Double-Dose Ranibizumab for Eyes with Refractory Exudative Age-Related Macular Degeneration

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Abstract: In this retrospective chart review of the 10 eyes (8 subjects) with exudative age-related macular degeneration that had persistent macular fluid on spectral-domain optical coherence tomography (SD-OCT) [after at least 3 monthly intravitreal ranibizumab (0.5mg) or bevacizumab (1.25mg)], central macular thickness was significantly lower after 2 monthly double-dose intravitreal ranibizumab injections (0.1mg, DDR) (324 ± 77µm at baseline vs 248 ± 50µm, P=0.02).

Seven of 10 eyes that received DDR had some qualitative anatomic improvement on SD-OCT with the first 2 DDR, but no further OCT improvements were noted thereafter with additional DDR. The DDR treatment effect was transient in 3 of 7 eyes despite sustained DDR treatment.

Best corrected visual acuity remained stable in 7 of 10 eyes over the initial period of DDR (first 2-3 injections), 2 eyes improved ≥ 2 lines and 1 eye had ≥ 2 lines of worsening. The improvement in BCVA did not correlate with improvement noted on SD-OCT.

Paracentesis was performed frequently for acute intraocular pressure elevation or as prophylaxis in eyes receiving DDR due to the higher volume injected intravitreally but no other ocular or systemic adverse effect was noted with DDR.

Keywords: Age related macular degeneration, pharmacology, ranibizumab, retina, tachyphylaxis, tolerance, non-responder.

INTRODUCTION

The targeting of vascular endothelial growth factor (VEGF) has significantly shifted the treatment paradigm for exudative age related macular degeneration (eAMD). The principle goals of anti-VEGF therapy include arresting growth of choroidal neovascularization and minimizing complications of the neovascular complex which may lead to vision loss such as macular hemorrhage, macular edema (ME) and sub-retinal fluid (SRF). Response to treatment can be gauged by clinical examination and anatomic improvement on optical coherence tomography (OCT). The goal of anti-VEGF therapy is to stabilize and/or improve vision. The MARINA study showed that 33.5% of subjects in the study receiving 0.5 mg ranibizumab monthly demonstrated improvement of visual acuity of 15 letters or more while 95% of the subjects lost less than 15 letters [1]. The exact incidence of eyes that are unresponsive or become refractory to anti-VEGF therapy is not known but 2% and 10% rates of tachyphylaxis have been reported in eyes following ranibizumab and bevacizumab therapy for eAMD, respectively [2-4]. There has been some debate in the literature regarding the terminology of non-responders. Although some have advocated for differentiating between tolerance and tachyphylaxis [4], others feel that resistance is a more appropriate description of the phenomena of non-response [5].

Although anti-VEGF therapy has dramatically improved the visual prognosis of eyes with eAMD, not all eyes have full anatomic resolution of macular edema or subretinal fluid on OCT with standard dose anti-VEGF therapy (ranibizumab 0.5mg or bevacizumab 1.25mg) monotherapy. Combining anti-VEGF therapy with intravitreal steroids shows some promise for eyes not fully responding to standard dose anti-VEGF monotherapy [6]. However, intravitreal steroid therapy can increase the incidence of cataract and glaucoma in these eyes.

Using a higher dose of anti-VEGF therapy may increase the efficacy of these drugs in treatment eAMD. Modarres *et al*. reported that bevacizumab (2.50 mg) had comparable efficacy to standard 1.25 mg dosing regiments in the treatment of primary eAMD [7]. Rosenfeld *et al*. examined the tolerability of higher dose ranibuizumab, up to 2.0 mg, and found that an incremental dose escalation strategy was well tolerated with a 40% rate of improvement in visual acuity that was similar to standard dosing regimens [8]. Among the four patients in a case series by Forooghian *et al* who were tried on 2.50 mg bevacizumab after tachyphylaxis to 1.25 mg doses, only 1 had improvement which was transient in nature [3]. Afilbercept has recently been introduced for the

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treatment of eARMD and also has shown early promise in the treatment of those with persistent fluid [9].

