Original Paper

Aflibercept Versus Bevacizumab as First-Line Therapy in Age-Related Macular Degeneration

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ABSTRACT: Background: AMD (age-related macular degeneration) is the main cause of central vision loss in the population over 60 years old. AMD does not affect peripheral vision and complete blindness does not occur, instead, central vision is affected both for distance and for near. The purpose of this study is to evaluate the neovascular form of AMD treatment and compare ocular and systemic effects after intravitreal injection of aflibercept, respectively after bevacizumab when administered in comparable dosages and regimens. We conducted a retrospective, single-center study from June 2021 to December 2022 and enrolled 20 patients with neovascular AMD who had not received any prior treatment for this condition. We randomly assigned them to two groups of 10: group one received aflibercept and group two received bevacizumab as intravitreal injections under aseptic conditions. We excluded 2 patients who did not meet the criteria and ended up with two groups of 9 patients who received monocular treatment. We gave the patients 3 monthly injections of anti-VEGF agent and followed them up at 1 month, 3 months, and 9 months after the treatment. We assessed their visual acuity, intraocular pressure and OCT appearance at each follow-up visit. The primary outcome was visual acuity. All 18 patients included in the study reported an improvement in visual acuity after the intervention. When comparing the two anti-VEGF agents, data revealed the effect of aflibercept was prompter and more long-lasting. Areas of retinal ischemia appeared in both cases. However, they were observed faster in the case of patients treated with aflibercept. Thus, neovascular AMD is a disease that occurs with age, it can be early detected by OCT and slowed the progression to central blindness with intravitreal treatment.

KEYWORDS: *AMD, Bevacizumab, Aflibercept, Avastin, Eylea.*

Introduction

Age-related macular degeneration (AMD), an acquired pathology of the retina that causes irreversible central vision loss in people over 60 years, represents 8.7% of all cases of blindness worldwide.

It is estimated that due to the increase of aging population, the prevalence will increase to 18.57 million by 2040, thus becoming a real public health problem that will also involve serious economic aspects [1].

Two forms of the disease are distinguished as follows: the exudative form, known as neovascular AMD, and the non-exudative form, which is characterized by the presence of geographic atrophy.

Whereas only 10% of patients develop the neovascular form, which causes severe central vision damage, 80% to 90% of patients experience debilitating symptoms as a result of the condition.

Regarding the physiopathological mechanism of neovascular AMD, the vascular endothelial growth factor (VEGF) plays a critical role and it is considered the main cause of increased angiogenesis, which in turn leads to complications such as subretinal hemorrhage, vitreous hemorrhage, fibrosis, and retinal scars [2].

The AMD treatment differs, depending on the evolutionary stage of the disease and its type.

In the case of the dry form of AMD, no effective therapeutic approach has been identified

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up to date, while for the neovascular form, several therapeutic protocols are known [3].

Although various therapeutic strategies have been developed for patients with neovascular AMD, the prognosis of this disease has changed significantly since the introduction of anti-VEGF agents (ranibizumab, bevacizumab, aflibercept).

According to current guideline recommendations, intravitreal injection of anti-VEGF preparations continues to be the first-line therapy in neovascular AMD even after almost a decade since their initial use [4].

Aflibercept (Eylea; Regeneron Pharmaceutical Inc, Tarrytown, New York, USA and Bayer Healthcare, Berlin, Germany) is one of the most recent anti-VEGF agents approved in the treatment of neovascular AMD (2011) [5].

Eylea (Aflibercept) is the first protein biologically engineered as a fully human fusion with a VEGF "trap" receptor role.

It consists of human VEGF receptor fragments (vascular endothelial growth factor) and the extracellular domains of VEGF-R1 and VEGF-R2 receptors.

Eylea was formulated as an isosmotic solution intended for intravitreal administration.

This special product, unlike other anti-angiogenic preparations (ranibizumab, bevacizumab), has several advantages: it neutralizes all VEGF-A isoforms, to which it binds with a high affinity, as well as two other members of the VEGF family: VEGF-B, and most importantly it also blocks the placental growth factor [6].

Studies have also demonstrated that the administration of aflibercept every two months achieves a visual gain comparable to the monthly administration of ranibizumab [7].

Aflibercept has a longer half-life than ranibizumab and bevacizumab, and, unlike them, it is able to penetrate all layers of the retina [8].

Also, the rate of non-responders is lower than that of the other anti-VEGF agents [9].

Since it is known that anti-VEGF therapy is a long-term treatment in neovascular macular degeneration, the question arises whether continuous neutralization of VEGF (essential in ocular homeostasis) may also cause unfavorable events, such as the exacerbation of atrophy of the retinal pigment epithelium [10].

Bevacizumab (Avastin, Roche) is known as a therapeutic agent in cancer based on the clinical results that test safety and effectiveness.

