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Research Article

Intravitreal Implant Dexamethasone vs Intravitreal Injection Aflibercept as a Start Therapy in Diabetic Macular Edema. Ewo Study

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Abstract

Objective: To compare the improvement in visual acuity (VA) and decrease in central macular thickness (CMT) in patients treated with a intravitreal implant dexamethasone 0.7 mg (Ozurdex® Allergan) versus intravitreal injection aflibercept 2 mg/0.05 mL (Wetlia® Bayer) as a start therapy in diabetic macular edema (DME) in pseudophakic patients.

Methods: Clinical, prospective, longitudinal, randomized and analytical trial, consisting of two study groups of 43 eyes of 46 patients performed in the Retina and Vitreous Service of the Central Military Hospital in Mexico City in patients with DME with central involvement. Patients in group 1 started with a loading monthly dose regimen of 3 intravitreal injection of aflibercept 2 mg/mL (Wetlia® Bayer), followed by monthly monitoring based on VA and CMT. Group 2 had 2 intravitreal implant dexamethasone 0.7 mg (Ozurdex® Allergan) applications; to determine the need for retreatment, it was decided after a loss of ≥ 5 letters of the ETDRS scale and/or increase in CMT ≥ 10%.

Results: Visual acuity improved in the two study groups in the 12 month follow-up period. An assessment of the VA of both treatment groups was performed 12 months later, observing that in the group treated with intravitreal injection 2 mg of aflibercept (Wetlia® Bayer) they had an average of 63 ± 7 and 64 ± 7 letters in those treated with 0.7 mg intravitreal implant dexamethasone (Ozurdex® Allergan), and we found a difference of 1 letter between both groups, but this was not statistically significant ($t = -0.606$, $df = 41$, $p > 0.05$). Patients treated with intravitreal injection of aflibercept 2 mg/.05 mL (Wetlia® Bayer) showed a CMT of 269.36 ± 22 µm and 263.52 ± 12.9 µm in the group treated with intravitreal implant dexamethasone 0.7 mg (Ozurdex® Allergan), so the total difference was 5.8 µm, not being statistically significant ($t = 1.054$, $df = 41$, $p > 0.05$). The number of application over a 12-month period was evaluated, and it was found that the intravitreal injection aflibercept 2 mg/2 mL (Wetlia® Bayer) group showed an average of 7.09 applications, while in the intravitreal dexamethasone implant 0.7 mg group (Ozurdex® Allergan) the average of applications was 2.28 ($p < 0.05$). There was an increase in the intraocular pressure in 3 patients in group 2 (6.97%).

Conclusion: There were no statistically significant differences in VA and CMT between both groups. The use of intravitreal dexamethasone 0.7 mg implant (Ozurdex® Allergan) is safe and no inferior compared against aflibercept (Wetlia® Bayer) in the resolution of the DME as an initial therapy; also displayed improvement in visual acuity in the case of pseudophakic patients, with this group having the lowest number of injections with statistically significant results, which can improve the attachment to the treatment and burden reduction generated by the actual regimens.

Keywords: *Diabetic Macular Edema; Intravitreal Implant Dexamethasone; Intravitreal Injection Aflibercept; Central Macular Thickness; Mexico*

Introduction

Diabetes mellitus (DM) is the most widespread disease in the world, it has been estimated an increase from 333 millions in 2005 to 435 millions in 2015 [1]. In Mexico, it is estimate edition that there are 11.5 million people with diabetes (15.8% of the population), from which the 33.9% are undiagnosed. The main cause of visual loss in diabetic patients is macular edema [2]. The most important clinical feature in DME is the decrease in central visual acuity, which can be associated with metamorphopsia [2].

