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Management of Macular Edema Secondary to Branch Retinal Vein Occlusion in an Eye with Prior Vitrectomy and Lensectomy

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Key Words
Branch retinal vein occlusion · Macular edema · Intravitreal injections · Ranibizumab · Bevacizumab · Aflibercept

Abstract
An 82-year-old male with a history of pars plana vitrectomy and lensectomy 6 years before presented with symptomatic macular edema (ME) from superotemporal branch retinal vein occlusion. He was sequentially treated with intravitreal agents, bevacizumab (IVB) 1.25 mg, ranibizumab (RBZ) 0.5, 1.0 and 2 mg, triamcinolone acetonide (IVTA) 1 mg, and aflibercept (IAI) 2 mg. The therapeutic benefit from IVB and RBZ was short-lived – although a decrease in ME and improvement in visual acuity were observed, a completely dry macula was not achieved even after 1 week of treatment with any dose of these agents, including 2.0 mg RBZ. IVTA achieved a dry macula for 7 weeks. IAI yielded a dry macula and improved vision with monthly injections. However, regression of the therapeutic benefit was noted at 5 weeks after the IAI injection. A stronger affinity of IAI to vascular endothelial growth factor (VEGF) compared to other anti-VEGF agents is likely responsible for the observed therapeutic effect for 1 month, making this agent preferable for the management of symptomatic ME in a vitrectomized eye.

Introduction

Vascular endothelial growth factor (VEGF) inhibitors such as intravitreal bevacizumab (IVB) and ranibizumab (RBZ), as well as triamcinolone acetonide (IVTA) are commonly

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employed in the management of center-involved macular edema (ME) secondary to branch retinal vein occlusion (BRVO) [1, 2]. However, the role of these agents in previously vitrectomized eyes presenting with ME from BRVO is not well established. IVB has previously been shown to be ineffective in eyes with diabetic ME after pars plana vitrectomy [3]. Experimental studies have shown that both lensectomy and vitrectomy procedures decrease the half-life of IVB in rabbit eyes [4]. Aflibercept (IAI) may exhibit a longer duration of the therapeutic effect primarily due to its stronger affinity for VEGF [5]. In the management of neovascular age-related macular degeneration, IAI administered every 2 months after the first 3 monthly loading doses was equivalent to monthly RBZ injections regarding visual outcomes, although a slight increase in central subfield thickness (CST) was noted 1 month after IAI injection [6]. Herein, we report our experience in the management of a patient with previous lensectomy and vitrectomy who presented with a recent onset of BRVO with center-involved ME.

Case Report

An 82-year-old male with a previous ocular history of pars plana vitrectomy, lensectomy, placement of an anterior chamber intraocular lens for retained cataract fragments in his left eye 6 years before, and medically controlled primary open-angle glaucoma presented with a 1-week history of decreased vision in his left eye secondary to center-involved ME from a superotemporal BRVO (fig. 1a–c). His relevant medical history included hypertension and coronary artery disease. His Snellen visual acuity (VA) had decreased to 20/100 from a baseline of 20/25, and spectral domain OCT confirmed significant ME (fig. 2a). Several interventions with IVB 1.25 mg, RBZ 0.5, 1.0 and 2.0 mg, IVTA (Triesence®; Alcon, Fort Worth, Tex., USA) 1 mg and IAI 2 mg were performed. Macular volume, CST, cube average thickness (as measured by Zeiss Cirrus® OCT machine; Carl Zeiss Meditec Inc., Dublin, Calif., USA), pinhole Snellen VA, and therapeutic interventions are summarized in table 1.

One week after IVB administration, CST was 488 μm with intraretinal cystic changes (fig. 2b) and deterioration at 2 weeks with loss of effect at 4 weeks. Following RBZ 1.0 mg, CST was 343 μm at 1 week after injection (fig. 2c). One month of therapeutic effect was not observed with either standard dose or even high dose (1 or 2 mg) RBZ. VA varied from 20/30 (1 week after RBZ 1 mg) to 20/200 (4 weeks after IVB).