The drug commission of the United States of America has approved Avastin for colorectal cancer.

Once a drug is approved by the drug commission, healthcare providers can use it outside the official recommendations (off label) in other conditions based on the evidence of some clinical studies.

In ophthalmology it is used off-label worldwide; after its appearance on the market in 2005, many publications supported for its good results and low cost.

Following the administration of this substance, no significant secondary ocular changes occur [11].

In this study, we aimed to investigate the modifications in visual acuity and the prevalence of retinal atrophy in patients with neovascular AMD who received aflibercept injections versus patients that received bevacizumab for the same pathology.

This study compares the ocular and systemic effects of intravitreal injections of aflibercept and bevacizumab when given in similar dosages and regimens in order to assess the treatment of neovascular AMD.

Material and Methods

In this study were included 18 patients with a mean age of 60+/-10 years.

A retrospective, single-center study was performed by us from June 2021 to December 2022.

Treatment outcomes between aflibercept and bevacizumab as first-line therapy in neovascular AMD was assessed in naive patients.

The exclusion criteria were as follows: patients who received less than 3 intravitreal injections with aflibercept or bevacizumab, patients who received other treatment than antivascular therapy (laser photocoagulation) patients with glaucoma, and those who were not properly followed up.

The study consisted of two distinct groups.

In each group we included 9 patients who received monocular treatment.

The patients from group 1 received intravitreal aflibercept as initial treatment, 2mg for 3 consecutive months.

The patients in group 2 received bevacizumab 0.05 mg monthly for 3 months.

We used a sterile injection technique to deliver the treatment to the vitreous body as it follows: after asepticizing the periocular teguments with povidone iodine 10%, we had applied a sterile speculum to separate the eyelids; a povidone iodine 5% solution was applied to the ocular surface and then a local anesthetic (oxybuprocaine).

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The injection site was chosen on the pars plana, 3,5mm posterior to the limbus for phakic patients and 4mm posterior to the limbus for pseudophakic patients.

We used a 30-gauge needle to inject the anti VEGF agent.

After the injection, the patients used netilmicin four times a day for one week.

All participants were informed about the procedure and the risks of the treatment and the informed consent form was obtained.

The agreement of the Ethics Committee of "Dr. Carol Davila" Central Military Emergency University Hospital Bucharest was also obtained before considering the data for publication (403/17.09.2020).

The three consecutive monthly intravitreal injections given to all 18 patients were part of the treatment protocol.

For each patient enrolled in the study we had performed visual acuity using the Snellen chart, intraocular pressure using the Goldmann tonometer, biomicroscopic examination and fundus examination with dilated pupil.

In addition, optical coherence tomography (SD-OCT, Heidelberg Spectralis) was performed in each case.

The visual acuity, intraocular pressure, biomicroscopic examination and OCT were measured at four time points: before the treatment, one month, three months and nine months after the 3rd injection.

The main efficacy parameter evaluated was visual acuity (VA) with the best correction.

The improvement of this parameter was considered the improvement in the number of rows in Snellen chart between visits.

The statistical analysis was performed using MedCalc Version19.4 (MedCalc Software Corp., Brunswick, ME, USA).

One-way ANOVA followed by Scheffe post-test (with alpha level 0.05) was used for comparison among groups.

Results

We enrolled 20 patients with neovascular AMD and excluded 2 patients who did not meet the criteria (one received the second injection elsewhere; one missed the follow-up exams).

The remaining 18 patients received monocular anti-VEGF treatment and were divided into two groups of 9: group 1 received aflibercept injections and group 2 received bevacizumab injections.

The mean age of the participants was 60+/-10 years.

We found that the bevacizumab group did not show any significant improvement in visual acuity after one month, while the aflibercept group showed a small increase in visual acuity.

The aflibercept group also had a lower average visual acuity before the treatment, but it improved significantly by the third month of treatment (Figure 1)

