Effectiveness and safety of ziv aflibercept in myopic choroidal neovascularisation patients

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Research article

Keywords: Central macular thickness, Choroidal neovascularization, Optical coherence tomography, Pathological myopia, Ziv-aflibercept

DOI: https://doi.org/10.21203/rs.3.rs-20287/v1

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Abstract

Background: Myopic choroidal neovascularization (CNV) is the most common sight threatening complication in high myopia. The present study evaluates the efficacy and safety of intravitreal injection of ziv-aibercept in patients with myopic CNV.

Methods: This is a prospective interventional study that was conducted on 20 eyes of 20 patients with active myopic CNV. Twelve patients were 40 years old or more. The study was performed in Ophthalmology department, Tanta University Eye Hospital , Tanta University, Egypt. Complete ophthalmic evaluation was performed including best corrected visual acuity (BCVA), fundus examination and anterior segment examination. OCT was done for all patients at baseline and monthly after injection during the 6 months follow up period of the study. Statistical calculations were performed using the computer program SPSS (S tatistical Package for the Social Science).

Results: The younger age group received lower number of injections than the older age group, the best corrected visual acuity (BCVA) and the central macular thickness (CMT) improved significantly in both groups with more improvement in the younger age group as regarding the BCVA. No significant correlation was found between the final BCVA and both the spherical equivalent and the central macular thickness after 6 months. No significant changes in IOP after intravitreal injection were detected in both groups. No complications were reported apart from mild sub conjunctival hemorrhage that occurred in three eyes after injection.

Conclusion: Ziv-aibercept is a highly effective and safe drug in cases of active myopic CNV that can produce similar results to other anti VEGF agents with less cost. The study was retrospectively registered with clinical trial.gov ID (NCT04290195) in 26-2-2020.

Background

The prevalence of pathological myopia in adults is about 1-3%, myopic choroidal neovascularisation (CNV) is one of the most sight- threatening complications that occurs in approximately 5-11% of pathological myopia patients [1,2]. Several treatment approaches were proposed due to the poor understand of its pathological nature [2]. Photodynamic therapy (PDT) is one of the treatment options for myopic CNV that can reduce the risk of visual loss which was supported by several studies [3, 4]. However, patients treated with PDT did not gain better mean visual acuity, and it did not prevent visual loss for longer than 2 years [5]. Recently anti-vascular endothelial growth factor (Anti-VEGF) agents such as bevacizumab, ranibizumab, and aibercept were introduced for the treatment of many retinal diseases with high safety profile. Bevacizumab is a recombinant humanized monoclonal antibody that binds all isoforms of VEGF-A [6], while ranibizumab is an antigen-binding fragment derived from bevacizumab [6]. Aflibercept is a soluble receptor fusion protein that binds VEGF-A, VEGF-B, and placental growth factor [6,7]. According to phase 3 RADIANCE trial [8], ranibizumab was recently approved for the treatment of visual impairment due to myopic CNV, in addition MYRROR; a phase 3 study, confirmed the efficacy and safety of intravitreal aflibercept in the treatment of CNV in pathological myopia patients [9].
Ziv-aibercept (Zaltrap; Regeneron, New York, USA) is a recombinant fusion protein which is nearly similar to aflibercept. It was approved by FDA in August 2012 for the treatment of resistant metastatic colorectal carcinoma. Recently, it was reported that off-label intravitreal ziv-aibercept is an effective and safe treatment at 4 weeks interval without any ocular toxicity in patients with age-related macular degeneration [10].

The present study evaluates the efficacy and safety of ziv-aibercept as a primary treatment in cases of myopic CNV.

