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Use of Bevacizumab and Aflibercept in the Treatment of Diabetic Macular Edema: Cost-effectiveness Analysis

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ABSTRACT

Background: The aim of this study was to evaluate the efficacy of aflibercept by comparison with bevacizumab in the treatment of diabetic macular edema.

Methods: The study included 159 patients; the first group consisted of 58 patients who underwent intravitreal application of aflibercept, and the second group of 101 patients underwent intravitreal application of bevacizumab.

Main Findings: There was a statistically significant decrease in edema during the optical coherence tomography (OCT) scans after the application of bevacizumab (533±152 μm vs. 384±104 μm, $p<0.001$) and aflibercept (500±110 μm vs. 354±80 μm, $p<0.001$). Moreover, a significant increase in central visual acuity was observed both for bevacizumab (0.29±0.20 μm vs. 0.36±0.22 μm, $p<0.001$) and aflibercept (0.40±0.30 μm vs. 0.48±0.31 μm, $p<0.001$).

Principal Conclusion: An intravitreal application of either aflibercept or bevacizumab resulted in a significant reduction in macular edema and a significant increase in central visual acuity. Although statistically more efficient, aflibercept use can hardly be justified, due to the high cost associated with its use. Bevacizumab achieved a higher cost-effectiveness compared with aflibercept. Therefore, its use should be considered depending on various healthcare systems, as well as socio-economic factors.

Key words: diabetic retinopathy, diabetic macular edema, bevacizumab, aflibercept, optical coherence tomography, visual acuity

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INTRODUCTION

Diabetic retinopathy is a complication of diabetes that causes damage to the blood vessels in the photosensitive tissue of the posterior eye segment (1). According to the early treatment of diabetic retinopathy study (ETDRS), diabetic retinopathy is divided into non-proliferative and proliferative diabetic retinopathy (2). Diabetic macular edema (DME) is a thickening of the macula due to fluid and lipoprotein accumulation caused by blood vessel leakage. As a complication of diabetes, it is one of the most common causes of central vision loss (3). DME is considered clinically significant if one of the following three signs is present: retinal thickening at or within 500 µm from the center of the macula, hard exudates with retinal thickening that can be more than 500 µm from the macula center or retinal thickening of at least one optic disc diameter (DD) within a distance of one DD from the macula center (4).

Hyperglycemic stimulation, oxidative stress and hypoxia induce the pathological effects of vascular endothelial growth factor (VEGF) in the retina, most often its isoform VEGF165 which increases the permeability of retinal blood vessels, causes the breakdown of the blood-retinal barrier and the development of retinal edema. The breakdown of the blood-retinal barrier results in the accumulation of plasma proteins (albumins) that increase osmotic pressure causing interstitial edema (5).

The clinical signs of DME are most often manifested as the following symptoms: floating dotted and spotted shadows in the field of view, blurred vision, fluctuating vision, color vision disorder, dark or white spots in the field of view or loss of vision (6). The diagnosis is established based on clinical signs, fluorescein angiography (FA), and OCT. OCT is a non-invasive diagnostic method, based on different absorptions and the reflection of light waves in individual parts of the retina. It gives a detailed view of retinal layers two-dimensionally and three-dimensionally and has a high sensitivity for detecting retinal lesions (98.6%) (7). The use of anti-VEGF therapy reduces the formation of pathological blood vessels and reduces the thickness of the retina, by reducing the amount of subretinal fluid, consequently improving visual acuity. Anti-VEGF drugs are applied in the form of intravitreal injections. They are administered in aseptic conditions, which include surgical hand disinfection, sterile gloves, sterile coverings, sterile eyelid specula and the availability of sterile paracentesis in the case of a sudden increase in intraocular pressure (8). Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that selectively binds to all isoforms of VEGF. It was first approved in the United States in 2004 by the Food and Drug Administration (FDA) for the treatment of solid tumors but is widely used "off label" in the treatment of DME (9). Aflibercept (Eylea) is a newer recombinant fusion protein that binds to all isoforms of VEGF and to PLGF. It was approved in March 2015 in the US by the FDA for the treatment of DME (10).

The main aim of this study was to investigate the efficiency of aflibercept vs. bevacizumab in the treatment of DME.

An additional objective of this study was to compare the cost effectiveness of each of the above treatments.

