Short-term safety of 2 mg of intravitreal ziv-aflibercept in different retinal pathologies

Seguridad del uso intravítreo de 2 mg de ziv-aflibercept a corto plazo en diferentes patologías retinianas

Alonso Meza-Anguiano^{1*}, Efraín Romo-García¹, Gilberto N. Gutiérrez-Ruiz¹, Silvia Paz-Camacho¹, Wilehaldo Quiñonez-Quiñonez¹, Juan C. Barrera-De León², Abel Ramón-Concepción¹, Talía J. Romero-Mendizábal¹ and Sergio Sital-Gastelum¹

¹Center for Research and Teaching in Health Sciences CIDOCS, Civil Hospital of Culiacán, Culiacán; ²High Specialty Medical Unit, National Pediatrics Hospital, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Mexico

Abstract

Purpose: To assess the safety and effectiveness of 2 mg ziv-aflibercept (ZA) in different retinal diseases. **Methods:** Single arm, open-label, prospective study. A 2 mg (0.08 mL) ZA dose was administered following the hospital protocols for topical anesthesia. The following were considered adverse effects: IOP >3 mmHg from baseline, retinal detachment, vitreous hemorrhage, endophthalmitis, retinal vasculitis, retinal necrosis, cataract progression, anterior and posterior uveitis. **Results:** The study included 91 eyes of 55 patients and 50% were men, with a median age of 64.26 ± 11.86 years, a mean of 1.68 ± 0.91 injections; baseline central foveal thickness (CFT) of 390.91 ± 162.01 microns compared to a final CFT of 319.02 ± 104.67 microns ($p = 0.000$). Baseline best corrected visual acuity (BCVA) in logMAR was 0.86 ± 0.49 compared to a final BCVA of 0.75 ± 0.48 ($p = 0.000$). No adverse effects were reported. **Conclusions:** ZA is a safe and effective medication for the treatment of macular edema, regardless of the etiology, and it is also an affordable medication. Long-term studies are needed to evaluate its effectiveness compared to those drugs already approved for intravitreal use.

Key words: Aflibercept. Ziv-aflibercept. Zaltrap. VEGF-trap. Bevacizumab.

Resumen

Objetivo: Evaluar la seguridad y efectividad del uso de ziv-aflibercept (ZA) en diferentes enfermedades retinianas a dosis de 2 mg. **Métodos:** Estudio de un único grupo, abierto, prospectivo; se administró una dosis de 2 mg (0,08 ml) de ZA siguiendo los protocolos de la unidad hospitalaria con anestesia tópica. Se consideraron efectos adversos: aumento de presión intraocular >3 mmHg de la basal, desprendimiento de retina, hemorragia vítrea, endoftalmitis, vasculitis o necrosis retiniana, progresión de la catarata, uveitis anterior y posterior. **Resultados:** Se incluyeron 91 ojos de 55 pacientes, 50% hombres, edad media 64.26 ± 11.86 años, una media de 1.68 ± 0.91 inyecciones, grosor foveal central inicial (GFC) 390.91 ± 162.01 micras comparado con un GFC final de 319.02 ± 104.67 micras ($p = 0.000$), y una agudeza visual mejor corregida (AVMC) en logMAR de la 0.86 ± 0.49 comparada con una AVMC final de 0.75 ± 0.48 ($p = 0.000$). No se reportaron efectos adversos en ninguna de las 149 administraciones de ZA. **Conclusiones:** ZA es un medicamento seguro y eficiente para el tratamiento del edema

Correspondence:

*Alonso Meza-Anguiano

Eustaquio Buelna, 91

Col. Burocrata

C.P. 80030, Culiacán Rosales, Sin., México

E-mail: dralonsomeza@gmail.com

Date of reception: 17-09-2018

Date of acceptance: 13-02-2019

DOI: 10.24875/RMOE.M19000062

Available online: 08-05-2019

Rev Mex Oftalmol (Eng). 2019;93(3):103-106

www.rmo.com.mx

2604-1731/© 2019 Sociedad Mexicana de Oftalmología. Published by Permanyer México SA de CV. This is an Open Access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

macular, independientemente de la causa, además de su costo accesible. Se necesitan estudios a largo plazo para evaluar la efectividad de este medicamento en comparación con los fármacos ya aprobados para el uso intravítreo.

