept dose. The results demonstrated that 83.4% of the eyes did not show an increase in IOP after 3 months of aflibercept therapy. Furthermore, all eyes had an IOP of 20 or less at the end of this study. Out of the 9 patients who did not show an improvement in OCT, 5 showed a decrease in IOP, 3 had the same IOP and 1 had an increase in IOP after 3 months. This is the first study to show a decrease in IOP in patients who did not show an improvement in OCT. Although aflibercept was unable to improve the OCT of these patients, it was able to show improvement in IOP and can potentially be used in patients to lower their IOP. Kim et al demonstrated that transient IOP elevations after intravitreal injections is a common side effect. They did not however explore if these increases were sustained over time or if the injections actually caused a sustained decrease in IOP.[20] A normal IOP is between 10-21mmHg which means that all patients fell in the normal zone after treatment with aflibercept. This shows that aflibercept can be used in patients with glaucoma since it will not increase their IOP and may even cause it to decrease.

AMD is a major cause of blindness and visual impairment in geriatric Americans. IV aflibercept is a novel intervention developed for the treatment of wet AMD. Significant mean retinal thickness reduction after once-monthly administration of IV aflibercept therapy for a minimum of 3 months was demonstrated in this study of 29 patients with AMD refractory to IV bevacizumab. Aflibercept appears to be an effective alternative to preserve vision in neovascular AMD which has been recalcitrant to anti-VEGF therapy.

The strengths of this study include a strict inclusion criteria as well as a 3-month follow up period where all variables were measured in patient eyes. Since aflibercept is a new drug that was FDA approved in 2012, only 29 patient charts were reviewed. Future studies will include increased sample size and longer treatment periods. Ongoing clinical trials will determine efficacy after prolonged treatment. Further studies include the review of more patient charts in increased geographical areas over a longer period of time. This was a retrospective review and would produce better results if it were conducted as a randomized double blind trial since this would eliminate bias.

CONCLUSION

AMD is a major cause of visual loss and impairment in geriatric Americans. IV aflibercept is a novel intervention developed for the treatment of wet AMD. Significant mean retinal thickness reduction after once-monthly administration of IV aflibercept therapy for a minimum of 3 months was demonstrated in this study of 29 patients with AMD refractory to IV bevacizumab. Also, no significant increase in IOP was demonstrated and the majority of patients actually showed a decrease. This is the first study to demonstrate that patient who did not show an improvement in OCT did show an improvement in IOP. Therefore, we recommend the use of IV aflibercept in patients suffering from wet AMD whose disease is refractory to the current standard of care, bevacizumab and also recommend aflibercept therapy be tested in patients with glaucoma.

REFERENCES

1. Klein R, Chou CF, Klein BE, Zhang X, Meuer SM, Saaddine JB. Prevalence of age-related macular degeneration in the US population. Arch Ophthalmol, 2011; 129(1): 75-80.
2. Bressler NM. Antiangiogenic approaches to age-related macular degeneration today. Ophthalmology, 2009; 116(10 Suppl): S15-23.
3. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol, 1984; 102(11): 1640-2.
4. Nagineni C.N., Kommineni V.K., William A., Detrick B., Hooks J.J. Regulation of VEGF expression in human retinal cells by cytokines: implications for the role of inflammation in age-related macular degeneration. J Cell Physiol, 2012; 227: 116–126.
5. Witmer AN, Vrensen GF, Van noorden CJ, Schlingemann RO. Vascular endothelial growth

factors and angiogenesis in eye disease. Prog Retin Eye Res., 2003; 22(1): 1-29.
6. Spilsbury K, Garrett KL, Shen WY, Constable IJ, Rakoczy PE. Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. Am J Pathol, 2000; 157(1): 135-44.
7. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci., 2003; 44(7): 3186-93.
8. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol, 2008; 92(5): 667-8.
9. Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs, 2009; 18(10): 1573-80.
10. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology, 2006; 113(3): 363-372.e5.
11. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare fee-for-service part B claims file. Am J Ophthalmol, 2011; 151(5): 887-895.e1.
12. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina (Philadelphia, Pa), 2006; 26(4): 383-90.
13. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age related macular degeneration. N Engl J Med, 2011; 364(20): 1897–908.
14. Jaffe GJ, Caprioli J. Optical coherence tomography to detect and manage retinal disease and glaucoma. Am J Ophthalmol, 2004; 137(1): 156-69.
15. T.J. Good, A.E. Kimura, N. Mandava, M.Y. Kahook. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents Br J Ophthalmol, 2011; 95(8): 1111–1114.
16. Ron A. Adelman, Qi Zheng, and Hylton R. Mayer. Journal of Ocular Pharmacology and Therapeutics. February, 2010, 26(1): 105-110.
17. Cho H, Shah, CP, Weber M, Heier J. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. BR J Ophthalmo, 2013; 97(8): 1032-1035.
18. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russel SR, Mahajan VB. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. Am J Ophthalmol, 2013; 156(1): 15-22.
19. Q.V. Hoang, L.S. Mendonca, K.E. Della Torre, J.J. Jung, A.J. Tsuang, K.B. Freund Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections Ophthalmology, 2012; 119(2): 321–326.
20. J.E. Kim, A.V. Mantravadi, E.Y. Hur, D.J. Covert Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents Am J Ophthalmol, 2008; 146 (6): 930–934.