Hyperglycemia is the most important risk factor in the pathogenesis of DME; however, the exact mechanism remains unknown. Hyperglycemia induces the development of DME related to four main biochemical pathways: polyols, end products of glycosylation, the protein kinase (PK) pathway, and hexosamine pathway. These biochemical pathways induce the expression of angiogenic and inflammatory chemical mediators, also producing aberrant growth signaling, which in turn is directly involved in neurodegeneration and vascular dysfunction.[4] Oxidative stress resulting from inflammation leads to an alteration in the regulation of intravascular growth factors and cytokines such as vascular endothelial growth factor (VEGF), angiopoietins, tumor necrosis factor (TNF), interleukins (ILs), and matrix metalloproteinases, all of them contribute to the development of DME. The main mediators involved in the pathogenesis of DME are VEGF and the synthesis of proinflammatory cytokines, both of them synthesized by the retina [3].

The most important molecule in the breakdown of the internal retinal barrier is the VEGF. The introduction of anti-VEGF and steroids for the treatment of DME have changed the previous knowledge about the pathophysiology. However, it has been proved that about 30% of the patients are resistant to intravitreal anti-VEGF treatment [4].

Since the Early Diabetic Retinopathy Study (ETDRS) in the 1980s, the laser photocoagulation has been the gold standard for DME treatment [5]. Before the anti-VEGF treatment focal photocoagulation was the treatment of choice for DME. With the arrival of drugs against VEGF, these significantly improved the functional and anatomical results compared to laser treatment. Focal/grid laser photocoagulation were primarily associated with stabilization of visual acuity.

The study group of the Clinical Research Network (DRCR.net) reported recently a 10-letter increase in 31% of patients, while the 19% of laser-treated patients exhibited progressive vision loss (worsening in 2 lines after 2 years of follow-up) and an increased risk of scotoma development [6].

Several multicenter studies have evaluated the efficacy and safety of antiangiogenic drugs like the Da Vinci Study: which compared Aflibercept vs. Laser in DME. This was a phase II study that included 221 patients where Aflibercept significantly improved visual acuity compared to laser [7]. The VIVID-VISTA study which compared the use of Aflibercept in a regimen dose of every 4 weeks or every 8 weeks vs laser in DME. Phase III study, which included 872 patients, Aflibercept was superior to laser in the two treatment schemes [5].

The BEVORDEX study, which compared bevacizumab versus dexamethasone implant for DME, both of intravitreal route of administration, demonstrated benefits of the VA superior to laser for the treatment of foveal center involved DME [8].

The MOZART study evaluated the efficacy and safety of dexamethasone intravitrael implant against DME. It included 113 eyes of 84 patients divided in 3 subgroups: treatment-naïve patients, pseudophakic patients and phakic patients, were no clinical differences between subgroups was proved [9].

The MEAD study compared the different intraocular concentrations of the dexamethasone implant between 0.35 mg versus 0.70 mg versus sham in the treatment of patients with DME [10].

Objective of the Study

Compare the improvement in visual acuity (VA) and reduction in central macular thickness (CMT) in patients treated with intravitreal dexamethasone 0.7 mg implant (Ozurdex®Allergan) versus intravitreal aflibercept (Wetlia® Bayer) 2 mg/mL injection as initiation therapy in DME.

Methods

Clinical, prospective, longitudinal, randomized and analytical trial, conducted in the retina and vitreous service of the Military Central Hospital in Mexico City. The study population consisted of patients older that 18 years of age who attended the external consult clinic of the aforementioned service who were recently diagnosed with DME in both clinical and (SD-OCT) spectral domain optical coherence tomography (Heidelberg Engineering GmbH©) methods. All patients were pseudophakic and without any previous treatment for this pathology. The study was approved by the Ethics and Research Committee of the Military Central Hospital of Mexico City under the principles avowed in the Declaration of Helsinki. Patients signed the informed consent in a voluntary fashion that included the participation in the study which was conducted over a 12-month period, from June 2018 to June 2019.