Methods

Study design: A prospective interventional case study that was conducted on 20 eyes of 20 patients with active myopic CNV who attended the outpatient clinic of Tanta University Eye Hospital from March 2019 till September 2019 after approval of the Ethical Committee of the Faculty of Medicine, Tanta University, Egypt (approval code 32970/02/19). Twelve patients were ≥ 40 years old and the remaining 8 patients were < 40 years old which is quite similar to Yoshida T et al [27] to detect the influence of age on the visual prognosis. All procedures were carried out under the tenets of the Helsinki Declaration. Written consent was provided by all participants after discussing the procedure, alternative treatment plans, follow-up schedules, and possible benefits and risks. The study was retrospectively registered with clinical trial .gov ID (NCT04290195) in 26-2-2020.

Participants: The study included treatment naive patients with recently diagnosed active myopic subfoveal or juxtafoveal CNV of less than two months duration confirmed by fundus fluorescein angiography (FFA) and optical coherence tomography (OCT). Pathological myopia patients with spherical equivalent more than 6 Diopters and axial length more than 26 mm were enrolled in the study.

Patients with history of previous intraocular surgery, coincident retinal pathology as diabetic retinopathy, retinal vein occlusion(RVO), CNV due to other causes like age related macular degeneration, angioid streaks, trauma, choroiditis and extrafoveal myopic CNV were excluded from the study. In addition patients who received other lines of treatment for CNV like photodynamic therapy, laser photocoagulation or intravitreal injection of triamcinolone or other anti VEGF agents, and those known to be glaucomatous or have IOP more than 20 mmHg were also excluded.

Furthermore, patients with other retinal pathology as prior ocular inflammation, retinal degeneration, dense media opacity including nuclear sclerosis and those who did not complete 6 months of follow up were not enrolled in the study.

Thorough ophthalmic evaluation was performed for all patients including BCVA using Snellen chart that was converted to logMAR for statistical analysis, IOP measurement using applanation tonometry, anterior segment examination using slit lamp, posterior segment examination by slit lamp bimicroscopy using +78 D lens and indirect ophthalmoscopy. Spectral domain OCT (Topcon 3D Optical Coherence Tomography)
was performed for all patients at baseline and at the postoperative first month visit then monthly for 6 months.

**Surgical procedure:**

*Preoperative preparation:* Patients were prepared by applying topical fluoroquinolone eye drops (Moxifloxacin hydrochloride 0.5% Vigamox, Alcon, USA) 4 times daily for three days before injection.

*Procedure:* The intravitreal injection was carried out in the operating room under complete aseptic technique with an operating microscope. After applying topical anaesthetic drops (Benoxinate hydrochloride 0.4%, Benox, Epico, Egypt) to the ocular surface followed by topical application of 10% povidone iodine (Betadine) for periocular area, lids and eye lashes and 5% povidone iodine inside the conjunctival sac for three minutes before the intravitreal injection. Injection of 0.05 ml of 1.25 mg of Zivaflibercept (Zaltrap) was done into the vitreous cavity in the inferotemporal quadrant of the globe using 30 gauge needle 4 mm from the limbus.

*Postoperative care:* After the injection, topical antibiotic drops were applied (Moxifloxacin hydrochloride 0.5% Vigamox, Alcon, USA) and the eye was patched for several hours. Patients were instructed to administer antibiotic drops four times daily for 3 days. Patients were examined the next day and the third day after injection to exclude any complication like elevation of the IOP, endophthalmitis, retinal break, retinal detachment and vitreous haemorrhage. All patients were followed up at 4 weeks interval after the first injection. At each visit, thorough ophthalmic examination and SD OCT were performed. Pro re nata (PRN regimen) was followed in this study in which additional intravitreal injection of Zaltrap was given after one month if persistent intraretinal or subretinal fluid was detected in SD OCT and/or haemorrhage was detected on clinical examination.

Statistical data were expressed as percentages or means ± SD when appropriate. Chi X2 was used to compare the findings. P-values < 0.05 were considered significant. All statistical calculations were performed using the computer program SPSS (Statistical Package for the Social Science; SPSS, Chicago, IL, USA) version 23 for Microsoft Windows, USA.