A dry fovea was observed after a 1-mg injection of IVTA, and remained for approximately 7 weeks (fig. 2d), with a loss of therapeutic effect at 10 weeks. The patient has advanced primary open-angle glaucoma with a vertical cup to disk ratio of 0.8 with inferior notch and corresponding superior arcuate field defect. The intraocular pressure rose to 17 mm Hg from the baseline of 12 mm Hg at 2 weeks after IVTA injection and was managed medically. He was maintained with alternating injections of RBZ and IVB every 2–3 weeks for the next 5 months. The patient began receiving monthly injections of IAI in November 2013 (CST 677 μm, VA 20/100). After 8 monthly injections of IAI between November 2013 and June 2014, his VA improved to 20/40, and OCT showed a dry fovea 1 month after a previous IAI injection with CST 289 μm (fig. 2e). However, 5 weeks after IAI injection, the patient was noted to have increased foveal thickness of 543 μm associated with a decrease in VA to 20/80. Chronological VA and CST values during the first year of treatment are shown in fig. 3.

Discussion

Intravitreal injections of anti-VEGF agents and IVTA are commonly administered agents in the treatment of a variety of retinal conditions, including neovascular age-related macular degeneration and ME secondary to retinal vein occlusion and diabetic retinopathy. However, very little information is known regarding the efficacy of these agents in previously vitrectomized eyes. It is possible that vitreous humor acts as a reservoir for intravitreally administered drugs, and its absence allows for rapid clearance of these pharmacological agents from the eye. Yanyali et al. [3] found no benefit from monthly IVB injections in previously vitrectomized eyes with diabetic ME. Since patients were not evaluated earlier than 1 month following intravitreal injections, it is not known whether the apparent lack of benefit was due to inefficacy of IVB or the reduced duration of the therapeutic effect resulting from increased clearance of the drug following vitrectomy.

Christoforidis et al. [4] determined the half-life of IVB and RBZ to be respectively 4.2 and 2.8 days in unoperated rabbit eyes, but that these values decreased to respectively 2.30 and 2.13 days following vitrectomy, and 2.08 and 1.79 days after lensectomy. In primate eyes, the half-life of IVB in the vitrectomized eyes decreased by 54% to a mean of 1.5 days from 2.8 in the nonvitrectomized group [7].

In human eyes, Moisseiev et al. [8] determined that the half-life of IVB ranged from 2.5 to 7.3 (mean 4.9) days in unoperated eyes, but that this value decreased to 0.66 days after vitrectomy. As shown by Meyer et al. [9], doubling the dose of IVB prolonged the effective duration of the therapeutic effect only by one half-life.

Although the macula was not completely dry, we observed a significant reduction in CST accompanied by an improvement in VA 1 week after RBZ. One week after IVB, VA improved to 20/40 from the baseline of 20/200, but CST was slightly worse at 488 μm compared to 462 μm (table 1). The most likely explanation for this apparently paradoxical observation is the delay between OCT recurrence of fluid and deterioration in vision, a well-known phenomenon both in neovascular age-related macular degeneration and retinal vein occlusion [10, 11]. The therapeutic effect of both IVB and RZB was further diminished at 2 weeks and beyond. Moreover, we were unable to significantly prolong the duration of the therapeutic effect by doubling or quadrupling the dose of RBZ. Previous studies in neovascular macular degeneration have shown that more frequent dosing, rather than administration of a higher dose, might be a more effective strategy for patients poorly responsive to standard therapeutic regimen of anti-VEGF agents [12].