Demographic data collected were: sex and age. Ophthalmological examination was performed complete that included taking VA with the ETDRS scale, clinical slit lamp biomicroscopy of the anterior segment, intraocular pressure measurement (IOP) with Goldman applanation tonometer, dilated binocular fundus examination of eye, SD-OCT and fasting glycemia levels at the beginning and the finalization of the treatment interval, for which glycemic control was carried by the Internal Medicine Service of the mentioned Hospital.

The patients were divided into two groups, group 1 under the "treat and extend" regimen using aflibercept 2 mg/0.05 mL intravitreal injection (Wetlia® Bayer) which consisted of: monthly application and then extending further applications to an additional two weeks if there were no increase in CMT, versus group 2 dexamethasone intravitreal 0.7 mg (Ozurdex® Allergan) implant every 4 months, followed by monthly monitorization that included VA, IOP control and SD-OCT. Treatment was suspended in case of achieving a stable vision and/or resolution of the DME (< 260 μm) for 2 consecutive months.

The retreatment criteria included loss of ≥ 5 letters from the ETDRS and/or CMT increase of ≥ 10%.

46 eyes of 41 patients were studied, of which 21 eyes were randomized to receive 0.7mg intravitreal dexamethasone implant and 22 received intravitreal aflibercept 2 mg/0.05 mL (Wetlia® Bayer) injection; two patients were treated in both eyes during the study timeline. Three eyes were excluded due to lack of adherence to treatment which (1 patient from the dexamethasone implant group and 2 patients from the aflibercept group). Of the total number of patients who completed the follow-up schedule, 23 (53.4%) were female and 20 (46.5%) were male. We found an average age of 67.3 years (Table 1). 3 patients from the dexamethasone 0.7 mg (Ozurdex® Allergan) group presented an increased intraocular pressure. They were treats with topical dorzolamide (1 drop every 12 hours) until the IOP was controlled.

PATIENT			FASTING BLOOD GLUCOSE		AFLIBERCEPT / DEXAMETHASONE	INTRAOCULAR PRESSURE MEASUREMENT (mmHg)				VISUAL ACUITY SCORE (ETDRS)				CENTRAL MACULAR THICKNESS (MICRON)		APPLICATION OR INJECTION NUMBER
Nº	AGE	GENDER	INITIAL	FINAL		INITIAL	MONTH 4	MONTH 8	MONTH 12	INITIAL	MONTH 4	MONTH 8	MONTH 12	INITIAL	FINAL	
1	76	F	260	255	A	18	17	16	17	50	55	60	64	340	255	8
2	81	F	210	160	D	12	12	12	12	50	55	60	64	336	240	2
3	67	M	290	160	A	13	16	15	16	36	50	56	60	370	260	7
4	85	F	260	170	D	16	18	18	18	36	51	56	66	364	346	3
5	88	F	230	200	A	18	14	11	11	30	37	51	57	409	362	6
6	61	F	190	140	D	17	27	16	15	40	53	55	62	330	286	2
7	67	M	300	160	A	15	14	12	13	30	47	56	66	424	240	9
8	76	M	230	190	D	14	18	18	16	31	37	41	55	460	370	3
9	60	M	240	180	A	16	14	14	14	37	47	56	56	397	280	8
10	60	F	180	170	D	12	13	14	14	32	37	38	62	330	297	3
11	65	F	180	130	A	16	14	11	13	30	56	43	67	373	240	6
12	72	F	170	130	D	13	15	15	15	38	44	47	71	291	258	1
13	73	F	190	140	A	17	12	12	12	38	59	44	73	324	262	6
14	76	F	220	160	D	13	16	14	14	32	37	38	64	329	282	3
15	71	F	190	140	A	15	14	11	14	36	58	44	66	337	260	7
16	57	F	190	130	D	14	17	17	16	27	43	34	57	340	280	3
17	67	M	200	140	A	15	15	15	15	34	55	36	63	337	260	8
18	74	M	220	160	D	15	17	16	15	30	36	41	63	437	265	3
19	66	F	230	140	A	16	15	15	15	40	51	56	50	382	280	8
20	72	M	250	190	D	14	21	15	15	50	62	66	70	371	375	2
21	68	F	200	170	A	13	13	13	13	40	57	44	66	368	379	7
22	61	F	200	120	D	15	17	14	14	36	54	57	67	364	270	3
23	70	M	190	140	A	13	13	13	13	38	59	63	67	352	271	8
24	71	M	230	140	D	13	15	14	14	37	44	48	68	446	280	3
25	43	F	240	180	A	13	13	13	13	25	38	55	64	386	280	8
26	59	F	230	130	D	13	17	16	12	32	58	59	63	405	286	2
27	66	F	200	170	A	15	14	14	14	40	54	58	68	364	256	8
28	81	M	206	130	D	14	16	17	14	35	57	59	62	425	264	2
29	73	M	240	180	A	13	13	12	13	29	38	58	63	404	274	7
30	62	M	240	150	D	15	18	16	15	30	51	56	58	406	250	3
31	53	M	240	260	A	16	15	15	15	36	48	53	58	421	260	8
32	72	M	280	130	D	14	17	14	14	40	50	61	70	438	270	3
33	64	F	190	130	A	14	13	14	14	40	52	63	67	389	273	7
34	74	M	180	120	D	13	17	13	14	32	56	61	71	351	270	2
35	64	M	240	190	A	18	14	12	13	38	50	66	76	371	261	6
36	71	F	190	120	D	15	28	15	13	47	55	61	66	433	268	3
37	53	M	240	200	A	16	15	15	15	36	40	52	62	462	288	8
38	54	F	230	250	D	14	18	16	14	34	40	41	42	531	305	3
39	58	F	180	130	A	15	14	14	14	38	62	66	77	387	267	6
40	78	M	230	140	D	14	19	15	14	32	57	61	65	367	267	2
41	67	M	180	150	A	13	12	11	12	37	56	66	76	434	265	8
42	65	M	220	170	D	13	15	16	14	40	51	61	63	426	275	3
43	66	F	222	150	A	17	12	12	13	32	56	55	66	389	245	8

