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Outcomes of and Surgical Technique for Treatment With High-Dose Aflibercept

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Abstract

Purpose: To describe an alternate delivery of high-dose aflibercept using previous formulations (ie, prefilled syringe, vial, or compounded). **Methods:** A prospective pilot study was performed to analyze the short-term safety and visual gain (expressed in logMAR), including increase in intraocular pressure (IOP), resulting from a modified regimen consisting of 0.18 mL paracentesis followed by an intravitreal injection of 0.18 mL aflibercept (prefilled syringe), 0.20 mL aflibercept (vial), or 0.22 mL ziv-aflibercept (compounded). **Results:** The study comprised 32 eyes (16 naïve; 18 neovascular age-related macular degeneration; 8 retinal vein occlusion). Over a follow-up of 4.1 (± 3.2) months, a mean (± SD) of 1.7 (± 0.9) high-dose injections were administered. The baseline best spectacle-corrected vision was 1.35 ± 0.71 (Snellen VA) and improved to 0.68 ± 0.46 at 1 month ($P < .001$) and 0.57 ± 0.43 at the final follow-up ($P < .001$). An increase in IOP of 0.43 ± 4.26 mm Hg was seen 1 minute after injection ($P = .58$). In 2 eyes (6.3%), reflux as a tiny bleb was noted. **Conclusions:** When high-dose aflibercept is neither available nor affordable, a patient's readily accessible and cost-effective regimen of aflibercept will allow an exact delivery of high-dose aflibercept, combining minimal drug reflux, minimal immediate increase in IOP, and potential clinical efficacy in the short term.

Keywords

high-dose aflibercept, age-related macular degeneration, burden, intravitreal injections, retinal vein occlusion, diabetic maculopathy, vitreous hemorrhage

Introduction

The hypothetical rationale of a higher dose of medication having a longer vitreous durability[1–13] was confirmed in several ongoing phase 2 and 3 trials of treatment for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and retinal vein occlusion (RVO). Visual and anatomic improvement were seen after intravitreal (IVT) administration of aflibercept 8 mg (114.3 mg/mL) in a 70 µL formulation (Eylea HD, Bayer) for nAMD, with a comparable safety profile to the standard 2 mg dose at the 44-week follow-up.[2] The phase 2 results converge with unpublished 1-year and 2-year results of phase 3 trials presented at major international meetings. The PHOTON trial enrolled 658 patients with DME, and the PULSAR trial enrolled 1009 patients with nAMD.[3,4] These pivotal trials (including the CANDELA trial) found robust anatomic and visual improvements with high-dose IVT 8 mg aflibercept compared with the standard 2 mg dose and no additional safety issues.[5] The current high-dose formulation is more expensive than the standard dose and was recently approved by the US Food and Drug Administration for nAMD, DME, and diabetic retinopathy. Until high-dose aflibercept is available outside the US, and to lower the cost to patients, an alternative technique to deliver 8 mg aflibercept using the 2 mg delivery system can be used. This technique is performed by injecting 0.20 mL of aflibercept (vs 0.05 mL), which avoids drug reflux after the injection (with prior paracentesis) and minimizes drug loss in the needle hub by using a 31-gauge needle (BD Micro-Fine Plus, Becton, Dickinson and Company).

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Methods

Consecutive patients from 2 clinics were prospectively enrolled in the study from January 1, 2023, to February 28, 2024. Inclusion criteria were poor best-corrected visual acuity (BCVA) (20/50 or less) due to any etiology; maculopathy unresponsive to previous vascular endothelial growth factor (VEGF) antagonists without a washout period; severe forms of nAMD, central retinal vein occlusion (CRVO), or branch retinal vein occlusion (BRVO); and severe vitreous hemorrhage (VH) from proliferative diabetic retinopathy (PDR) or nAMD. Exclusion criteria were a shallow anterior chamber; vitrectomized eyes; cataract surgery less than 1 year ago; uncooperative patients; head tremor (ie, Parkinson disease); inability to rest the chin on the slitlamp (ie, severe kyphosis); and children and adolescents.

The study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained for each patient before treatment. Ethical approval for this study was obtained from the Beirut Eye Ear Specialty Hospital Ethics Committee.

Injections were performed in an office-based setting using sterile procedures.

With the patient's chin resting on the slitlamp, topical anesthesia is instilled, followed by 5% betadine-povidone and a sterile lid speculum. Paracentesis of 0.17 to 0.20 mL is performed with a 0.5 mL syringe (Ultra-Fine Syringe, 31-gauge, 6 mm, Becton, Dickinson and Company). Special care is taken to ensure the tip of the needle is kept near the corneal entrance and away from the lens capsule in phakic patients. A quick analysis of the anterior chamber depth is made to estimate the maximal volume that can be aspirated, and this is balanced by knowing the drug volume to be injected. The second and third finger are used to stabilize the syringe while the thumb retracts the plunger. An 18-gauge, 5-µm sterile filter needle is used to filter the aflibercept drug, which is transferred to a 0.5 mL syringe and a target volume of 0.18 to 0.22 mL injected into the vitreous cavity.