Palabras clave: Aflibercept. Ziv-aflibercept. Zaltrap. VEGF-trap. Bevacizumab.

Introduction

In 2017 in Mexico, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) made a statement mentioning that the registration of bevacizumab (Avastin, Genentech, San Francisco, California, USA) was not authorized for ophthalmological use and that sanctions would be applied if ophthalmologists used it. This forced us to look for alternatives for patients who cannot acquire ranibizumab (Lucentis, Genentech, San Francisco, California, USA) or aflibercept (Eylea, Regeneron, Tarrytown, New York, USA) due to their high cost. For some years, like bevacizumab, ziv-aflibercept (Zaltrap, Regeneron, Tarrytown, New York, USA) (ZA) has been used as an off-label therapy for the treatment of different retinal pathologies. Like aflibercept, ZA has a molecular weight of 115 kDa and only differs in presentation and hyperosmolality (1,000 mOsm/l). Aflibercept is available in 0.5 ml of a 40 mg/ml solution and ZA in 4 ml of a 100 mg/4 ml solution¹.

There have been few studies on its short-term safety, reporting varying doses from 1.25, 1752 and 2 mg, and the most studied dose is the one of 1.25 mg. These studies have demonstrated its safety and efficacy in pathologies such as diabetic macular edema (DME)³, wet age-related macular degeneration (AMD)^{4,5}, polypoidal choroidal vasculopathy⁶, edema secondary to branch retinal vein occlusion⁷, neovascular membranes⁸ not associated with age and in patients not responding to other antiangiogenic therapies⁹. In most studies, the dose of 1.25 mg has been used because a higher mitochondrial toxicity rate was found with ZA compared to ranibizumab in cultured cells of human retinal pigment epithelium (RPE) at higher therapeutic concentrations, but without affecting cell viability, a similar result with bevacizumab¹⁰, a drug that, in multiple studies, has proven its safety and efficacy.

There have been few studies on the effect of multiple doses of ZA, finding favorable results,¹¹ although there is still not much information for the 2 mg dose.

Objective

The objective of this study is to evaluate the safety and efficacy of the use of ZA in different retinal pathologies with a 2 mg dose.

Material and methods

This is a single-group, open, non-blinded and prospective study, conducted from June to December 2017 at the Civil Hospital of Culiacan.

Selection criteria

Patients who were injected with ZA (2 mg/0.8 ml) in the study period and who met the following criteria were included: age over 18 years, not pregnant, without clinical history of stroke or cardiological disease, with follow-up data at 24 hours and one month after treatment application. Patients with history of prior uveitis or vitrectomy were excluded. Patients who did not attend the 2 examinations after the application of ZA were also excluded.

Procedure

A complete ophthalmological examination of the anterior and posterior segments was performed, intraocular pressure (IOP) measurement with GOLDMAN tonometer and optical coherence tomography (SD-OCT) (RTVue Model RT100 Software version 6.8), prior to the application of ZA, at 24 hours and at 30 days. SD-OCT was evaluated by two experts (AMA and ERG) blinded to patient's data; who decided subsequent ZA injections based on central foveal thickness (CFT) and neurosensory retina characteristics, taking as a minimum CFT of <250 microns to decide retreatment.

Intervention

Under topical anesthesia with tetracaine 5 mg/ml, periocular asepsis was performed with 10% iodopovidone and 5% iodopovidone in the conjunctival sac, then a dose of 2 mg (0.08 ml) of intravitreal ZA was applied at 3.5 mm of the corneoscleral limbus in the superotemporal quadrant (without the use of a blepharostat).

Adverse effects were IOP elevation > 3 mmHg from baseline, retinal detachment, vitreous hemorrhage, endophthalmitis, retinal vasculitis, retinal necrosis, cataract progression, anterior and posterior uveitis.

No electrophysiology studies were performed on any patient, since we do not have this technology in our

institution. CFT and the best-corrected visual acuity (BCVA) were used as safety parameters.

Statistical analysis

Frequencies and percentages were used for qualitative variables, and means and standard deviation for quantitative variables, as well as inferential statistics with Chi-square for qualitative variables and Student's t-test for means. The statistical package SPSS version 24.0 was used.