Brown *et al*. have recently demonstrated improved acuity and anatomic response with 2.0 mg ranibuzumab injections in patients who demonstrated persistent disease despite standard dosing therapy [10]. This 2mg dose of ranibuzmab is delivered *via* a new drug formulation that is not yet FDA-approved. However, ranibizumab 1mg (double the standard dose) can be administered by doubling the volume of the currently FDA-approved formulation of ranibizumab. Given the recent interest in alternative dosing regiments for anti-VEGF therapy, in this study, we sought to investigate the success of double dose ranibizumab (DDR) in treating cases of eAMD refractory to standard dosing of ranibizumab and bevacizumab.

METHODS AND MATERIALS

We performed a retrospective chart review of eyes treated with DDR (1.0mg/0.1ml) for eAMD from October 2010 until November 2011. Inclusion criteria were DDR treatment for persistent macular fluid on SD-OCT in the study eye attributed to eAMD after at least 3 monthly intravitreal injections of ranibizumab 0.5mg or bevacizumb 1.25mg, absence of other concurrent retinal pathology that may affect vision, and within at least 3 month follow up after initiation of DDR. Exclusion criteria included history of use of photodynamic therapy, ocular surgery, or intravitreal steroid injection within the past six months prior to initiating DDR. Charts were reviewed until the introduction of alternative therapies (such as intravitreal steroids) or ocular surgery (including cataract). Results of OCT performed at each visit were reviewed (Cirrus, Zeiss); measurements of central macular thickness (CMT), i.e. central 1mm zone of the ETDRS macular thickness map, as well as the degree of SRF, ME, and pigement epithelial detachment (PED) height were examined as outcomes measures. Changes in CMT of >100 µm were considered clinically significant. Follow-up OCTs were also investigated for the presence of retinal pigment epithelial tears. Any documented changes in intraocular pressure (IOP) (usually by Tonopen) or need for paracentesis following intravitreal injection were noted. Best corrected Snellen visual acuity (BCVA) was recorded in the charts were noted during the study period for significant changes (≥ two lines of improvement of worsening). Student's t-test (two samples assuming unequal variance) was used for statistical analysis. A P value of <0.05 was considered statistically significant.

Institutional review board approval was obtained from the University of California, Davis Medical Center Office of Human Protection prior to initiation of this retrospective review.

RESULTS

The medical records of 18 eyes (14 subjects) with eAMD treated with DDR were reviewed with 10 eyes (8 subjects) meeting the inclusion criteria. A summary of all 10 eyes is provided in Table **1**. All patients were originally primarily treated with standard dose (0.5mg) ranibizumab. Three eyes had received other therapies for eAMD previously (i. e. bevacizumab, pegaptanib, proton beam irradiation) but none of these treatments were concurrent with DDR. DDR was initiated for persistent SRF or ME on SD-OCT in all 10 eyes. The patients received an average of 21.00 $\pm$ 14.13 standard dose anti-VEGF treatments (range 9 to 36 doses) over a course of 36.60 $\pm$ 13.30 months (range 19 to 58 months) prior to initiation of DDR. As the time of initiation of DDR, 9 eyes had PED, 7 eyes SRF, and 5 eyes had ME on SD-OCT. The average CMT was 324 $\pm$ 77.6 µm (range 210 to 441 µm). The total number of doses of DDR received ranged from 2 to 16 (average 5.3 $\pm$ 4.8) over a mean of 6.2 $\pm$ 4.9 months (range 2 to 16 months).

Seven of 10 eyes had some qualitative improvement anatomically on SD-OCT during the follow-up period reviewed in this study, 4 of which maintained the improvement after at least one additional DDR treatment. The improvement was transient in 3 of the 7 eyes. Average CMT among all eyes after the first injection was 280 $\pm$ 70.5 µm (range 196 to 436 µm) after the first DDR injection which was not statistically different from baseline (P=0.20). Average CMT after the second DDR was 248.6 $\pm$ 50.1 µm (178 to 333 µm) which was significantly lower than baseline CMT prior to DDR (P=0.02). The average CMT after the third DDR was 294 $\pm$ 62.8 µm (range 210 to 401 µm, P=0.23) which was not significantly different from baseline. In all but two eyes the second and third dose of DDR was delivered monthly and sequentially (see Table **1** for details). One patient received an interval dose of standard dose therapy ant-VEGF therapy per physician discretion between the first and second dose of DDR while another did not receive any therapy for a 3 month interval after her first DDR due to insurance issues.