We were able to observe a fluid-free macula for approximately 7 weeks after 1 mg IVTA (Triesence®; Alcon). As shown by the SCORE Study [2], both 1 and 4 mg doses of IVTA (Trivaris®, Allergan, Inc., Irvine, Calif., USA, not available commercially) were equally effective in the management of ME secondary to BRVO, but the 1 mg dose was significantly safer. Since patients received injections every 4 months in the SCORE Study, and our patient had complete regression of the therapeutic effect by week 10, it is apparent that effective duration of the therapeutic effect of IVTA is also significantly decreased in a vitrectomized eye. In rabbit eyes, Chin et al. [13] observed that intravitreal concentration of TA decreased 1.5 times faster in the vitrectomized eyes than in the nonvitrectomized group, and that the mean half-life of TA in vitreous was 2.89 days in the nonvitrectomized group and 1.57 days in the vitrectomized group. They calculated that the effect duration of IVTA was expected to be about 44 days for the vitrectomized group and about 66 days for the nonvitrectomized group. In a human vitrectomized eye, Beer et al. [14] calculated the half-life of IVTA to be 3.2 days compared to a range of 14.2–26.4 days (mean 18.6) in the nonvitrectomized group. We chose not to repeat IVTA due to the patient's advanced glaucoma and risk of elevation of

intraocular pressure following IVTA injection. Intravitreal 0.7 mg dexamethasone implant (Ozurdex®; Allergan, Inc.) gradually releases dexamethasone over a period of several months. Since the rate of the release of active drug is not affected by prior vitrectomy, Ozurdex may provide a similar duration of the therapeutic effect in both vitrectomized and nonvitrectomized eyes. The CHAMPLAIN Study found Ozurdex to be effective for up to 26 weeks in the management of diabetic ME in vitrectomized eyes [15]. However, its use was contraindicated in our patient due to absence of posterior capsule, predisposing the eye for migration of implant into the anterior chamber that can lead to permanent corneal damage [16].

In contrast to IVB and RZB, IAI was effective for approximately 1 month, with loss of the therapeutic effect at 5 weeks. IAI is a fusion protein consisting of portions of human VEGF receptors 1 and 2 fused to the Fc fragment of human IgG1. The molecular weight of IAI is 115 kDa compared to 48 kDa for RZB and 149 kDa for IVB. In rabbit eyes, Christoforidis et al. [17] calculated the half-life of IAI to be 4.58 days compared to 2.8 days for RZB and 4.2 days for IVB. Although no data on the pharmacokinetics of IAI in vitrectomized eyes is available, based on the molecular weight and half-life data of these agents in nonvitrectomized eyes, clearance of IAI from the vitreous cavity is expected to be intermediate between RZB and IVB. However, the binding affinity of IAI to VEGF is 140 times that of RZB, which in turn has a 5–20 times stronger binding affinity to VEGF compared to IVB. The anti-VEGF activity of IAI at 28 days following a 2.0-mg injection has been estimated to be 84 times that achieved with RZB 0.5 mg every 2 weeks [12]. Therefore, increased binding affinity of IAI to VEGF, rather than increased half-life, appears to be the explanation for longer duration of the therapeutic effect in our patient. These findings suggest that IAI might be superior to other anti-VEGF agents in the management of symptomatic ME caused by BRVO in vitrectomized eyes.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY: Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:1594–1602.

2 Scott IU, Ip MS, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M, Chan CK, Gonzalez VH, Singerman LJ, Tolentino M; SCORE Study Research Group: A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol 2009;127:1115–1128.

3 Yanyali A, Aytug B, Horozoglu F, Nohutcu AF: Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes: Am J Ophthalmol 2007;144:124–126.

4 Christoforidis JB, Williams MM, Wang J, Jiang A, Pratt C, Abdel-Rasoul M, Hinkle GH, Knopp MV: Anatomic and pharmacokinetic properties of intravitreal bevacizumab and ranibizumab after vitrectomy and lensectomy. Retina 2013;33:946–952.

5 Stewart MW, Rosenfeld PJ: Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–668.

6 Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups: Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–2548.