Table 1: *Study population characteristics.*
A: Aflibercept; D: Dexamethasone Implant.

Results

Statistical analysis

Results obtained between the two treatment groups (2 mg/0.05 mL intravitreal injection aflibercept (Wetlia® Bayer) versus intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant) were evaluated, taking into account the VA and CMT as well as number of injections or implants applied, with the following results:

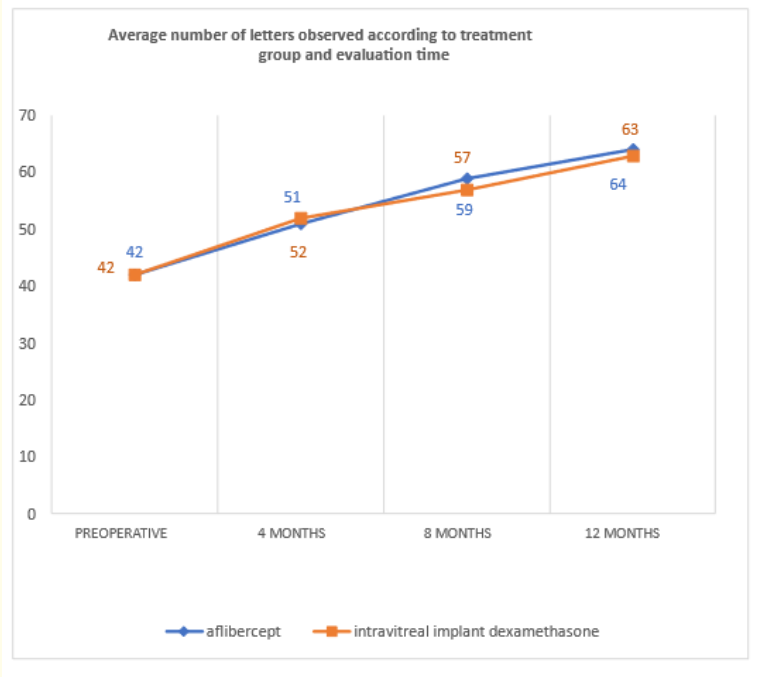
The average number of letters seen by the patients in both groups was calculated before the intravitreal application. In the analysis and estimation of the average number of letters observed in treatment group were compared using a t-test independent, in such a way that it was observed that the mean number of letters observed was 42 ± 12 for the intravitreal aflibercept 2 mg/0.05 mL (Wetlia® Bayer) injection group and 42 ± 13 in the dexamethasone implant (Ozurdex® Allergan) group; observing a similar behavior between both groups. The independent student's t test determined that there was no statistically significant difference among both of them (t - value (t) = -. 088, degree of freedom (df) = 41, p > 0.05), which indicates the similarity between both groups in the evaluation after medication application. After completing 12 months of follow up, we carried a new clinical evaluation taking into account the previous variables and they were