PARTICIPANTS AND METHODS

Participants

The study included 159 patients who were treated at the University Hospital (UHC) Mostar from January 1, 2015 until January 1, 2020, with intraocular application of anti-VEFG drugs (aflibercept or bevacizumab). The first group consisted of 58 patients who underwent intravitreal application of 2 mg of aflibercept and the second group of 101 patients underwent intravitreal application of 1.5 mg of bevacizumab. The variables that were analyzed included the determination of visual acuity by

ETDRS optotypes, examination of the fundus by indirect ophthalmoscopy using a Volk lens 90 diopters, and the measurement of the thickness of macular edema using OCT (Optopol Technology, Zawiercie, Poland).

Methods

Data were collected from the Department of Ophthalmology, University Hospital Mostar. All of the data obtained from medical records were divided into input and output parameters. The input parameters that were observed were: age, sex, treatment year of application, working diagnosis, visual acuity and OCT measurement before treatment. The output parameters were visual acuity and OCT measurement after treatment.

Statistical analysis

The parameters were processed with Microsoft Excel (version 10, Microsoft Corporation, Redmond, WA, USA), and SPSS for Windows (version 23.0, SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. The differences in categorical variables were tested by the chi-square test and Fisher's exact test, as necessary. The differences between continuous variables were tested by the Student t-test. The probability level of $p < 0.05$ was considered statistically significant.

RESULTS

There was a statistically significant difference in the frequency of different drug applications regarding the treatment of DME at UHC Mostar in favor of bevacizumab (Table 1).

There were significantly more male patients in this study regardless of the drug used. There was no statistically significant difference in age between the two subgroups, aflibercept and bevacizumab (Table 1).

Table 1. Applied drugs, sex distribution and mean age of patients receiving bevacizumab and aflibercept

	Male n(%)	Female n(%)	Age ($\bar{X}$±SD)
bevacizumab	60 (38%)	41 (26%)	64.9±11 y
aflibercept	37 (23%)	21 (13%)	67±11 y

There was a statistically significant decrease in edema at the OCT scans following the application of both bevacizumab and aflibercept. Aflibercept was more efficient in reducing macular edema compared with aflibercept but had no statistical significance (Table 2).

There was a significant increase in central visual acuity following the application of both bevacizumab and aflibercept. Aflibercept was also superior in improving visual acuity compared to bevacizumab, but had no statistical significance (Table 3).

Aflibercept and bevacizumab demonstrated similar levels of efficacy in improving visual acuity and reducing DME. Given the much higher cost of aflibercept, bevacizumab achieves higher cost-effectiveness (Table 4).

DISCUSSION

In this 5-year cross-sectional study, we have analyzed 159 patients diagnosed with DME. The intravitreal application of aflibercept and bevacizumab individually resulted in a significant reduction of macular edema, as measured by OCT, and a significant increase in central visual acuity. However, these treatments demonstrated comparable levels of efficacy in improving visual acuity and reducing DME.

The incidence of diabetic retinopathy increases with the duration of diabetes and many patients with diabetic retinopathy will develop DME. Additionally, DME occurs more frequently in patients diagnosed with diabetes in the older age group (6) which correlates with the demographic characteristics of our patient population. The results of our study were comparative to those reported by Wells et al. in a 2-year comparative effective clinical trial of aflibercept, bevacizumab and ranibizumab in which the mean age of the patients was 61±10 years (11). Furthermore, the incidence of diabetes is comparable between the sexes, although men appear to be at a higher risk of microvascular complications, including the presence and severity of diabetic retinopathy,

also reported by Abatte et al. (12). Although the reasons for men's more increased susceptibility for DME remain largely unknown, sex appears to be a significant factor in certain aspects of the microvascular complications of diabetes (12). In a randomized clinical trial, designed for optimization of the anti-VEGF treatment for DME, 660 patients were enrolled of which 53% were male, indicating a marginal predisposition of this pathological process towards men (13).

A recent comparative study of diabetic retinopathy showed that in patients with DME and an initial visual acuity of 0.4 or less, aflibercept therapy exhibited a marked improvement in VA at 1 year compared with bevacizumab. In contrast, no difference was found in the mean improvement in VA for patients with an initial VA of 0.5 to 0.6 (14). Although we did not classify patients into groups according to their level of visual acuity, our results indicate that both aflibercept and bevacizumab have similar efficacy in improving VA and decreasing DME, as measured by OCT.