7 Kakinoki M, Sawada O, Sawada T, Saishin Y, Kawamura H, Ohji M: Effect of vitrectomy on aqueous VEGF concentration and pharmacokinetics of bevacizumab in macaque monkeys. Invest Ophthalmol Vis Sci 2012;53:5877–5880.
8 Moisseiev E, Waisbourd M, Ben-Artsi E, Levinger E, Barak A, Daniels T, Csaky K, Loewenstein A, Barequet IS: Pharmacokinetics of bevacizumab after topical and intravitreal administration in human eyes. Graefes Arch Clin Exp Ophthalmol 2014;252:331–337.
9 Meyer CH, Krohne TU, Holz FG: Intraocular pharmacokinetics after a single intravitreal injection of 1.5 mg versus 3.0 mg of bevacizumab in humans. Retina 2011;31:1877–1884.
10 Muether PS, Hermann MM, Viebahn U, Kirchhof B, Fauser S: Vascular endothelial growth factor in patients with exudative age-related macular degeneration treated with ranibizumab. Ophthalmology 2012;119:2082–2086.
11 Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM; OZURDEX GENEVA Study Group: Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134–1146.
12 Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF: Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). Retina 2012;32:434–457.
13 Chin HS, Park TS, Moon YS, Oh JH: Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. Retina 2005;25:556–560.
14 Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M: Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology 2003;110:681–686.
15 Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, Liu CC, Lou J, Whitcup SM; Ozurdex CHAMPLAIN Study Group: Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915–923.
16 Khurana RN, Appa SN, McCannel CA, Elman MJ, Wittenberg SE, Parks DJ, Ahmad S, Yeh S: Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. Ophthalmology 2014;121:67–71.
17 Christoforidis JB, Williams MM, Kothandaraman S, Kumar K, Epitropoulos FJ, Knopp MV: Pharmacokinetic properties of intravitreal I-124-aflibercept in a rabbit model using PET/CT. Curr Eye Res 2012;37:1171–1174.

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Table 1. Snellen VA, macular volume, CST, average cube thickness and therapeutic interventions

Date	Snellen VA	CST, μm	Macular volume, mm^3	Cube average thickness, μm	Time since last intervention, days	Intervention
5/29/12	20/100	622	12	333		IVB 1.25 mg
7/3/12	20/200	462	13.3	369	35	IVB 1.25 mg
7/10/12	20/40	488	11.9	331	7	None
7/31/12	20/200	517	13.4	374	28	IVB 1.25 mg
8/14/12	20/80	479	12.2	338	14	IVB 1.25 mg
8/29/12	20/70	504	12.4	346	15	IVB 1.25 mg
9/11/12	20/40	402	12.3	341	13	RBZ 2 mg
10/11/12	20/80	698	13.5	375	30	IVB 1.25 mg
10/25/12	20/70	516	12.5	347	14	RBZ 0.5 mg
11/19/12	20/40	568	12.9	357	25	IVB 1.25 mg
12/14/12	20/100	732	14.0	389	25	RBZ 1 mg
12/21/12	20/30	343[a]	11.5	320	7	None
1/10/13	20/50	512	12.8	356	27	IVB 1.25 mg
1/31/13	20/60	446	12.8	356	21	IVTA 1 mg
2/15/13	20/50	297	10.9	303	15	None
3/18/13	20/50	280[b]	11	306	46	None
4/15/13	20/80	698	13.2	368	74	IVB 1.25 mg

[a] Intraretinal fluid on raster images. [b] Completely dry macula.