analyzed using the independent student's t-test, observing a gain in the average number of letters observed in both treatment groups, this, compared to the previous values obtained before treatment, concluding that the patients managed with intravitreal aflibercept 2 mg/0.06 mL (Wetlia® Bayer) injection had an average of 64 ± 7 and those treated with a 0.7mg dexamethasone implant (Ozurdex® Allergan) observed 63 ± 7 letters. The end point showed a difference of 1 letter between both groups, but this was not statistically significant ($t = -0.606$, $df = 41$, $p > 0.05$) (Table 2).

Number letters				
Intravitreal injection/implant	**Aflibercept**	**Dexamethasone**	**Difference**	**p**
Pre treatment.	42	42	0	> 0.05
12 meses treatment	64	63	1	> 0.05

Table 2: *Average number of letters observed and their difference according to time of evaluation and treatment regimen.*

The number of letters observed during the duration of the study according to the drug administered, showed a gain in the average number of letters observed after the 4 post-treatment evaluations in comparison to the preoperative ones. When we used the analysis of variance (*ANOVA*) statistical tool, we observed that during the time of follow up there was a gain of letters ($F = 126.030$, $df = 1.606$, $p < 0.05$). However, when it was compared between treatment groups, there were no statistically significant difference ($F = 0.128$, $df = 1$, $p > 0.05$) (Graph 1).



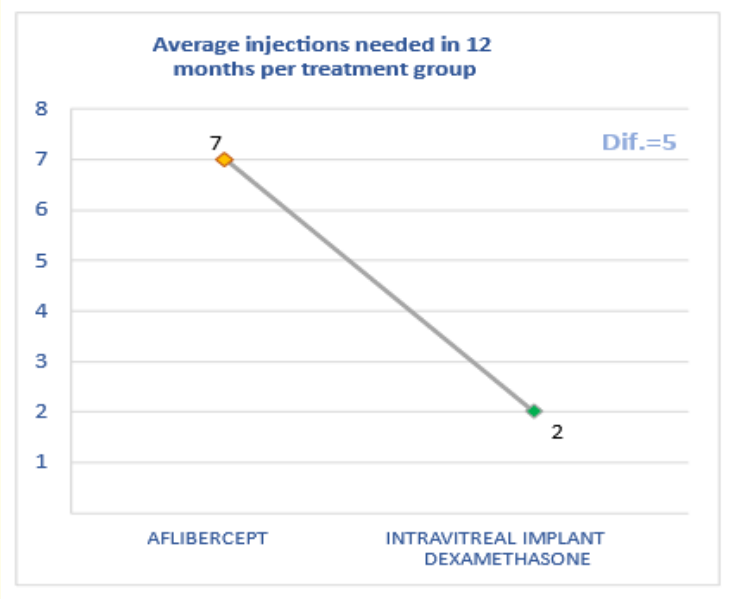
Graph 1: *Average number of letters observed according to treatment group and evaluation time.*