In the present study, a simplified formula for the incremental cost-effectiveness ratio (ICER=C1-C0/E1-E0) was used as previously described by Ross et al. (15). We demonstrated that although statistically more effective, aflibercept does not achieve higher cost-effectiveness compared to bevacizumab. This result poses a major challenge to clinicians, patients and healthcare systems, as efficacy and superiority do not coincide with the treatment cost. Based on wholesale costs for 2015, aflibercept (2.0 mg) costs $ 1850 and bevacizumab (1.25 mg) approximately $ 60. These medications can be given nine to 11 times in the first year of treatment, and on average 17 times over 5 years, indicating the importance of comparing the cost effectiveness of each treatment. The use of these medicines for the treatment of wet, age-related macular degeneration in 2010 amounted to a total cost of ~$2 billion, equivalent to 1/6 of the entire Medicare budget. Given these costs, Diabetic Retinopathy Clinical Research (DRCR) network researchers considered it important to analyze the relative cost-effectiveness of DME treatment using each agent. They conducted a large study in which the VA levels of each participant on each visit were converted to QALYs using data from Brown at al. who linked VA in a patient's better-seeing eye with the health-related quality-of-life (16). Authors have demonstrated that the cost of aflibercept should be 60-90% lower or below $250 to become more cost-effective than bevacizumab for the treatment of DME (in the United States under Medicare). At the time of writing, the price of aflibercept in Bosnia and Herzegovina amounts to ~€600 (~$670), and €30 (~$35) for bevacizumab. Considering the cost-effectiveness data from the US (15), aflibercept should fall to €166 (~$185) to become more cost-effective than bevacizumab in the treatment of DME. In Bosnia and Herzegovina, the price of aflibercept is around €600 and bevacizumab is €30. If we consider the cost-effectiveness data from the US, aflibercept should fall to €166 to become more cost-effective than bevacizumab in DME treatment.

Although aflibercept demonstrated superior efficiency from a statistical perspective compared to bevacizumab in the treatment of DME, this does not justify its much higher price. Bevacizumab is an "off label" intraocular drug that consistently demonstrates more cost-effectiveness in the treatment of DME compared to aflibercept. Healthcare systems can utilize this information to develop optimal DME treatment protocols, based on available funds and treatments.

Table 2. OCT before and after application of bevacizumab and aflibercept

Drug		$\bar{X}$	SD	t	p
bevacizumab	OCT before	533.06	163.41	11.236	<0.001
	OCT after	376.92	101.86		
aflibercept	OCT before	518.62	136.08	10.749	<0.001
	OCT after	359.09	113.62		
	Edema reduction				
bevacizumab	156.14±13.9 µm			0.15	0.8
aflibercept	159.53±14.8 µm				

Table 3. VA before and after application of bevacizumab and aflibercept

Drug		$\bar{X}$	SD	t	p
bevacizumab	VA before	0.29	0.22	9.471	<0.001
	VA after	0.37	0.25		
aflibercept	VA before	0.34	0.27	7.046	<0.001
	VA after	0.43	0.29		
	Visual improvement				
bevacizumab	0.08±0.01			0.6	0.4
aflibercept	0.09±0.008				

Table 4. Cost-effectiveness analysis of bevacizumab and aflibercept

	Cost	OCT1-OCT2	VA2-VA1	OCT/Cost	VA/Cost
bevacizumab	€30	156.14	0.08	5.20467	0.00267
aflibercept	€600	159.53	0.09	0.26588	0.00015

CONCLUSIONS

An intravitreal application of aflibercept or bevacizumab resulted in a significant reduction of macular edema, as measured by OCT, and a significant increase in central visual acuity. Both treatments demonstrated similar levels of efficacy in improving visual acuity and reducing DME. Although more efficient, the clinical superiority of aflibercept did not justify its much higher price tag.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Author contributions: K.K. and I.M. conceived and designed the study; K.K., A.S., A.P.S., I.S., I.Ć. and I.M. collected the data; K.K. and I.M. analyzed the data; K.K., A.S., A.P.S., I.S., I.Ć. and I.M. interpreted the results; K.K. and I.M. prepared the figures; K.K. drafted the manuscript; K.K., A.S., A.P.S., I.S., I.Ć. and I.M. edited and revised manuscript; K.K., A.S., A.P.S., I.S., I.Ć. and I.M. approved the final version of the manuscript.

ETHICAL BACKGROUND

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Mostar (Mostar, July 7, 2020).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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