ISSN: 2573-9573

Research Article

Journal of Ophthalmology & Clinical Research

Efficacy and Safety of Primary Intravitreal 2 mg Aflibercept for Cystoid Macular Edema after Phacoemulsification

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Submitted: 01 June 2018; **Accepted**: 08 June 2018; **Published**: 15 June 2018

Abstract

Purpose: *To evaluate the clinical efficacy and safety of primary intravitreal 2 mg aflibercept (Eylea) in patients with cystoid macular edema (CME) after phacoemulsification.*

Methods: *In this retrospective study, 13 eyes of 13 consecutive patients affected by CME after uncomplicated phacoemulsification administered at least one intravitreal injection of 2 mg aflibercept as a primary treatment were recruited. At baseline and follow-up visits, best-corrected visual acuity (BCVA) and central foveal thickness (CFT) were determined and ophthalmoscopic examination was performed.*

Results: *The mean follow-up period was 30 weeks (range 24-49 weeks). The mean duration of CME before treatment with aflibercept was 3.3 months (range 2-8 months). Mean baseline BCVA was 0.83 ± 0.28 logarithm of the minimum angle of resolution (logMAR) and it had improved to 0.45 ± 0.30 logMAR at the final follow-up ($p < 0.001$). Mean CFT at baseline was 465.5 ± 100.2 µm, and it had decreased significantly to 282.9 ± 63.1 µm at the final follow-up ($p < 0.001$). Four Patients (30.8%) required a second intravitreal injection, and 3 (23.1%) required a third injection. No significant systemic or ocular complications were observed.*

Conclusion: *Short-term results suggest that primary intravitreal aflibercept is effective and safe in eyes with macular edema associated with phacoemulsification. Treated patients exhibited a significant decrease in CFT and improvement in BCVA. Further prospective controlled studies including more subjects and longer follow-up periods are warranted, to evaluate the efficacy and safety of intravitreal aflibercept injection.*

Keywords: Cystoid macular edema, Eylea, Intravitreal aflibercept, Phacoemulsification, Pseudophakic

Introduction

Cystoid macular edema (CME) may cause reduced vision after cataract extraction surgery. It can be detected via fluorescein angiography after uncomplicated extracapsular and intracapsular cataract extraction in up to 30% and 60% of eyes, respectively. The incidence of clinical CME is much lower however, ranging from 0.1-13.0% and the rates of clinical and angiographic CME after modern phacoemulsification surgery are 1% and 20%, respectively [1-5].

CME after cataract extraction resolves spontaneously in approximately 90% of patients, and only a small percentage suffer permanently reduced vision [4,6]. Given the large number of patients undergoing phacoemulsification worldwide however, this small percentage of eyes constitutes a large enough number to warrant research aimed at identifying appropriate treatment protocols [4]. Different treatment modalities including vitrectomy, topical non-steroidal anti-inflammatory drugs (NSAIDs), acetazolamide and topical, periocular, intraocular and systemic steroids have been used to treat CME after cataract surgery, with varying rates of success [3-5].

The precise mechanisms of the pathogenesis of CME after phacoemulsification are still not well understood, but the condition is thought to be multifactorial. The primary cause appears to involve upregulation of inflammatory mediators in the eye after surgical trauma. Inflammation breaks down the blood-aqueous barrier and blood-retinal barrier (BRB), leading to exaggerated vascular permeability [7]. Transudate accumulates mainly in the inner nuclear and outer plexiform layers of the retina, forming small pockets that

coalesce to create larger cysts of fluid. These large cysts may rupture in chronic cases, resulting in lamellar macular hole [1].

It has previously been reported that intravitreal anti-vascular endothelial growth factor (VEGF) medications improve visual acuity and reduce retinal vascular permeability in eyes with macular edema secondary to vascular leakage, and may constitute a viable initial treatment for PCME [8,9]. Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was approved by the United States Food and Drug Administration in 2011 for the intravitreal treatment of wet age-related macular degeneration [10]. Studies have shown that aflibercept has a higher affinity for VEGF, inhibits more isoforms of the VEGF receptor, has a longer-lasting effect in comparison with other anti-VEGF agents and that it binds to placental growth factor (PGF) [11-13].

The main aims of the current study were to evaluate the clinical effectiveness, feasibility and safety of intravitreal aflibercept as a primary treatment in eyes with macular edema following uneventful phacoemulsification.