Four of 7 eyes demonstrated some further anatomic improvement on SD-OCT between the first and second injection of DDR (decrease in SRF and PED in one

Table 1: Summary of Subjects Receiving Double Dose Ranibizumab (DDR)

Subject	Age	Prior therapy	Baseline BCVA and CMT, anatomic changes on SD-OCT	1 month s/p DDR #1: BCVA and CMT & anatomic changes on SD-OCT	1 month s/p DDR #2: BCVA and CMT & anatomic changes on SD-OCT	1 month s/p DDR #3: BCVA and CMT & anatomic changes on SD-OCT	Notes.
1 (OD)	78	9 (ranibizumab) over 40 months	20/100, 266, + SRF, PED, ME.	20/100, 277, no anatomic improvement	20/80, 267, no anatomic improvement	20/60, 277, no anatomic improvement	IVT given after 3rd DDR.
1 (OS)	78	8 (ranibizumab) over 40 months	20/100, 306,+SRF, PED, ME, intraretinal edema	20/100, 238, no improvement	20/100, 283, no improvement	20/70, 298, no improvement	8 total doses of DDR (over 9 months) without significant improvement on OCT . Final BCVA: 20/100 Final CMT: 240
2 OD*	86	9 (ranibizumab) over 19 months	20/40, 210, mild SRF	20/50, 244, no improvement	20/50,218, no improvement	N/A	Stable vision and OCT after second dose; no additional DDR given.
2 OS*	86	9 (ranibizumab) over 19 months	20/50, 288, + SRF and PED	20/50, 210, **improved SRF and PED**	20/60, 213, unchanged from baseline	20/50, 210, unchanged from baseline	Stable vision and OCT after third dose; no additional DDR given.
3	76	20 (ranibizumab) over 23 months	20/50, 282, +SRF and large PED	20/50, 288, **improvement in SRF**, no change in PED	20/50, 289 **continued improvement in SRF**, no change in PED	20/60, 258, **minimal improvement of SRF from baseline**, no change in PED	Switched back to standard dose ranibizumab at 3 doses given lack of significant improvement on DDR
4	79	**20 (ranibizumab), 4 (bevacizumab) over 32months**	20/50, 370, + PED and ME	20/200, 351, no improvement	20/80, 333, **slight improvement in ME,** no change PED	20/150, 401, ME return to baseline, no change PED	Given IVT after 3rd DDR given lack of improvement.
5	86	12 (Pegaptanib), 34 (ranibizumab) over 49 months	20/60, 424, + PED and ME	20/60, **291**, stable PED, **improved ME**	20/60, **225,** stable PED, **resolved ME**	20/60, **242**, stale PED, **resolved ME**	Returned to standard dose ranibizumab after 3rd DDR given improvement in ME
6**	86	36 (ranibizumab) over 38 months, Proton beam therapy 2 years prior.	20/400 (ETDRS), 223, mild SRF and +PED	20/640 (ETDRS), 196, no improvement	20/400 (ETDRS) 178, **trace SRF, decreased PED**, resolution of ME that developed after interval SDL.	20/400, 303**, trace SRF**, return of PED and ME to baseline.	Trial of bevacizumab after 9 treatments of DDR with a period of observation thereafter followed by a return to DDR after a hemorrhage into PED. Received a total of 16 DDR before electing to return to standard dose ranibizumab due to poor visual potential and response. 17 months of DDR. Final BCVA: 20/400 Final CMT: 194

(Table 1). Continued.