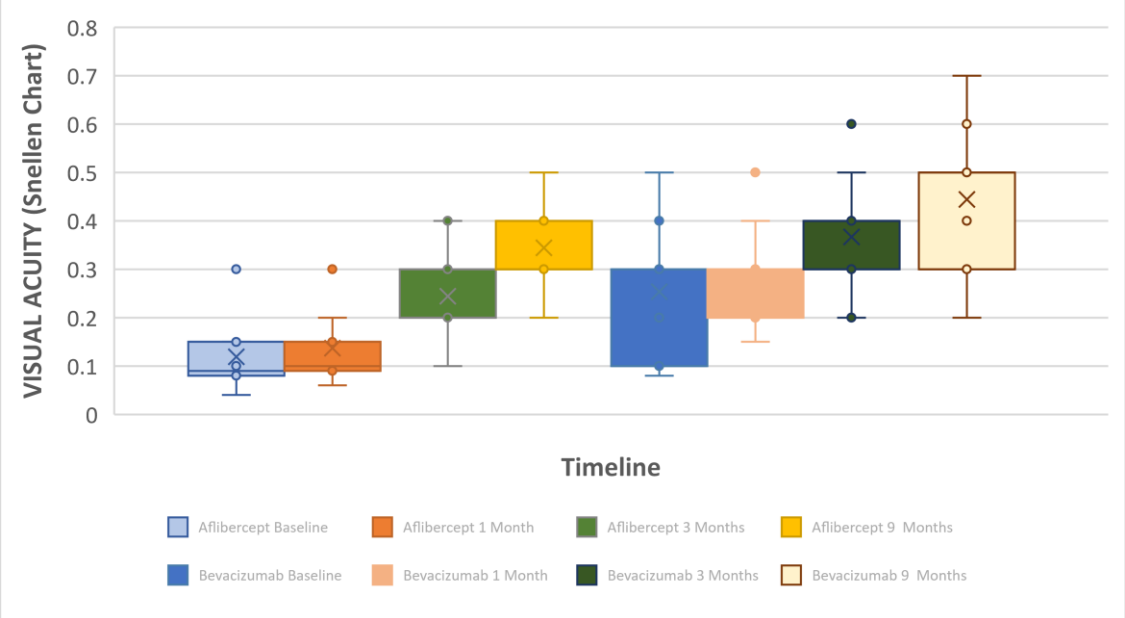

Figure 1. Visual acuity measured at baseline, 1, 3 and 9 months after the administration of three injections with the anti VEGF agents aflibercept/bevacizumab.

The difference between the initial and final visual acuity of the aflibercept group was statistically significant ($p<0.001$ based on ANOVA test method) meaning that it was unlikely to be due to chance.

Based on the Scheffe test, the only non-significant difference was between baseline and 1 month.

All other pairwise comparisons were significant (Table 1).

Table 1. Aflibercept Scheffe test for all pairwise comparison.

Factor	N	Mean	SD	Different from factor
baseline	9	0,11	0,07	(3) (4)
1 month	9	0,13	0,07	(3) (4)
3 months	9	0,24	0,09	(1) (2)
9 months	9	0,34	0,08	(1) (2) (3)

The bevacizumab group (group 2) showed an improvement in the visual acuity compared to the baseline values, with a $p<0.02$, based on ANOVA test method.

Except for baseline and 1 month, and 1 month and 3 months, which had non-significant differences, the Scheffe test showed that all other pairwise differences were significant (Table 2).

Table 2. Bevacizumab Scheffe test for all pairwise comparison.

Factor	N	Mean	SD	Different from factor
baseline	9	0,25	0,14	(3) (4)
1 month	9	0,28	0,11	(4)
3 months	9	0,36	0,13	(4)
9 months	9	0,44	0,15	(1) (2) (3)

The results based on the Scheffe test, which is used to determine if there are significant differences between group means indicates that the intravitreal treatment was successful in improving the visual acuity.

Compared to bevacizumab, aflibercept led to a greater increase in visual acuity after the first three injections.

Aflibercept had a higher therapeutic efficacy from the first injection onwards, enhancing the patients' vision more effectively.

We performed a fundus examination with dilated pupil at each follow-up visit to assess the condition of the retina and the choroid.

We observed that both groups showed a reduction of neovascularization after the first month, indicating that the anti-VEGF treatment was effective.

In both groups, all the patients showed signs of neovascularization at the beginning of the study.

One month after treatment, signs of neovascularization were observed in 55.5% of the patients who received aflibercept and in 77.7% of the patients who received bevacizumab.

We also did not find any new signs of neovascularization or hemorrhage in the interval between the injections of between the check-up for either group.

This was the criteria we used to decide not to shorten the interval between the injections, or to administrate another one, as we wanted to minimize the risk of complications and side effects.

We monitored the patients for any adverse effects of the intravitreal injections during the follow-up period.

We did not observe any ocular complications, such as high intraocular pressure, endophthalmitis, vitreous hemorrhage, or retinal detachment, that could affect the vision or health of the patients.

We also did not record any systemic complications, such as allergic reactions, infections, or cardiovascular events, that could be related to the anti-VEGF agents.

We measured the central retinal thickness (CRT) using optical coherence tomography (SD-OCT, Heidelberg Spectralis).

In both groups we had noticed the presence of retinal atrophy; in aflibercept group, two patients (22,22%) developed retinal atrophy 6 months after the first injection; in bevacizumab group, one patient (11,11%) developed retinal atrophy 12 months after the first injection.

The two groups of patients were followed-up 9 months after the three injections.

The visual acuity examination and the ocular tomography were always carried out and interpreted by the same retina specialist.

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Discussions

Anti-VEGF therapy remains the first line of treatment in the therapeutic management of neovascular AMD.