Subjects and Methods

This retrospective study included 13 eyes of 13 patients with CME after uncomplicated phacoemulsification who received intravitreal 2 mg aflibercept injection between July 2016 and March 2018. The study was approved by the Ethics Committee and the Institutional Review Board. Informed consent was obtained from all patients prior to injection. The nature of off-label use of aflibercept for CME following phacoemulsification and its potential risks and benefits were extensively discussed with potential participants. Inclusion criteria included newly diagnosed patients without any previous treatment for CME after uneventful phacoemulsification who were treated with at least one intravitreal injection of 2 mg aflibercept and underwent a minimum follow-up of 6 months. Exclusion criteria included diagnosis of retinal diseases such as diabetic retinopathy, retinal vein occlusion and retinitis pigmentosa, a history of intraocular surgery prior to phacoemulsification, uveitis and the use of medications that can cause cystoid macular edema. Patients with vitreoretinal pathology such as epiretinal membrane or vitreomacular traction in the study eye, which could prevent improvement in visual acuity were also excluded.

In all patients, best-corrected visual acuity (BCVA) was measured via Early Treatment Diabetic Retinopathy Study visual acuity testing and an ophthalmic examination, including slit-lamp biomicroscopy and intraocular pressure (IOP) measurement. Fluorescein angiography was performed in all patients, revealing central macula leakage typical for Irvine-Gass syndrome macular edema. Baseline CFT characteristics were evaluated by spectral domain optical coherence tomography (Stratus OCT-3, Humphrey-Zeiss, San Leandro, CA) through a dilated pupil by a retina specialist. Retinal thickness of the 1.0-mm central retina was obtained from the macular thickness map for use in calculations. Patients received an intravitreal 2 mg aflibercept injection in the study eye at the baseline visit (day 1). The eye was prepared and draped in the standard manner, using topical antibiotics (0.5% gatifloxacin) and 5% povidone-iodine solution. A single-use short 30-gauge needle was used to inject aflibercept into the vitreous cavity 3.5 mm posterior to the limbus through the inferotemporal pars plana under topical anesthesia (0.4% oxybuprocaine). All injections were performed in a minor operating room. Retinal artery perfusion and IOP were assessed following the injection. Patients were scheduled for regular post-injection follow-up visits at week 2, week 4 and then monthly thereafter. At each visit, the patients underwent a complete eye examination including BCVA testing, ophthalmoscopic evaluation and optical coherence tomography (OCT) imaging. Patients were reinjected with aflibercept if there was a recurrence of edema. Recurrence was defined as an increase in CFT associated with reduced BCVA after resolution at a previous visit.

The main efficacy outcome measures were change in CFT as determined by OCT, and change in BCVA from baseline to the final follow-up. Statistical calculations were performed using the Statistical Package for Social Sciences (version 21.0, SPSS Inc., Chicago, IL). Mean changes from baseline CFT and BCVA (converted to the logarithm of the minimum angle of resolution [logMAR]) were analyzed via paired Student's t-tests, and $p < 0.05$ was deemed to indicate statistical significance.

Results

Thirteen eyes of 13 consecutive patients who were followed up for at least 6 months were included in the study. Table 1 shows the patients' demographics. Their mean age was 62 ± 7.1 years and 62% (8/13) were male. All eyes had clinical CME at the initial examination. None of the patients had received any previous treatment for CME. The mean duration from phacoemulsification to intravitreal aflibercept injection was 3.3 months (range 2-8 months).

Table: Demographics and Clinical Features of the Patients

Patient No.	Gender	Age (Years)	Duration of CME Before aflibercept (Months)	BCVA (logMAR)		Foveal thickness (µm)	
				Baseline	Final	Baseline	Final
1	M	62	2	0.7	0.4	536	326
2	F	70	13	0.9	0.0	430	224
3	M	53	10	0.6	0.6	450	375
4	M	75	4	1.0	1.0	590	420
5	F	55	8	1.0	1.0	550	239
6	M	64	9	0.7	0.4	399	225
7	M	65	9	1.6	0.2	611	230
8	F	55	7	0.1	0.1	340	225
9	M	59	3	0.6	0.6	483	232

10	M	73	5	0.5	0.5	424	306
11	F	58	7	0.2	0.2	534	280
12	M	56	6	0.5	0.5	259	308
13	F	60	6	0.3	0.3	445	288

Mean CFT was 465.5 ± 100.2 µm at baseline and it had decreased significantly at the final follow-up to 282.9 ± 63.1 µm ($p < 0.001$). The difference between mean baseline BCVA (0.83 ± 0.28 logMAR) and final mean BCVA (0.45 ± 0.3 logMAR) was statistically significant ($p < 0.001$) (Figure 1 and 2). In 9 eyes (69.2%) BCVA increased, in 4 eyes (30.8%) it remained stable, and it did not decrease in any eye.