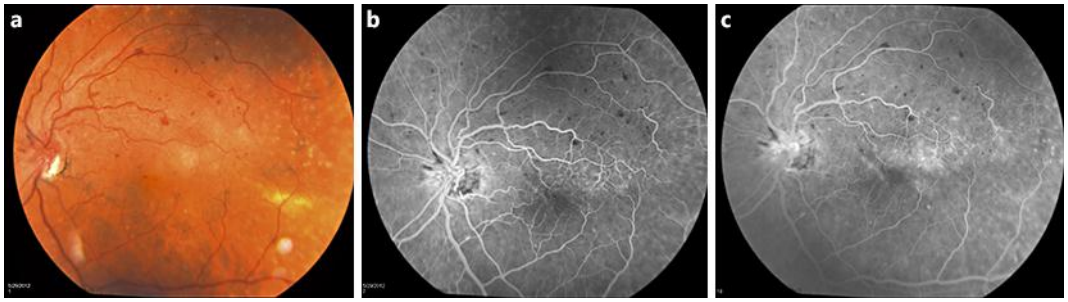

Fig. 1. **a–c** Color fundus photograph and fluorescein angiogram of the left eye at presentation. **a** Scattered hemorrhages in the superotemporal quadrant consistent with BRVO are seen. **b** Fluorescein angiogram of the left eye at 35 s showing dilated capillaries superior to the fovea and mild irregularity as well as enlargement of the foveal avascular zone. **c** Fluorescein angiogram of the left eye at 2 min showing leakage of the dye superior to the fovea and from the nerve. Staining of veins and mild perivenular leakage of dye are also noted. The blocked fluorescence corresponds to retinal hemorrhages in **b** and **c**.

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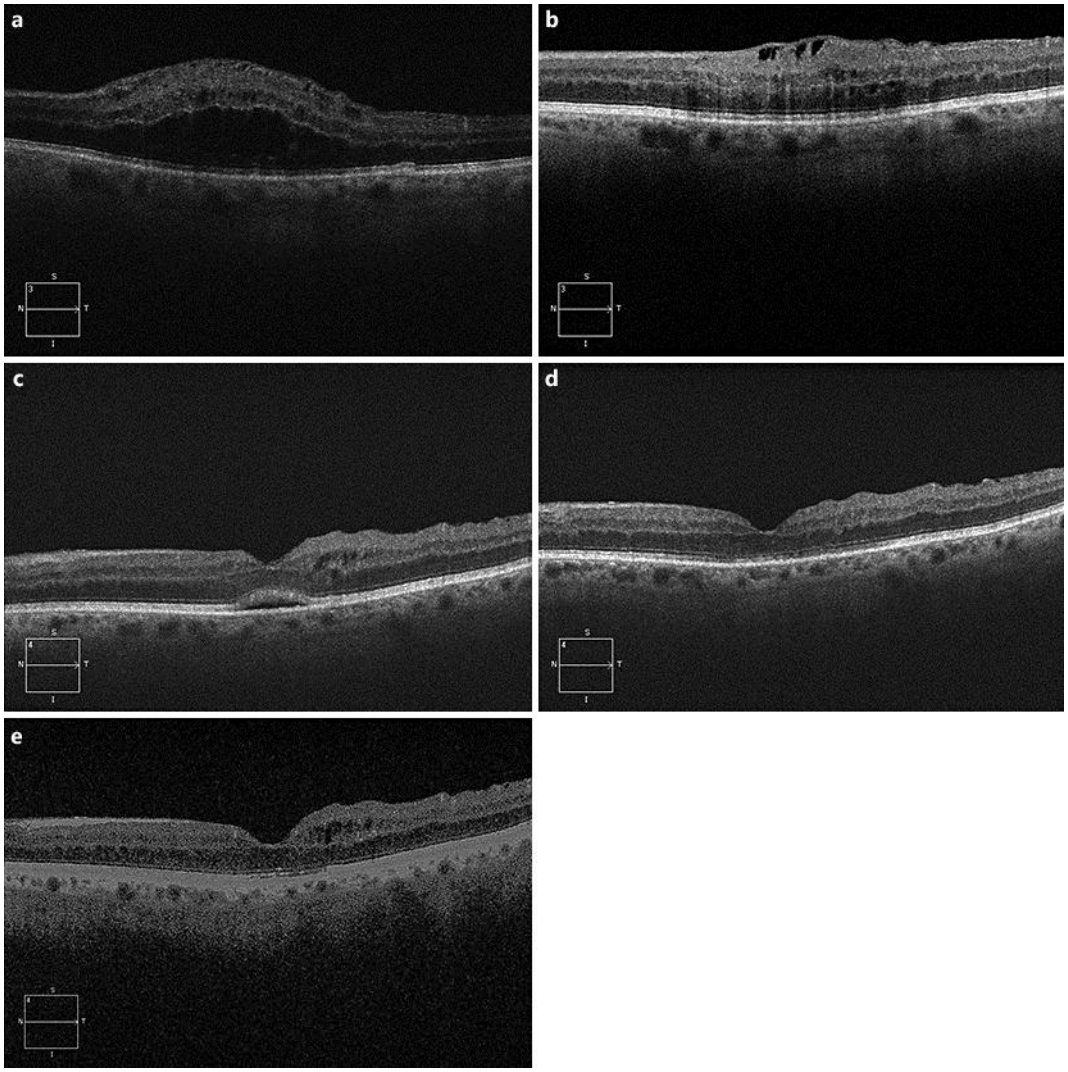