**Results**

The study was performed from March 2019 till September 2019. Twenty eyes of active myopic CNV were included in the study, the baseline demographic data of all patients including; age, gender, spherical equivalent and number of injections were recorded. Patients with myopic CNV less than 40 years old needed lower number of injections (2.00±0.76) than patients 40 years old or more (2.50±1.00), this is shown in table (1). The BCVA improved significantly after 6 months of injection in both age groups with more improvement in the younger age group, (p=0.001) in patients <40 years and (p=0.028) in patients ≥40 years old. Furthermore, the central macular thickness (CMT) decreased significantly in both groups after 6 months follow up (p=0.001) as shown in table (2).
No significant changes in IOP after intravitreal injection were detected in both groups after 6 months (p=0.140) as illustrated in table (3).

Also, there was no significant correlation between the final BCVA and both the spherical equivalent and the final CMT after 6 months (figure 1, figure 2). During injection, subconjunctival haemorrhage occurred in 3 eyes, no cases of reaction, endophthalmitis, retinal breaks, retinal detachment or vitreous haemorrhage were reported. No systemic complications like myocardial infarction, stroke or death were reported during the study. For example; in a 55 years old female patient with active myopic CNV with retinal haemorrhages as documented by fluorescein angiography (figure3), the BCVA improved by 3 consecutive injections from 1 to 0.52 by logMAR, also the CMT declined from 283 um (figure4) to 226 um, 213 um, 184 um after 3 monthly injections (figure 5 a, b, c). The CNV remained inactive till the last follow up visit.

**Discussion**

Various methods of treatment were attempted for myopic CNV before the era of anti-VEGF as laser photocoagulation, transpupillary thermotherapy (TTT), PDT (photodynamic therapy), submacular surgery and macular translocation. In spite of all these attempted treatment approaches, results were unsatisfactory with no evident clinical improvement. Damage of the adjacent photoreceptors and atrophic scar progression hindered the clinical improvement and decreased the BCVA in laser photocoagulation treated patients with subfoveal CNV due to age-related macular degeneration [11,12], with even poorer results in myopic extrafoveal CNV despite of the stoppage of activity [13-16].

This advocated the shift to PDT with verteporfin which resulted in more satisfactory results angiographically and clinically in myopic CNV patients. Many studies supported the use of verteporfin especially those reported by Photodynamic Therapy Study Group; that detected improvement of BCVA in PDT treated group in the first 2 years that declined afterwards [4,17]. Another study that included 24 eyes of myopic CNV patients reported that PDT may result in good visual outcome in patients with extrafoveal CNV lesions with the laser spot adjusted to spare the fovea [18].

Regarding anti VEGF treatment for myopic CNV; Baba et al [19] compared the efficacy of bevacizumab and PDT, intravitreal bevacizumab showed more improvement of BCVA than PDT in eyes with myopic CNV. Also; Arias et al [20] found that the mean visual acuity improved by 8.4 letters following an average of 1.5 intravitreal bevacizumab injections after 6 months follow-up. Another study conducted by Ikuno et a1[21] reported improvement in the mean BCVA in a case series of 63 eyes of myopic CNV following one to six Bevacizumab injections during the 12 months of observation. As regard to ranibizumab; the REPAIR study [22,23] reported improvement of 13.8 letters following median of 3 ranibizumab injections based on PRN regimen after 12 months. RADIANCE study confirmed the results of REPAIR study [8]; it showed that around 40% of ranibizumab treated patients gained 15 or more letters of visual acuity at the third month compared with only 15% in PDT-treated patients. Whereas, after 1 year, the BCVA improved by 13.8 letters in the first group of ranibizumab (based on visual acuity stabilisation in the preceeding two follow up visits) and 14.4 letters in the second group of ranibizumab (based on disease activity criteria) compared with 9.3 letters improvement for PDT- treated patients, in addition some patients in PDT group switched to
ranibizumab injection from the third month onwards (with a median number of 2.0 injections between 3 and 12 months).