Subject	Age	Prior therapy	Baseline BCVA and CMT, anatomic changes on SD-OCT	1 month s/p DDR #1: BCVA and CMT & anatomic changes on SD-OCT	1 month s/p DDR #2: BCVA and CMT & anatomic changes on SD-OCT	1 month s/p DDR #3: BCVA and CMT & anatomic changes on SD-OCT	Notes.
7	85	12 (ranibizumab) over 48 months	20/40, 331, +SRF, + PED	20/40, 269, **improved SRF**, stable PED	20/40, 287, **SRF improved from baseline worse than after first dose**, stable PED	N/A	Patient elected to stop DDR due to eye pain following injections (required anterior chamber paracenthesis after both injections)
8	80	3 (pegaptanib), 2 (bevacizumab), 32 (ranibizumab) over 58 months, prior history of remote triple therapy and IVK	20/80, 441, + ME	20/125, 436, unchanged	20/100, **193, decreased ME**	20/100, 363, worsened ME	Received 10 total doses of DDR on prn basis (over 12 months) with occasional improvement in ME after most injections. Eventually switched to aflibercept Final BCVA: 20/200 Final CMT: 302
Averages	82	21.00+/-14.13	324.1+/-77.6	280+/-70.5 (P=0.2)	248.6+/-50.1 (P=0.02)	294+/-62.8 (P=0.23)	5.3+/-4.6 total injections of DDR

All visual acuity are best corrected Snellen visual acuity unless otherwise specified.
ME=macular edema, PED=pigment epithelial detachment, SRF=subretinal fluid, IVT=intravitreal triamcinolone.
Significant anatomic changes **bolded.**
*Subject with 3 month interval between first and second DDR doses due to insurance issues. Improvement in left eye was seen at 6 week follow up but injection was not given. At follow up 2 months later (when second DDR provided) anatomic markers had returned to baseline.
** Interval of standard dose therapy between first and second DDR injections.

eye, decrease in SRF in two eyes, and decrease in ME and CMT decrease >100 microns in one eye) with the latter three eyes listed maintaining their improvement after the next treatment of DDR. None of the seven eyes treated with more than two consecutive monthly injections of DDR demonstrated new changes after the second monthly dose.

BCVA was also monitored. BCVA remained stable in most eyes during the initial three DDR injections. Two eyes demonstrated ≥ two lines of improvement after initiating DDR and one eye lost ≥ two lines of BCVA. Of note, the two eyes that demonstrated improvement of ≥ two lines of vision did not have significant anatomic improvement on SD-OCT.

Of the 53 total injections of DDR administered among our 10 study eyes, anterior chamber paracenthesis was preformed 42% of DDR injections either as a result of acute elevation of IOP and/or decrease in vision or as prophylaxis for history of acute elevation of IOP and vision loss from prior DDR injection. For purposes of comparison, the 5 regular dose anti-VEGF injections administered prior to the initiation of DDR were reviewed for each study eye (for a total of 50 injections) and none required post-injection anterior chamber paracenthesis. Pre-injection IOP did not change from baseline (mean 14.7 $\pm$ 4.2 mm Hg, range 8 to 22 mm Hg) at one month after starting DDR (mean 13.8 $\pm$ 2.5mm Hg, range 10 to 17mm Hg), two months after starting DDR (mean 14.1+/-3.5mm Hg, range 8 to 10) or three months after starting DDR (mean 12.8 $\pm$ 3.9mm Hg, range 9 to 20mm Hg). The difference between baseline IOP and the final follow up IOPs was not statistically significant. There were no other ocular or systemic adverse event noted.

DISCUSSIONS

The approach to patients who have become resistant and/or not fully responsive to standard dose anti-VEGF therapy presents a clinical challenge. In our retrospective study, we studied the effect of using DDR in eyes with eAMD previously treated with regular dose ranibuzumab and/or becacizumab monthly without full anatomic response, i.e. persistent macular fluid on OCT. Although in theory a difference exists between tachyphylaxis and tolerance, in clinical practice it is

often difficult to differentiate the two [4]. Those who are exhibiting tolerance would be expected to respond to higher drug doses (as in this study) or shorter intervals. The challenge presented by non-responders has been gaining increasing attention as new pharmacologic modalities are being introduced for the treatment of eARMD and will require greater creativity in the management of these patients.