Ethics

The protocol was submitted to the Research and Ethics Committee of our hospital. According to the General Health Law, the protocol is considered a study with a risk greater than the minimum, so informed consent was requested for each patient prior to injection. The protocol considers the human research principles established in the Declaration of Helsinki.

Results

We included 91 eyes of 55 patients, of which 50% were male, with a mean age of 64.26 ± 11.86 , an average of 1.68 ± 0.91 injections; an initial CFT of 390.91 ± 162.1 microns compared to a final CFT of 319.02 ± 104.67 microns ($p = 0.000$), and an initial BCVA mean in logMAR of 0.86 ± 0.49 compared with a final BCVA of 0.75 ± 0.48 ($p = 0.000$) (Table 1 and Fig. 1). The pathologies for which ZA was applied were DME (70.3%), AMD (14.2%), macular edema secondary to retinal vein occlusions (9.7%) and other pathologies (low-risk proliferative diabetic retinopathy, pseudophakic macular edema, etc.) (Table 2). No adverse effects were reported in any of the 149 ZA applications.

Discussion

The cost of the drugs approved by COFEPRIS ranibizumab (Lucentis, Genentech, San Francisco, California, USA) or aflibercept (Eylea, Regeneron, Tarrytown, New York, USA) is exponentially higher than ZA. In addition, the ability to fractionate the commercial presentation for intravitreal doses (in 50 doses of 2 mg) further reduces the cost of therapy. Despite this, the varied frequency of application of anti-angiogenics in our institution is due to the fact that our hospital is a referral center for civil assistance for low-income individuals without any kind of social security.

Table 1. General characteristics and comparison of best-corrected visual acuity and central foveal thickness

General characteristics		p
Patients	55	-
Number of eyes	91	-
Gender (male/female)	45/46	-
Age (years): mean $\pm$ SD (range)	64.26 ± 11.86 (31-91)	-
Right eye	45 (49.5%)	-
Left eye	46 (50.5%)	-
Number of injections: mean $\pm$ SD (range)	1.68 ± 0.91 (1-4)	-
Initial CFT (μ m): mean $\pm$ SD (range)	390.91 ± 162.01 (206-946)	0,000*
Final CFT (μ m): mean $\pm$ SD (range)	319.02 ± 104.67 (163-800)	
Initial BCVA, logMAR: mean $\pm$ SD (range)	0.86 ± 0.49 (0-1.60)	0,000*
Final BCVA, logMAR: mean $\pm$ SD (range)	0.75 ± 0.48 (0.90-1.60)	

*Statistical significance.

BCVA: best-corrected visual acuity; SD: standard deviation; CFT: central foveal thickness.

Figure 1. Patient number 2 before treatment with ziv-aflibercept. Central foveal thickness was 391 microns (A); after ziv-aflibercept injection, central foveal thickness was 272 microns (B).

The main controversy about the use of ZA is its osmolarity, which is different to aflibercept's, and its possible retinal toxicity, suggested in a study of RPE cell culture that evaluated cell viability in concentrations

Table 2. Pathologies

Pathologies	(%)
Wet age-related macular degeneration	13 (14.3)
Diabetic macular edema	64 (70.3)
Macular edema secondary to BRVO	7 (7.7)
Macular edema secondary to CRVO	2 (2.1)
Others	5 (5.5)

BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion.

10 times higher than the therapeutic ones; a similar feature reported for aflibercept and bevacizumab. A decrease in mitochondrial membrane potential was observed with ZA and bevacizumab¹⁰ at therapeutic concentrations. The latter has been widely used and evaluated regarding efficacy and clinical safety in randomized clinical trials¹¹⁻¹³. In addition, De Oliveira Dias, et al.¹³ carried out a 6-month study that did not find changes in baseline multifocal electroretinogram (ERG) compared to ERGs performed at weeks 4, 13 and 26 in patients with AMD with a dose of 1.25 mg¹⁴. Also, Chhablani, et al.¹⁶ conducted studies where they used ZA at doses of 1.25 mg and 2 mg and did not find adverse effects or toxicity measured with ERG 30 days after the injection compared to baseline ERG¹⁵⁻¹⁷. In our study, we did not perform electrophysiology studies, but we relied on the changes in BCVA and CFT, and we did not find any adverse effects after ZA intravitreal application. This data reinforce the idea that ZA is a safe and affordable medication for the general population.