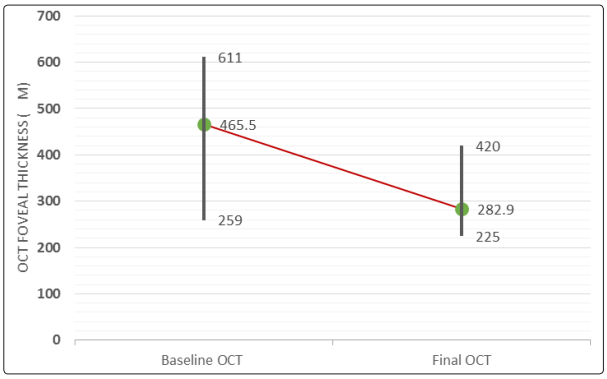

Figure 1: Mean changes from baseline foveal thickness. Improvement in foveal thickness observed at final follow up

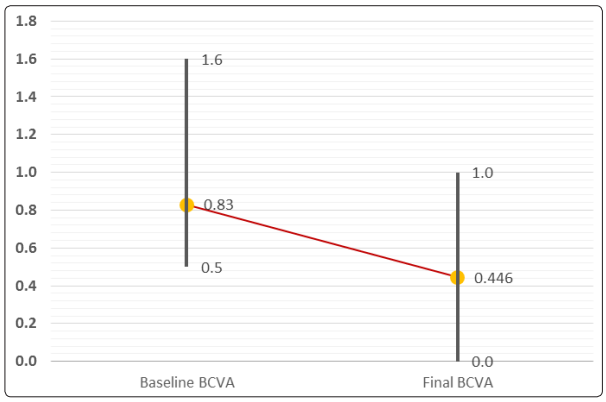

Figure 2: Mean changes from baseline BCVA. Improvement in BCVA observed at final follow up

All eyes received intravitreal aflibercept injection at the initial visit, and recurrences were treated by reinjection with aflibercept. Four eyes (30.8%) required a second intravitreal injection after a mean interval of 10.3 weeks, and 3 eyes (23.1%) required a third injection after a mean interval of 8.2 weeks. No serious ocular or systemic adverse effects such as thromboembolic events were noted during the observation period in any patient.

CME can develop after uneventful phacoemulsification. This cystoid edema is a major cause of reduced postoperative visual acuity. While spontaneous resolution of CME in weeks or months is the most likely natural outcome, in some patients who have an active lifestyle or those with persistent CME, observation until spontaneous resolution occurs is not the optimal form of management, and they should be treated. Macular edema persisting for months can cause permanent damage to the macula, and immediate treatment upon recognition of the pathology is justified [14].

Several theories have been proposed in an effort to explain the pathogenesis of CME after cataract surgery [15,16]. These theories involve changes in perifoveal vascular permeability leading to leakage of plasma into the retina, which eventually causes macular thickening due to excess interstitial fluid. The thickening of the retina results in distortion and stretching of neural cells, and the excess interstitial fluid is likely to disrupt fluxes of ions [17].

It is well known that inflammatory mediators disrupt the BRB after surgical trauma and contribute to the formation of CME [15,16]. Accordingly, most treatment approaches have targeted the inflammatory cascade. There are numerous reports that corticosteroids and NSAIDs reduce postoperative inflammation [2]. NSAIDs inhibit the activity of cyclooxygenase enzymes, and thereby affect the synthesis of prostaglandins and thromboxanes [18]. Many studies have investigated the efficacy of NSAIDs in the treatment of CME after cataract extraction [15,19]. Though topical drug application generally results in significantly less drug penetrating the posterior segment, topical diclofenac, indomethacin, and ketorolac tromethamine have been used for treatment or prophylaxis in CME [15,20,21]. Complications of topical NSAIDs include mydriasis, eye irritation, superficial punctate keratopathy, and conjunctival redness [15].