Another case series conducted on ranibizumab in 16 patients with myopic CNV by Lai et al [24]; that reported improvement of the mean BCVA of 3 lines after 1 year in 75% of eyes with recurrence demonstrated by angiography in only 2 eyes after 3 months that required retreatment between the 3rd and 9th month. Significant reduction in the mean central foveal thickness was also reported by OCT.

In respect to aflibercept in myopic CNV, the MYRROR study in 2015 reported a mean change of +13.5 letters in BCVA in aflibercept-treated patients after a median of 2 injections within 12 weeks compared with +3.9 letters in patients received sham treatment that was maintained through 48 weeks. No further injections were needed till the end of the study. The visual gain correlated significantly with reduction of the central retinal thickness [9]. Other studies confirmed the efficacy of aflibercept in myopic CNV patients like Brue and coauthors that showed improvement of BCVA from 0.69 LogMAR to 0.15 LogMAR after 18 months [25]. Moreover, Pece and Milani reported improvement of 10.6 letters after 1 year follow-up [26].

The present study evaluated the efficacy and safety of ziv-aflibercept in myopic CNV patients and reported that a lower number of injections was needed in patients less than 40 years old, in addition the BCVA improvement was more significant in the younger age group, these results are similar to Yoshida et al [27] who also showed better clinical improvement in patients younger than 40 years. The rational for less improvement in older patients can be related to several factors such as decreased integrity and function of the retinal pigment epithelium in myopic patients which might reduce the inhibition of angiogenesis that lead to the formation of larger and more active CNV, as well as a delay in the regression of CNV in these older patients. Moreover, myopic CNV in older patients has clinico-pathological correlation of both AMD and high myopia and tends to develop chorioretinal atrophic changes that markedly affect visual acuity [19].

Also, the improvement of BCVA and the reduction of the CMT after injection was achieved in both groups with statistical significance that reflects the efficacy of the new drug in myopic CNV patients with high safety profile and lower cost, this was quite similar to recent studies performed on ziv-aflibercept on a larger number of patients [28,29] that discussed application of ziv-aflibercept in different retinal diseases and detected reasonable safety profile for the drug comparable with other anti VEGF agents.

In contrast to a study performed by Chhablani et al (2017) on age related macular degeneration patients that suggested immediate IOP elevation after injection in 4 eyes that needed anterior chamber paracentesis [30], anterior chamber paracentesis was not performed in the present study as the IOP did not change significantly after injection of ziv-aflibercept either immediately or after a period of injection. This demonstrates the safety of ziv-aflibercept on IOP.

The cost per dose of intravitreal bevacizumab and ziv-aflibercept is low [31, 32], however that of aflibercept and ranibizumab is 20 to 30 times more [33]. This can be of great benefit to the low income countries with deficient insurance coverage.
Conclusions

Ziv aflibercept is a cheap and effective anti VEGF agent in patients with active myopic CNV with a high safety profile. The authors recommend the use of this new anti VEGF agent in retinal diseases like myopic CNV. However, larger number of patients with longer period of follow up are needed in further studies to confirm these results.

Abbreviations

AMD: Age related macular degeneration.
BCVA: Best corrected visual acuity.
CMT: Central macular thickness.
CNV: Choroidal neovascularisation.
FFA: Fundus fluorescein angiography.
IOP: Intraocular pressure.
IVA: Intravitreal aflibercept.
IVB: Intravitreal bevacizumab.
IVR: Intravitreal ranibizumab.
IVZ: Intravitreal ziv-aflibercept.
OCT: Optical coherence tomography.
PDT: Photodynamic therapy.
TTT: Transpupillary thermotherapy.
VEGF: Vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate:

The research was approved by the Ethical Committee of the Faculty of Medicine, Tanta University, Egypt (approval code 32970/02/19). Written consent was obtained from all participants.

Consent for publication:

Not available
**Data Availability:**

The datasets used during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

The authors declare that they have no competing interests.