Conclusions

In our short-term study, the greatest weakness is the lack of electrophysiology studies to evaluate the possible short-term toxicity of ZA, although published studies have not found ERG changes¹³⁻¹⁶. ZA seems to be a safe and effective medication for the management of macular edema, regardless of the cause, in addition to its accessible cost. Long-term studies are needed to evaluate the effectiveness of this medication compared to those approved for intravitreal use.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

- De Oliveira Dias JR, Andrade GC, Novais EA, Farah ME, Rodrigues EB. Fusion proteins for treatment of retinal diseases: aflibercept, ziv-aflibercept, and conbercept. *Int J Retina Vitreous*. 2016;2:3.
- De Oliveira-Dias JR, Xavier CO, Maia A, de Moraes NS, Meyer C, Farah ME, Rodrigues EB. Intravitreal injection of ziv-aflibercept in patient with refractory age-related macular degeneration. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46:91-4.
- De Andrade GC, de Oliveira Dias JR, Maia A, Farah ME, Meyer CH, Rodrigues EB. Intravitreal injections of ziv-aflibercept for diabetic macular edema: a pilot study. *Retina*. 2016;36:1640-5.
- Hodjat-Jalali K, Mehravaran S, Faghihi H, Hashemi H, Kazemi P, Rastad H. Intravitreal injection of ziv-aflibercept in the treatment of choroidal and retinal vascular diseases. *J Curr Ophthalmol*. 2017;29:228-31.
- Mansour AM, Al-Ghadban SI, Yunis MH, El-Sabban ME. Ziv-aflibercept in macular disease. *B J Ophthalmol*. 2015;99:1055-9.
- Videkar C, Kapoor A, Chhablani J, Narayanan R. Ziv-aflibercept: a novel option for the treatment of polypoidal choroidal vasculopathy. *BMJ Case Rep*. 2015;18:2015.
- Ozkaya A, Tulu B, Garip R. Aflibercept in macular edema secondary to retinal vein occlusion: A real life study. *Saudi J Ophthalmol*. 2017;31:211-5.
- Braimah IZ, Stewart M, Videkar C, Dedhia CJ, Chhablani J. Intravitreal ziv-aflibercept for the treatment of choroidal neovascularisation associated with conditions other than age-related macular degeneration. *Br J Ophthalmol*. 2017;101:1201-5.
- Braimah IZ, Agarwal K, Mansour A, Chhablani J. One-year outcome of intravitreal ziv-aflibercept therapy for non-responsive neovascular age-related macular degeneration. *Br J Ophthalmol*. 2018;102:91-6.
- Malik D, Tarek M, del Carpio JC, Ramirez C, Boyer D, Kenney MC, Kuppermann BD. Safety profiles of anti-VEGF drugs: bevacizumab, ranibizumab, aflibercept and ziv-aflibercept on human retinal pigment epithelium cells in culture. *Br J Ophthalmol*. 2014;98:i11-6.
- Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med*. 2015;372:1193-203.
- Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology*. 2016;123:1351-9.
- De Oliveira Dias JR, de Andrade GC, Kniggenndorf VF, Novais EA, Maia A, Meyer C, et al. Clinical and electrophysiological evaluation after intravitreal ziv-aflibercept for exudative age-related macular degeneration. *Retina*. 2017; 37:1499-1507.
- Kniggenndorf VF, Novais EA, Maia A, Meyer C, Watanabe SE, Farah ME, Rodrigues EB. Clinical and electrophysiological evaluation after intravitreal ziv-aflibercept for exudative age-related macular degeneration. *Retina*. 2017; 37:1499-507.
- Chhablani J, Narayanan R, Mathai A, Yogi R, Stewart M. Short-term safety profile of intravitreal ziv-aflibercept. *Retina*. 2016;36:1126-31.
- Chhablani J, Dedhia CJ, Peguda HK, Stewart M. Short-term safety of 2 mg intravitreal ziv-aflibercept. *Retina*. 2017;37:1859-65.