We have found that the majority of subjects (7 of 10) treated with DDR in our study had some anatomic improvement on SD-OCT, although this improvement was transient in 3 of these eyes despite sequential dose of DDR. All eyes that demonstrated improvement on SD-OCT did so after first two doses of DDR. Central macular thickness demonstrated a statistically significant decrease following the second DDR injection that the decrease was smaller and not significant after the third dose of DDR. No new improvements of anatomic parameters were seen following the second injection.

We also studied to the effect on DDR on BCVA. Over the initial first three monthly injections of DDR BCVA remained stable in 7 of 10 eyes with two eyes gaining ≥ two lines of vision and one eye loosing ≥ two lines of vision; however, the eyes demonstrating improved vision did so despite a lack of anatomic improvement on SD-OCT. Of three eyes that had more than 3 injections, vision remained stable in two eyes. One of the eyes with long term DDR had gradual decline in vision from 20/80 to a final vision of 20/200. Although 2.0 mg ranibizumab has been found to improve vascularized PED in treatment naïve patients when compared to 0.5 mg ranibizumab [10], we found that only two of nine eyes with PED at baseline had improvement in PED size with DDR. This improvement was noted after the first dose of DDR and not sustained.

We also reviewed how well the eyes tolerated the increase in volume injected with DDR. Anterior chamber paracenthesis was employed after 42% of all injections as prophylaxis or due to elevated IOP with acute decrease in vision immediately following DDR. Compared to standard dose intravitreal ranibizumab (0.05ml=0.5mg) or bevacizumab (0.05ml1.25mg), DDR exposes the vitreous to a larger drug volume (0.1ml=0.1mg). The higher volume of DDR undoubtedly increases the risk of acute intraocular pressure spikes following injections and this should be of particular concern in patients with glaucoma; however, none of the eyes had any acute permanent loss of vision as a complication of this event and none of the eyes has sustained elevations in IOP that required chronic treatment. Additionally, IOP was checked often immediately after injection and it is foreseeable that the pressure would have decreased on its own after a brief (~30 minute) interval. Short term variations in IOP following administration of standard dose bevacizumab and ranibizumab have been investigated and although significant rises in intraocular pressure have been noted acutely following injection these typically resolve within minutes without intervention [11-13]. Choi *et al*. found that 5.5% of patients had sustained increases in intraocular over long term follow-up when treated with standard anti-VEGF therapy [14]. Data regarding effects of higher volume intravitreal injections (0.1ml) are limited, but Kotliar *et al*. found that immediately following 0.1 ml intravitreal triamcinolone, IOP was elevated by an average of 40.6+/-12.1 mmHg compared to initial pressure ($P<0.001$) and eyes with shorter axial length had higher immediate post-injection IOP elevations ($p<0.05$) [15]. Understanding effect that changes in intraocular volume has on intraocular pressure remains an active area of research. Newer models provide insights based on living human subjects, as opposed to Friedenwald's equation which was based on measurements on cadaver eyes. Silver and Geyer's equation gave larger volume increment for a given increment of pressure and Dastiridou *et al*. found a nonlinear pressure-volume relationship with increase rigidity at higher intraocular pressure levels [16, 17].

There are several limitations to this study. First of all, it is a small restrospective case series. Thus, the number of injections of regular dose anti-VEGF therapy applied before changing therapy to DDR was variable. In addition, the number and frequency of DDR administered also varied. Nonetheless, this study is the first to study the effect of DDR in eyes with eAMD that have not fully responded anatomically to regular dose anti-VEGF therapy and provides some insights regarding efficacy of this therapy for eAMD eyes with macular fluid resistant with standard dose of anti-VEGF.

In summary, we have found that some eyes with eAMD without a full anatomic response with standard dose anti-VEGF therapy will tolerate DDR with some potential further anatomic improvement on SD-OCT although the effect may be transient. Based on our study, the eyes that do not show anatomic response after the first two consecutive doses of DDR may be less likely to show response to continued use of DDR

but further studies may be needed to confirm our impressions. In such eyes resistant to DDR, alternative treatment strategies such as combination therapy or newer anti-VEGF therapy may be considered. The risk of acute, recurrent transient increases of intraocular pressure need to be weighed against the benefit of DDR therapy using this higher volume of drug. A larger prospective randomized study will be needed to validate our impressions and to better identify eyes that may respond to higher dose anti-VEGF therapy.