**Funding:**

The research was not supported by any funding agent.

**Authors' contribution:**

AEN performed clinical examination, investigations like fundus fluorescein angiography and optical coherence tomography and intravitreal injection of all patients during the period of the research.

HMS performed follow up of all patients, data collection, statistical analysis and results of the research.

All authors shared in writing, reading and approval of the manuscript.

**Acknowledgments:**

The authors would like to acknowledge Tanta University Eye Hospital, Tanta University in which the whole study was performed.

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Tables

Table (1): Demographic data and the number of injections needed for both age groups during six months:

|                         | Total       | <40 years   | ≥ 40 years   |
|-------------------------|-------------|-------------|--------------|
| Age (years)             | Range 31–63 | 31–39       | 40–63        |
| Gender                  | Male (%) 8  (40%) | 3 (37.5%) | 5 (41.7%)    |
|                         | Female (%) 12 (60%) | 5 (62.5%) | 7 (58.3%)    |
| Spherical equivalent    | Range (-8)-(-6.25) | (-7.25)-(-6.25) | (-8)-(-6.25) |
|                         | Mean ± S. D -7.05±0.52 | -6.78±0.36 | -7.23±0.55   |
| No of injections         | Range 1-4    | 1-3         | 1-4          |
|                         | Mean ± S. D 2.30±0.92 | 2.00±0.76  | 2.50±1.00    |

No: Number S.D: Standard deviation

Table (2): BCVA and CMT at the base line and after 6 months of follow up.
| BCVA          | Total          | <40 years | ≥ 40 years |
|--------------|---------------|-----------|-----------|
| Before injection | Range   | 0.4–1.4 | 0.4–1.4 | 0.4–1 |
|               | Mean ± S. D  | 0.77±0.28 | 0.88±0.28 | 0.60 ± 0.21 |
| After 6 months | Range   | 0.1–1 | 0.22–1 | 0.1 – 0.7 |
|               | Mean ± S. D  | 0.42±0.24 | 0.48±0.23 | 0.33 ± 0.24 |
| **T: test**   |         | 17.609 | 14.443 | 5.998 |
| **P value**   |         | 0.001* | 0.001* | 0.028* |

| CMT(um)      |               |           |           |
|--------------|---------------|-----------|-----------|
| Before injection | Range   | 212–289 | 212–289 | 213–287 |
|               | Mean ± S. D  | 247.95±25 | 242.88±23 | 251.33±26 |
| After 6 months | Range   | 165–235 | 165–210 | 175–235 |
|               | Mean ± S. D  | 194.70±16 | 191.13±13 | 197.08±17 |
| **T: test**   |         | 63.252 | 28.223 | 34.663 |
| **P value**   |         | 0.001* | 0.001* | 0.001* |

BCVA: Best corrected visual acuity  
CMT: Central macular thickness.

Table (3): Illustrates changes in IOP after injection.
|                  | Before injection | After 6 months | T. test | P. value |
|------------------|------------------|----------------|---------|----------|
| **Range**        | 10 – 16          | 10 – 16        | 1.517   | 0.140    |
| **Mean ± SD**    | 12.53 ± 1.77     | 13.47 ± 1.60   |         |          |

IOP: Intraocular pressure

**Figures**

**Figure 1**

linear correlation between the BCVA after 6 months and spherical equivalent in all eyes.
Figure 2

Correlation between the final BCVA and the final CMT after 6 months in all eyes.

Figure 3

Fluorescein angiography of a female patient 55 years old with left active myopic subfoveal CNV.
Figure 4

OCT of the same patient showing active subfoveal CNV, the CMT is 283 um.

Figure 5

A: OCT after the first injection of ziv-aflibercept with reduced CMT to 226 um. B: OCT after the second injection of ziv-aflibercept with reduced CMT to 213 um. C: OCT after the third injection of ziv-aflibercept, the CMT declined to 184 um.
Supplementary Files

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