Steroids have been used for the treatment of CME because they target mediators in both angiogenic and inflammatory cascades [22]. Topical steroid, despite effectively suppressing postoperative ocular inflammation, has many complications including reactivation of herpetic keratitis, increased IOP, exacerbation of infection, and cataract formation [15,23]. Intravitreal injection of triamcinolone is one of the most direct ways to deliver a high dose of steroid into the vitreous cavity, though it is associated with some possible adverse effects including increased IOP, retinal detachment, and endophthalmitis. Injection of intravitreal triamcinolone acetonide has been used as a treatment for chronic and refractory CME [24]. Thach, et al. have reported that retrobulbar injection of triamcinolone may reverse macular edema and improve visual acuity in CME [22]. This treatment modality has the advantage of being less invasive than intravitreal injections despite the fact that it delivers a lower intravitreal concentration. In a previous study with a small sample, 11 eyes underwent dexamethasone implant injection (Ozurdex, Allergan, Irvine, CA) for refractory pseudophakic CME, and functional and anatomical improvements were reported [25].

Phacoemulsification generally results in a variable degree of inflammation caused by the release of inflammatory mediators (cytokines, prostaglandins, immune complexes and endotoxin) that can lead to increased expression of VEGF. VEGF is a well-known potent inducer of retinal vascular permeability, which causes disintegration of the BRB and secondary increases in perifoveal

capillary permeability and macular edema formation [26].

Intravitreal bevacizumab injection targets only VEGF and it may be effective for inflammatory macular edema conditions such as CME after phacoemulsification [27]. Ranibizumab has also been used in the treatment of PCME, and favorable outcomes were reported [28].

Aflibercept is a 115-kDa recombinant fusion protein and acts like a VEGF trap. Similar to bevacizumab and ranibizumab, aflibercept inhibits the activity of all VEGF A subtypes. Moreover, aflibercept inhibits VEGF-B and PGF [29]. In a study investigating the biological activity of 2 mg aflibercept at 83 days, it was reported that it was similar to 0.5 mg ranibizumab at 30 days suggesting that aflibercept can maintain significant VEGF-binding activity for approximately 10 weeks after a single injection [30]. It is hypothesized that aflibercept may be more effective than bevacizumab and ranibizumab because it inhibits VEGF-A, VEGF B and PGF in conjunction with a longer duration of action.

Intravitreal aflibercept has obvious effects on macular edema associated with increased intravitreal VEGF due to various causes including wet age-related macular degeneration, diabetic macular edema, and retinal vein occlusion macular edema [10,31,32]. Lin, et al. recently reported a significant improvement in eye with refractory CME treated with intravitreal aflibercept in terms of vision and macular thickness [33]. In the current study, intravitreal treatment with aflibercept safely reduced CFT and improved visual acuity in consecutive eyes with macular edema caused by cataract extraction throughout the follow-up period. A reduction in CFT as determined via OCT was evident at the final follow-up in the majority of eyes.

Moreover, the current study suggested a reduced risk of vision loss in patients with CME treated with intravitreal aflibercept injection. Four eyes (30.8%) required a second intravitreal injection after a mean interval of 10.3 weeks, and three eyes (23.1%) required a third injection a mean interval of 8.2 weeks. This suggests that VEGF induces macular thickening, which is a conclusion supported by the additional improvement in macular thickness that was observed after further aflibercept injections. In the current study, the visual and anatomical benefits of one aflibercept injection were maintained over 6 months in six eyes (46.1%). To date, there is no optimum dosing protocol for intravitreal aflibercept in PCME, so we elected to hold reinjections until there was a recurrence of edema. In the present series, no major side effects were recorded (e.g., infection, inflammation, retinal tear, retinal detachment, or increased IOP) and aflibercept injection was well tolerated. The current study suggests that intravitreal aflibercept injection may have a beneficial effect on both vision and foveal thickness.

We believe that chronic complications of CME including permanent visual loss can be reduced or avoided via intravitreal aflibercept, which rapidly and effectively stabilized the BRB and achieved regression of macular edema.

This study had several limitations. It was a retrospective and open-label, and the fact that it was short-term precluded any evaluation of the long-term safety or efficacy of intravitreal aflibercept injection. A significant limitation was that it only included 13 eyes. Moreover, the natural course of CME after phacoemulsification can be self-limiting in some eyes, which may have led to a false-positive result with regard to intravitreal aflibercept, due to the lack of a control group.

In conclusion, intravitreal aflibercept can induce the regression of CME after cataract extraction, with a concomitant improvement in BCVA. It may be effective and safe treatment modality for patients who are known steroid responders and are unresponsive to NSAIDs. The favorable results of the current study suggest the need for a prospective controlled study with a larger sample size and longer follow-up period, to evaluate the efficacy and safety of intravitreal aflibercept and compare it with other treatment options for CME after phacoemulsification.