Fig. 2. **a–e** Horizontal spectral domain OCT image of the left eye. **a** At presentation, a marked intraretinal edema is seen (CST 622 μm). **b** One week after a 1.25-mg IVB injection, decreased intraretinal fluid is seen. CST improved to 488 μm. **c** One week after a 1-mg RBZ injection, mild subretinal and intraretinal fluid is seen (CST 343 μm). **d** Seven weeks after a 1-mg IVTA injection, a completely dry macula is seen (CST 280 μm). **e** At 1 month after a 2-mg IAI injection, the center of the fovea is dry (CST 289 μm). Mild intraretinal fluid is noted in the temporal to fovea.

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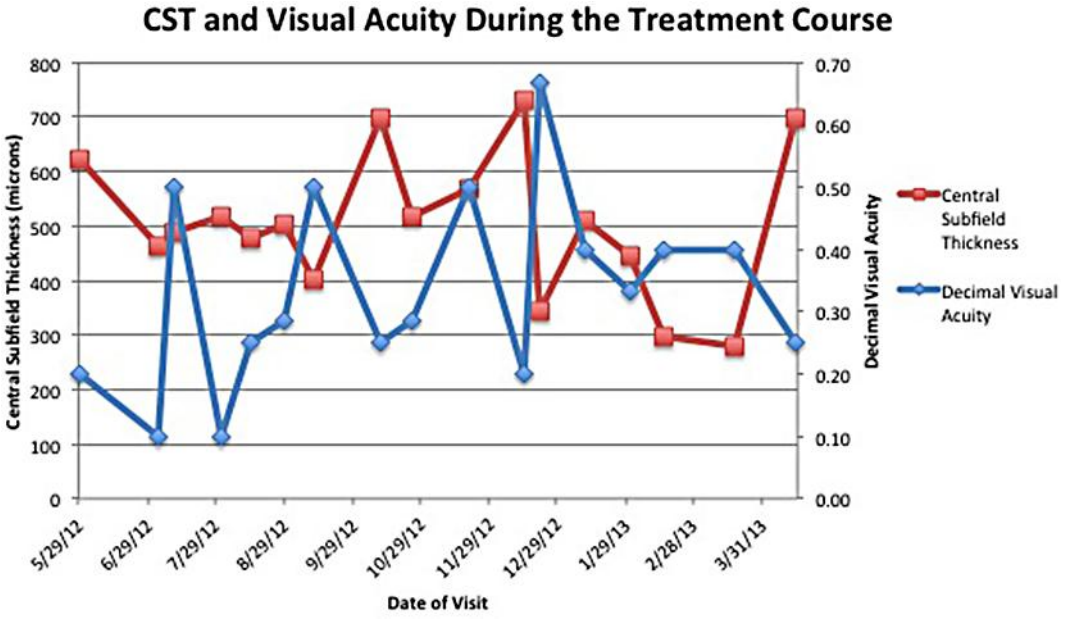

Fig. 3. CST and decimal VA during the first year of treatment.