Alternatives to high-dose aflibercept include aflibercept (Eylea, Bayer AG) in a vial containing 0.28 mL of a 40 mg/mL solution (total 11.1 mg aflibercept), aflibercept in a prefilled syringe containing 0.18 mL of a 40 mg/mL solution (total 7.1 mg aflibercept), and compounded ziv-aflibercept (Zaltrap, Regeneron) containing 0.22 mL (25 mg/mL) (total 5.5 mg aflibercept). Only a single vial or syringe of medication was used per treated eye. Injections were given monthly for the first 3 months and then bimonthly.

Vitreous reflux, defined as either fluid flowing from the vitreous body through the punctured site or bleb formation resulting from conjunctiva closure while the sclera hole remains open, was detected on the slitlamp immediately after IVT injection. The IOP was measured before and 1 minute after the injection using a noncontact tonometer (TRK-2P, Topcon). The BCVA was measured using Snellen charts and converted into logMAR notation for analysis.

The primary outcome measures of the current study were improvement in BCVA from baseline at the 1-month follow-up (or sooner), increase in IOP 1 minute after the injection, and vitreous reflux immediately after the injection. Secondary outcome measures included the identification of complications from the procedure. Statistical analyses were performed using SPSS software (version 25.0, SPSS Inc). A 2-tailed paired Student *t* test for dependent variables and a 1-sample *t* test were used and values expressed as mean ± SD.

Results

The study population included 32 eyes of 30 patients (13 women, 17 men). The mean (± SD) age was 73 ± 11 years (Table 1). Systemic diseases reported by the patients included hypertension (n = 9), diabetes mellitus (n = 7), and coronary artery disease (n = 2). Laterality included 21 right eyes and 11 left eyes. Thirteen eyes were phakic, and 19 were pseudophakic. Ophthalmologic diseases included nAMD (n = 18), CRVO (n = 6), BRVO (n = 2), DME (n = 4), and VH (n = 2) from nAMD breakthrough retinopathy or PDR. Special indications for use of high-dose aflibercept included travel issues (n = 2), severe CRVO (central macular thickness >500 µm or severe disc edema) (n = 6), severe BRVO (central macular thickness >500 µm) (n = 2), large submacular bleed (n = 8), extensive choroidal neovascularization (CNV) or extensive RPE detachment (n = 3), severe VH (n = 2), large amount of subretinal fluid (SRF) (n = 2), and drug-resistant nAMD (n = 2).

Aflibercept was used in 16 eyes and ziv-aflibercept in 16 eyes. Fifteen eyes were treatment naïve, and 17 eyes had a history of monotherapy (n = 12) or alternate therapy (n = 5), which included brolucizumab (Beovu, Novartis AG) (5 eyes), dexamethasone IVT implant (Ozurdex, Allergan Inc) (4 eyes), ranibizumab (Lucentis, Genentech Inc) (6 eyes), aflibercept (Eylea) (1), ziv-aflibercept (Zaltrap) (4 eyes), and bevacizumab (Avastin, Genentech) (1 eye).

The mean (± SD) number of injections of high-dose aflibercept was 1.7 ± 0.9 (median, 2.5; range, 1-5) over a mean (± SD) follow-up of 4.1 ± 3.2 months (median, 3; range, 1-12). The mean (± SD) baseline BCVA was 1.35 ± 0.71 (Snellen equivalent, 20/448) (median, 1.24; range, 0.40-3.0), which improved significantly by 1 month to 0.68 ± 0.46 (Snellen equivalent, 20/100) (median, 0.68; range, 0.0-1.6) ($t = -6.55$; $P < .001$) and 0.57 ± 0.43 (Snellen equivalent, 20/78) (median, 0.60; range, 0-1.60) at the final follow-up ($t = -7.7$; $P < .001$). The mean (± SD) baseline IOP of 17.6 ± 4.2 mm Hg (median, 16; range, 12-30) increased to 18.0 ± 3.8 mm Hg (median, 18; range, 12-27) ($t = 0.56$; $P = .58$) 1 minute after the first injection and stabilized by the final follow-up to 16.3 ± 3.4 mm Hg (median, 16; range, 10-25) ($t = 2.30$; $P = .028$) (Table 1). The change in IOP from baseline to 1 minute after injection was 0.4 ± 4.3 mm Hg (median, 2; range, −10 to +8) and was insignificant ($t = 0.56$; $P = .58$). In 2 eyes (6.3%), there was a small reflux in the form of a tiny bleb after the injection.