References

1. Irvine SR (1953) A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 36: 599-619.
2. Spaide RF, Yannuzzi LA, Sisco LJ (1993) Chronic cystoid macular edema and predictors of visual acuity. Ophthalmic Surg 24: 262-267.
3. Levin DS, Lim JI (2002) Update on pseudophakic cystoid macular edema treatment options. Ophthalmol Clin North Am 15: 467-472.
4. Benitah NR, Arroyo JG (2010) Pseudophakic cystoid macular edema. International Ophthalmol Clin 50: 139-153.
5. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, et al. (2007) Clinical pseudophakic cystoid macular edema; risk factors for development and duration after treatment. J Cataract Refract Surg 33: 1550-1558.
6. Jacobson DR, Dellaporta A (1974) Natural history of cystoid macular edema after cataract extraction. Am J Ophthalmol 77: 445-447.
7. Benitah NR, Arroyo JG (2010) Pseudophakic cystoid macular edema. Int Ophthalmol Clin 50: 139-153.
8. Kimoto K, Kubota T (2012) Anti-VEGF agents for ocular angiogenesis and vascular permeability. J Ophthalmol 2012: 852183.
9. Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, et al. (2009) Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology 116: 1481-1487.
10. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, et al. (2012) Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 119: 2537-2548.
11. Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N (2006) Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. Ophthalmology 113: 623.
12. Ohr M, Kaiser PK (2012) Intravitreal aflibercept injection for neovascular (wet) age-related macular degeneration. Expert Opin Pharmacother 13: 585-591.
13. Browning DJ, Kaiser PK, Rosenfeld PJ, Stewart MW (2012) Aflibercept for age-related macular degeneration: a gamechanger or quiet addition? Am J Ophthalmol 154: 222-226.
14. Reis A, Birnbaum F, Hansen LL, Reinhard T (2007) Successful treatment of cystoid macular edema with valdecoxib. J Cataract Refract Surg 33: 682-685.
15. Flach AJ (1998) The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc 96: 557-634.
16. Stark WJ Jr, Maumenee AE, Fagadau W, Datiles M, Baker CC, et al. (1984) Cystoid macular edema in pseudophakia. Surv Ophthalmol 28: 442-451.
17. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, et al.

(2006) Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthalmol 142: 961-969.
18. Rho DS (2003) Treatment of acute pseudophakic cystoid macular edema: Diclofenac versus ketorolac. J Cataract Refract Surg 29: 2378-2384.
19. McCafferty S, Harris A, Kew C, Kassm T, Lane L, et al. (2017) Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo. BMC Ophthalmol 17: 16.
20. Geroski DH, Edelhauser HF (2000) Drug delivery for posterior segment eye disease. Invest Ophthalmol Vis Sci 41: 961-964.
21. Sivaprasad S, Bunce C, Wormald R (2005) Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review. Br J Ophthalmol 89: 1420-1422.
22. Thach AB, Dugel PU, Flindall RJ, Sipperley JO, Sneed SR (1997) A comparison of retrobulbar versus sub-Tenon's corticosteroid therapy for cystoid macular edema refractory to topical medications. Ophthalmology 104: 2003-2008.
23. Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulos I, et al. (2004) Macular edema. Surv Ophthalmol 49: 470-490.
24. Conway MD, Canakis C, Livir-Rallatos C (2003) Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg 29: 27-33.
25. Al Zamil WM (2015) Short-term safety and efficacy of intravitreal 0.7-mg dexamethasone implants for pseudophakic cystoid macular edema. Saudi J Ophthalmol 29: 130-134.
26. Miyake K, Ibaraki N (2002) Prostaglandins and cystoid macular edema. Surv Ophthalmol 47: S203-218.
27. Spitzer MS, Ziemssen F, Yoeruek E (2008) Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. J Cataract Refract Surg 34: 70-75.
28. Demirel S, Batioglu F, Özmert E (2012) Intravitreal ranibizumab for the treatment of cystoid macular edema in Irvine-Gass syndrome. J Ocul Pharmacol Ther 28: 636-639.
29. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, et al. (2012) Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis 15: 171-185.
30. Stewart MW, Rosenfeld PJ (2008) Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 92: 667-668.
31. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, et al. (2014) Intravitreal aflibercept for diabetic macular edema. Ophthalmology 121: 2247-2254.
32. Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, et al. (2013) Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol 155: 429-437.
33. Lin CJ, Tsai YY (2016) Use of aflibercept for the managmement of refractory pseudophakic macular edema in Irvine-Gass Syndrome and literature review. Retin Cases Brief Rep 12: 1.