Regarding the CMT, it was evaluated according to the treatment group assigned; then the values were compared using an independent student's t-test, which indicated the following: the average value was 383 ± 51 microns for the group treated with intravitreal aflibercept 2 mg/mL (Wetlia® Bayer) injection and 384 ± 56 for the group treated with intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant, observing a total difference of 1 micron between the groups, however, this difference was not statistically significant (t = -0.67, df = 41, p > 0.05). In turn, an evaluation and analysis of the CMT at the end of the follow-up period (12 months), using the independent Student's t-test for independent variables in both treatment groups. A tendency to CMT decline was observed in comparison to the values documented prior to the start of treatment. It was concluded that the CMT observed in patients treated with intravitreal aflibercept 2 mg/mL (Wetlia® Bayer) injection was 269.36 ± 22 microns and 263.52 ± 12.9 microns in those managed with intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant, thus, the total difference found was 5.84 microns, not being statistically significant (t = 1.054, df = 41, p > 0.05). (Table 3)

Central macular thickness (µm)	Difference in the CMT			
	Aflibercept	Intravitreal implant dexamethasone	Differences	p
Pre treatment	382.95	384.05	1	> 0.05
12 months post treatment	269.36	263.52	5.8	> 0.05

Table 3: *Average CMT values and their difference according to time and medicine applied.*

Regarding the number of applications during 12 months of follow-up by treatment group, finding that this was higher in the group treated with intravitreal injection aflibercept 2 mg/mL (Wetlia® Bayer), where the average of injections was 7.09, while in the dexamethasone intravitreal implant group 0.7mg (Ozurdex® Allergan) the average number of applications needed was 2.28 (Table 4) having a total difference of 5 injections in the study period between both treatment groups, for which a Student's t test was performed independent, determining that this difference is statistically significant, that is, the number of injections required is associated with treatment (Graph 2). There was an increase in the intraocular pressure in 3 patients in group 2 (6.97%).



Graph 2: *Number of applications needed in a 12-month period per treatment group.*

Average injections/implant	Difference in the number of applications			
	Aflibercept	Intravitreal implante dexamethasone	Differences	p
12 months treatment	7.09	2.28	5	< 0.05

Table 4: *Average injection needed in 12 month per treatment group.*

Discussion

DM is one of the main causes of morbidity and mortality in the world. Our hospital, which belongs to the National Health System in Mexico, has treatment options for DME and they include the widely studied antiangiogenic drugs like ranibizumab and aflibercept, as well as the dexamethasone intravitreal implant. This study is the first to compare the use of aflibercept intravitreal injection versus intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant in pseudophakic patients with a follow-up period of 12 months for the treatment of DME as initial therapy in Mexican population. The characteristics baseline in the present study, included: age, sex, and fasting blood glucose levels; similar variables that those reported in other clinical studies. The role of glycemic balance and blood pressure in the genesis and worsening of DME have been well known in type 1 and type 2 diabetic patients since the DCCT and the UKPDS studies, respectively. Letter gain in patients treated with aflibercept intravitreal injection 2 mg/mL (Wetlia® Bayer) was an average of 62 ± 7 and 64 ± 7 in those treated with intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant, therefore, there was a difference of 1 letter between both groups, but this hasn't been proved statistically significant (t = - 0.606, fd = 41, p > 0.05). At the time that we reviewed the results of the Bevordex study regarding the BCVA, we found an improvement of 10 or more letters in 17 of 42 eyes (40%) in those treated with bevacizumab compared to 19 of 46 eyes treated with intravitreal dexamethasone implant (41%; P = 0.83) [8]. None of the 42 eyes in the bevacizumab group, in the aforementioned study, lost 10 letters or more, while 5 of 46 (11%) eyes treated with the dexamethasone 0.7 mg (Ozurdex® Allergan) implant did, mainly due to the development of cataract, an outcome that was not present in our study since all of our patients were pseudophakic. Another variable compared against the Bevordex study was the mean CMT, which reported a decreased of 122 µm on the bevacizumab treated eyes and 187µm on the intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant treated eyes (P = 0.015). We had similar results in our study, where we discover a decrease on the CMT of 113.59 µm on the aflibercept group in comparison to the 120.53 µm with the intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant. Therefore, the total difference found was 5.8 microns, not being statistically significant between the two groups (t = 1.054, df = 41, p > 0.05).