Half of the patients consented for daily examinations the first week after the injection. In 2 subjects, a few self-resolving anterior chamber cells were noted after the injection, lasting for 1 day. No decline in vision, retinal vasculitis, uveitis, lens rupture, or increase in IOP was seen at any patient's follow-up visit. A total of 55 injections were administered during the study period. Of note was the rapid improvement in vision within days after injection of high-dose aflibercept.

Table 1. Patient Demographics and Ocular Parameters in Patients Treated With High-Dose Aflibercept.

Characteristic	Value
Sex	
Female	13
Male	17
Mean age (y) ± SD	72.8 ± 10.7
Ocular disease	
nAMD	18
CRVO	6
BRVO	2
DME	4
VH	2
Systemic disease	
HTN	9
DM	7
CAD	2
Lens status	
Phakic	13
Pseudophakic	9
Reason for megadose	
Travel issues	2
Severe CRVO	6
Severe BRVO	2
Large submacular bleed	8
Extensive CNV	2
Severe VH	2
Large amount of SRF	2
Resistant nAMD	2
Previous therapy	
No	15
Yes	17
Drug used	
Eylea	16
Zaltrap	16
Laterality	
Right eye	21
Left eye	11
Mean logMAR BCVA ± SD	
Initial	1.35 ± 0.71
At 1 month	0.68 ± 0.46
Final	0.57 ± 0.43
Mean IOP (mm Hg) ± SD	
Initial	17.6 ± 4.2
1 minute after injection	18.0 ± 3.8
Final	16.3 ± 3.4
Mean follow-up (mo) ± SD	4.1 ± 3.2

Abbreviations: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CAD, coronary artery disease; CNV, choroidal neovascularization; CRVO, central retinal vein occlusion; DM, diabetes mellitus; HTN, hypertension; IOP, intraocular ocular pressure, nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid; VA, visual acuity; VH, vitreous hemorrhage.

Conclusions

This pilot study offers a proof of concept that maximal use of the regular 2 mg aflibercept preparation allows delivery of a high dose without a clinically significant IOP spike. We reserve this approach for severe cases of nAMD with macular hemorrhage, DME, RVO, unresponsive cases,[6] or patients with poor ambulation or those travelling long distances. The rapid clinical response to this high dose was impressive in some closely followed patients (data not shown here) and deserves further investigation.

In a meta-analysis,[14] the average IOP spike was 26 mm Hg, and the rate of vitreous reflux within 1 minute after an injection of 0.05 mL of medication using a 30-gauge needle was 53%.[15] With the novel 0.07 mL high-dose aflibercept, both the immediate IOP increase and drug reflux would be expected to be higher than with the 0.05 mL dose, hence reducing the effective dose of 8 mg injected into the vitreous. However, a minimal increase in IOP and drug leakage due to previous paracentesis was noted with the current technique.

Overall, the technique described in the current study offers potential advantages such as the ready administration of a therapy comparable to high-dose 8 mg aflibercept, a reduction of global costs ($1958 USD for Eylea vs. $2625 USD for high-dose Eylea, Regeneron; https://investor.regeneron.com>static-files), in addition to a lower rate of drug leakage and a decrease in IOP.[16,17] On the other hand, the technique requires paracentesis and cannot be performed in eyes with a shallow anterior chamber. The current study is prone to several limitations because of the scant and heterogeneous patient sample, the short follow-up, and the absence of a control group treated with 8 mg aflibercept. Theoretically, alternative techniques could consist of a 4 mg biweekly or 2 mg weekly regimen; the most similar clinical trial (not using the high-dose aflibercept formulation) used a 4 mg monthly regimen.[18] In a retrospective case series of 33 eyes with nAMD resistant to monthly bevacizumab/ranibizumab, patients were switched to 2 mg aflibercept every 8 weeks, escalated to 2 mg aflibercept monthly, and then to 4 mg aflibercept monthly. Significant decreases in central foveal thickness, intraretinal and SRF, and height of the RPE detachment were seen 1 month after the switch to 4 mg aflibercept monthly.[18]

In conclusion, high-dose aflibercept could be reserved for select cases that require injections 3 times a month, including severe visual loss from submacular blood or dense VH, resistant cases of nAMD, patients travelling long distances, or those patients with difficulty ambulating. Further studies are needed to validate the safety of the technique.

Authors' Note

Drs. Mansour and Lima contributed equally to this work.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and validation of all protected patient health information were performed in a US Health Insurance Portability Accountability Act–compliant manner.

Statement of Informed Consent

Informed consent was obtained, including permission for publication of all photographs and images included herein, before the procedure was performed.

Declaration of Conflicting Interests

The authors declared no potential conflicts with respect to the research, authorship, and publication of this article.

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