Currently, aflibercept is one of the most used anti-VEGF agents and its effectiveness has been demonstrated through numerous studies.

Ohiji et al observed in their study that intravitreal treatment with aflibercept, administrated to naive patients with neovascular AMD, using two different administration regimens, improved the visual acuity after a year, and the benefits lasted until the end of the second year [12].

However, some studies have also reported that aflibercept can have a negative effect on the blood flow in the retina, leading to areas of reduced oxygen supply or ischemia.

In a study published in 2018 by Sabaner et al, 29 patients diagnosed with diabetic macular edema were treated monocularly with three intravitreal injections of aflibercept monthly.

The conclusion of this study was that after intravitreal treatment with aflibercept can alter the blood flow in the retina by decreasing the width of the retinal arteries, making the choroid layer thinner [13].

Also, Mursch et al. have shown that the diameter of retinal arterioles decreases significantly one week after aflibercept injection and this decrease continues up to five weeks after the third injection in patients with neovascular macular degeneration [14].

In another study in which 20 patients with neovascular AMD were enrolled, Mursch et al. concluded that three intravitreal injections of aflibercept led to modifications in ocular circulation, resulting a reduction in perfusion of the optic nerve head and the choroid [15].

The second anti-VEGF agent used in our study was bevacizumab, which is not specifically designed for ophthalmic use, unlike other anti-VEGF drugs such as ranibizumab (Lucentis), aflibercept (Eylea), brolucizumab (Beovu), and faricimab (Vabysmo). Bevacizumab (Avastin) was initially used to treat various types of cancer, such as colon, lung, brain, kidney, cervical, ovarian, and liver cancer.

In ophthalmology, bevacizumab it is used off-label, with good results in neovascular retinal diseases.

One of the advantages to use bevacizumab is the price; it is much cheaper than other anti-VEGF drugs, which makes it an attractive option for many patients and health care providers.

On the other hand, there are some disadvantages and risks associated with bevacizumab use.

One of them is the need for compounding, which is the process of preparing individual doses of bevacizumab from a larger vial.

Compounding can introduce variability in the concentration and quality of the drug, as well as increase the risk of contamination and infection.

Another issue is the lack of long-term data on the safety and efficacy of bevacizumab for wet AMD, especially compared with other anti-VEGF drugs.

In our study we used bevacizumab as first line therapy for patients diagnosed with neovascular AMD.

After three monthly injections with bevacizumab, we observed an improvement in visual acuity and reduction of central macular thickness.

Visual improvement after intravitreal injection with bevacizumab was also supported by Yoganathan et al in their study over 50 eyes.

In this case, only 14 eyes were naïve patients, 36 eyes received prior treatment with pegaptanib or photodynamic therapy.

They concluded that bevacizumab administrated intravitreal has improved the visual acuity in both naïve and prior treated patients, with better results in naïve patients [16].

In 2020 Tomas Bro and his collaborators analyzed the degree of use of bevacizumab in Europe.

Despite the demonstration of effectiveness in Europe, no consensus was reached, each country having its own approach [17].

Retinal atrophy was observed in both groups, but at different times and rates.

In the aflibercept group, two out of nine patients (22.22%) had retinal atrophy after six months of treatment.

In the bevacizumab group, one out of nine patients (11.11%) had retinal atrophy after 12 months of treatment.

Gala Beykin talks in paper he elaborated, that over time the visual acuity deteriorates due to the atrophy that sets in approximately two years after the first injection [18].

A multicenter study conducted in Japan by Hideki Koizumi et al evaluates the changes and the speed of progression in macular atrophy after intravitreal injection of aflibercept for neovascular AMD.

The results show that macular atrophy is more likely to occur in eyes that have reduced vision

and fluid accumulation in the retina at the baseline [19].

Other criteria studied was the intraocular pressure.

We obtained no cases of long-time intraocular pressure after the intravitreal delivery of anti VEGF agents.

Intravitreal injections can lead to elevation of intraocular pressure short time after the intervention or in a long-term.

Some authors reported a transient intraocular pressure after the intravitreal injection, followed by normalization, without the need of antiglaucomatous medication [20].

Conclusions

To sum up, the two anti-VEGF agents showed a beneficial effect regarding the inhibition of neovessels of the retina in patients with neovascular AMD.

Our study evidentiated an improvement in visual after the intravitreal injections.

Comparing the two groups of patients, in which group 1 received intravitreal injection with aflibercept, and group 2 received intravitreal injections with bevacizumab, we obtained better results regarding visual acuity in patients treated with aflibercept.

We also observed that aflibercept over time leads to macular atrophy faster than bevacizumab.

We could not determine in our study the factors that predispose to macular atrophy.

Further studies must be developed to be able to appreciate the degree of retinal atrophy and the main factors that lead to the retinal atrophy.

Conflict of interests

The authors declare no conflicts of interest

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