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CONFLICTS OF INTEREST

Drs. Morse and Park have received grant support and honoraria for consulting and lecturing on behalf of Genentech, Inc, manufacturer of ranibizumab. None of the other authors have conflict of interest.

REFERENCES

[1] Rosenfeld PJ, Brown DM, Heier JS, *et al*. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006; 355(14): 1419-31. http://dx.doi.org/10.1056/NEJMoa054481

[2] Eghoj MS, Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2012; 96(1): 21-3. http://dx.doi.org/10.1136/bjo.2011.203893

[3] Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina 2009; 29(6): 723-31. http://dx.doi.org/10.1097/IAE.0b013e3181a2c1c3

[4] Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? Br J Ophthalmol 2012; 96(1): 1-2. http://dx.doi.org/10.1136/bjophthalmol-2011-301236

[5] Arjamaa O, Minn H. Resistance, not tachyphylaxis or tolerance. Br J Ophthalmol 2012; Epub 2012/04/19.

[6] Tao Y, Jonas JB. Intravitreal bevacizumab combined with intravitreal triamcinolone for therapy-resistant exudative age-related macular degeneration. J Ocul Pharmacol Ther 2010; 26(2): 207-12. http://dx.doi.org/10.1089/jop.2009.0131

[7] Modarres M, Naseripour M, Falavarjani KG, Nikeghbali A, Hashemi M, Parvaresh MM. Intravitreal injection of 2.5 mg versus 1.25 mg bevacizumab (Avastin) for treatment of CNV associated with AMD. Retina 2009; 29(3): 319-24. http://dx.doi.org/10.1097/IAE.0b013e318198148e

[8] Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. Ophthalmology 2006; 113(4): 623 e1.

[9] Cho H, Shah CP, Weber M, Heier JS. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. Br J Ophthalmol 2013; Epub 2013/06/15.

[10] Brown DM, Chen E, Mariani A, Major JC, Jr. Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration-primary end point. Ophthalmology 2013; 120(2): 349-54. http://dx.doi.org/10.1016/j.ophtha.2012.08.008

[11] Mojica G, Hariprasad SM, Jager RD, Mieler WF. Short-term intraocular pressure trends following intravitreal injections of ranibizumab (Lucentis) for the treatment of wet age-related macular degeneration. Br J Ophthalmol 2008; 92(4): 584. Epub 2008/03/29.

[12] Sharei V, Hohn F, Kohler T, Hattenbach LO, Mirshahi A. Course of intraocular pressure after intravitreal injection of 0.05 mL ranibizumab (Lucentis). Eur J Ophthalmol 2010; 20(1): 174-9.

[13] Falkenstein IA, Cheng L, Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). Retina 2007; 27(8): 1044-7. http://dx.doi.org/10.1097/IAE.0b013e3180592ba6

[14] Choi DY, Ortube MC, McCannel CA, *et al*. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. Retina 2011; 31(6): 1028-35. http://dx.doi.org/10.1097/IAE.0b013e318217ffde

[15] Kotliar K, Maier M, Bauer S, Feucht N, Lohmann C, Lanzl I. Effect of intravitreal injections and volume changes on intraocular pressure: clinical results and biomechanical model. Acta Ophthalmol Scand 2007; 85(7): 777-81. http://dx.doi.org/10.1111/j.1600-0420.2007.00939.x

[16] Silver DM, Geyer O. Pressure-volume relation for the living human eye. Curr Eye Res 2000; 20 (2): 115-20. http://dx.doi.org/10.1076/0271-3683(200002)2021-DFT115

[17] Dastiridou AI, Ginis HS, De Brouwere D, *et al.* Ocular rigidity, ocular pulse amplitude, and pulsatile ocular blood flow: the effect of intraocular pressure. Invest Ophthalmol Vis Sci 2009; 50(12): 5718-22. http://dx.doi.org/10.1167/iovs.09-3760

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