Regarding the number of injections, we had an average of 2 intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant applications compared to 7 injections for intravitreal aflibercept 2 mg/0.05 mL (Wetlia® Bayer), which was statistically significant between the two groups. If we compare our results with the BEVORDEX study, that reported an average of 8.6 injections for the aflibercept group compared to 2.7 dexamethasone implant 0.7 mg (Ozurdex® Allergan) applications; these results were similar to the ones described in our study, although is worth mentioning that the BEVORDEX study applied the 0.7 mg dexamethasone implant (Ozurdex® Allergan) every 6 months and not every 4 months as our study proposed [8].

An increase in intraocular pressure was found on the dexamethasone 0.7 mg (Ozurdex® Allergan) implant group, with values above 10 mmHg described on 3 (6.9%) patients, which represented the 7% of the study population and 11 patients presented IOP values above 5 mm Hg, equivalent to 25.6%, meanwhile, the MEAD study (0.7 - mg and 0.35 - mg dexamethasone intravitreal implant vs. sham treatment) found an increase in IOP above than 10 mm Hg in 27.7% of their population but no difference was made between phakic and pseudophakic patients [10,11]. On the Bevordex study, 46% of the studied patients had elevated IOP of more than 10 mm Hg [8]. In the aflibercept intravitreal injection group (Wetlia® Bayer) no patient presented ocular hypertension.

One disadvantage our study was the size of the sample. Additional studies with larger samples are recommended to establish predictors for the results of BCVA and CMT in diabetic macular edema treated with aflibercept (Wetlia® Bayer) and dexamethasone intravitreal implant (Ozurdex® Allergan).

Conclusion

In this study, patients experienced visual and anatomical improvement after receiving both, 2 mg/0.05 mL aflibercept intravitreal injection (Wetlia® Bayer) as with dexamethasone 0.7 mg (Ozurdex® Allergan) intravitreal implant with very similar results; and there weren't statistically significant differences when comparing both groups of study composed with pseudophakic patients. It has been described on several clinical series that the use of intravitreal corticosteroids carries adverse effects at ocular level, such as increased IOP and the development of cataract, which is implied as the main cause of visual loss, in this study being pseudophakic patients we didn't evaluate this finding. However, 3 patients presented secondary ocular hypertension that was controlled with topical treatment. For all the aforementioned we concluded that the intravitreal dexamethasone 0.7 mg (Ozurdex® Allergan) implant is safe and no inferior compared against aflibercept intravitreal injection (Wetlia® Bayer) in the resolution of DME as an initial therapy, as well as in the improvement of VA, showing fewer number of applications with statistically significant results. This contributes to an improvement in the patient adherence to the treatment regimen, also reducing the burden of institutional treatment and ultimately decreasing costs. Finally, this study represents the first clinical trial described in Latino population that can be used as a reference for future studies.

Conflict of Interests

The authors declare that does not exist an interest conflict.

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This study did not receive any specific funding from the public sectors, commercial or non-profit.

Ethical Responsibilities

Protection of people and animals: The authors declare that the procedures followed they conformed to the ethical standards of the experimentation committee responsible human body and in accordance with the World Medical Association and Declaration of Helsinki.

Confidentiality of the Data: The authors declare that they have followed the protocols on the publication of patient data.

Right to Privacy and Informed Consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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